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COMPREHENSIVE
CLINICAL
NEPHROLOGY
SEVENTH EDITION

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DEDICATION

To our mentors in nephrology—especially Bill Couser,
Karl M. Koch, and Kailash Jindal
To our colleagues and collaborators, as well as others, whose research
continues to light the way
To our wives and families, who have once again endured the preparation of
this seventh edition with unfailing patience and support
To our patients with renal disease, for whom it is a privilege to care
Jürgen Floege
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PREFACE

The seventh edition of Comprehensive Clinical Nephrology remains the textbook aimed for Fellows preparing for their boards, for practicing nephrologists who want to rapidly review the key aspects for diagnosis and management of their patients, and for a short updated review for both the novice and expert alike on the pathogenesis and treatment of kidney diseases. As always, this remains a single-volume textbook that provides comprehensive coverage of clinical nephrology yet also ensures that inquiring nephrologists can find the key scientific issues and pathophysiology that underlie their clinical work.

The seventh edition boasts updated chapters providing state-ofthe-art recommendations for the diagnosis and management of kidney diseases. This includes a new chapter on ultrasound use from a nephrologist’s perspective. Other highlights include chapters on geriatric nephrology and palliative nephrology, the mysterious epidemics of CKD that have been identified in various regions of the world, and continued emphasis on ICU nephrology.

By popular demand, we continue to offer readers digital access to the images from the book, and each chapter also includes a larger number of references available online as well as the answers to the multiplechoice questions in each chapter. This is also the fourth edition to feature access to a companion eBooks+ website with fully searchable text, a downloadable image library, and links to PubMed.

Enjoy the new updated book, and feel free to give us suggestions for the next editions!

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SECTION I Essential Renal Anatomy and Physiology

1

Renal Anatomy

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The complex structure of the mammalian kidney is best understood in the unipapillary form that is common to all small mammalian species. Fig. 1.1 is a schematic coronal section through a unipapillary kidney, with a cortex enclosing a pyramid-shaped medulla, the tip (papilla) of which protrudes into the renal pelvis. The medulla is divided into an outer and an inner medulla; the outer medulla is further subdivided into an outer and an inner stripe.

STRUCTURE OF THE KIDNEY

The specific components of the kidney are the nephrons, the collecting ducts, and a unique microvasculature.[1] The multipapillary kidney of humans contains about 1 million nephrons, although this number varies considerably. The number of nephrons is established during prenatal development; after birth, new nephrons cannot be developed, and lost nephrons cannot be replaced.

Nephrons

A nephron consists of a renal corpuscle (glomerulus) connected to a complicated and twisted tubule that finally drains into a collecting duct (Fig. 1.2 and Table 1.1). Three types of nephrons can be distinguished by the location of renal corpuscles within the cortex: superficial, midcortical, and juxtamedullary nephrons. The tubular part of the nephron consists of a proximal tubule and a distal tubule connected by a loop of Henle (for details see later, as well as Kriz and Bankir[2]). Superficial and midcortical nephrons have short loops that turn back in the outer medulla or even in the cortex. Juxtamedullary nephrons have long loops that turn back at successive levels of the inner medulla.

Collecting Ducts

A collecting duct is formed in the renal cortex when several nephrons join. A connecting tubule is interposed between a nephron and a cortical collecting duct. Cortical collecting ducts descend within the medullary rays of the cortex. They then traverse the outer medulla as unbranched tubes. On entering the inner medulla, they fuse successively and open finally as papillary ducts into the renal pelvis (see Fig. 1.2 and Table 1.1).

Microvasculature

The microvascular pattern of the kidney is similarly organized in mammalian species[1,3] (Fig. 1.3; see also Fig. 1.1). The renal artery, after entering the renal sinus, finally divides into the interlobar arteries, which extend toward the cortex in the space between the wall of the pelvis (or calyx) and the adjacent cortical tissue. At the junction between cortex and medulla, the interlobar arteries divide and pass over into the arcuate arteries, which also branch. The arcuate arteries give rise to the cortical radial arteries (interlobular arteries), which ascend radially through the cortex. No arteries penetrate the medulla. Afferent arterioles supply the glomerular tufts and generally arise from cortical radial arteries. Aglomerular tributaries to the capillary plexus are rarely found. As a result, the blood supply of the peritubular capillaries of the cortex and the medulla is exclusively postglomerular. Glomeruli are drained by efferent arterioles. Two basic types of efferent arterioles can be distinguished: cortical efferent arterioles, which derive from superficial and midcortical glomeruli, supply the capillary plexus of the cortex. Efferent arterioles of juxtamedullary glomeruli supply the renal medulla. Within the outer stripe of the medulla, these vessels divide into the descending vasa recta and then penetrate the inner stripe in cone-shaped vascular bundles. At intervals, individual vessels leave the bundles to supply the capillary plexus at the adjacent medullary level. A fraction of the descending vasa recta enters the inner medulla; few of them reach the papillary region.

Ascending vasa recta drain the renal medulla. In the inner medulla, the vasa recta arise at every level, ascending as unbranched vessels, and traverse the inner stripe within the vascular bundles. The ascending vasa recta that drain the inner stripe may join the vascular bundles; the majority ascends directly to the outer stripe between the bundles. All the ascending vasa recta traverse the outer stripe as individual wavy vessels with wide lumens interspersed among the tubules. Because true capillaries derived from direct branches of efferent arterioles are relatively scarce, the ascending vasa recta form the capillary plexus of the outer stripe. The ascending vasa recta empty into arcuate veins.

The vascular bundles represent a countercurrent exchanger between the blood entering and leaving the medulla. The organization of the vascular bundles also separates the blood flow to the inner stripe from the blood flow to the inner medulla. Descending vasa recta supplying the inner medulla traverse the inner stripe within the vascular bundles. Therefore blood flowing to the inner medulla has not been exposed previously to tubules of the inner or outer stripe. All ascending vasa recta originating from the inner medulla traverse the inner stripe within the vascular bundles. Thus blood that has perfused tubules of the inner medulla does not subsequently perfuse tubules of the inner stripe. However, the blood returning from either the inner medulla or the inner stripe afterward does perfuse the tubules of the outer stripe. This arrangement in the outer stripe may function as the ultimate trap to prevent solute loss from the medulla.

Coronal Section Through a Unipapillary Kidney
Short-looped
nephron

Long-looped
nephron

Glomeruli

Renal
artery

Subdivisions of the Nephron
and Collecting Duct System

TABLE 1.1
Section
Nephron
Renal corpuscle

Cortex
Outer
medulla
Inner
medulla

Subsections
Glomerulus: term used most frequently to refer to
entire renal corpuscle
Bowman's capsule

Proximal tubule

Convoluted part
Straight part (pars recta) or thick descending limb of
Henle loop

Intermediate
tubule

Descending part or thin descending limb of Henle loop
Ascending part or thin ascending limb of Henle loop

Distal tubule

Straight part or thick ascending limb of Henle loop:
subdivided into medullary and cortical parts; the
cortical part contains the macula densa in its
terminal portion
Convoluted part

Renal
Collecting
vein
duct
Fig. 1.1 Coronal section through a unipapillary kidney.

Collecting Duct System
Connecting tubule
Includes the arcades in most species

Nephrons and the Collecting Duct System
9

8

Collecting duct

Cortical collecting duct
Outer medullary collecting duct: subdivided into an
outer stripe and an inner stripe portion
Inner medullary collecting duct: subdivided into basal,
middle, and papillary portions

1
9

Cortex

7

2

8
1

7

2

Medullary
ray

10
3

Outer stripe
Outer
medulla

3

6
6

Inner
stripe

11
4

Central to the renal drainage of the kidney are the arcuate veins, which, in contrast to arcuate arteries, do form real anastomosing arches at the corticomedullary border. The arcuate veins accept the veins from the cortex and the renal medulla. The arcuate veins join to form interlobar veins, which run alongside the corresponding arteries. The intrarenal arteries and the afferent and efferent glomerular arterioles are accompanied by sympathetic nerve fibers and terminal axons representing the efferent nerves of the kidney.1 Tubules have direct contact to terminal axons only when the tubules are located around the arteries or the arterioles. Tubular innervation consists of occasional fibers adjacent to perivascular tubules.4 The density of nerve contacts to convoluted proximal tubules is low; contacts to straight proximal tubules, thick ascending limbs of Henle loops, and collecting ducts (located in medullary rays and outer medulla) have never been encountered. The vast majority of tubular portions have no direct relationships to nerve terminals. Afferent nerves of the kidney are sparse.5

Glomerulus (Kidney Corpuscle)

Inner
medulla

1.
2.
3.
4.
5.
6.

4

Renal corpuscle
Proximal convoluted tubule
Proximal straight tubule
Descending thin limb
Ascending thin limb
Distal straight tubule
(thick ascending limb)

5

12

7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

Fig. 1.2 Nephrons and the Collecting Duct System. Shown are shortlooped and long-looped nephrons, together with a collecting duct (not drawn to scale). Arrows denote confluence of further nephrons.

The glomerulus includes a tuft of specialized capillaries attached to the mesangium, both of which are enclosed in a pouch-like extension of the tubule, which represents Bowman’s capsule (Figs. 1.4 and 1.5). The capillaries, together with the mesangium, are covered by epithelial cells (podocytes), forming the visceral epithelium of Bowman’s capsule. At the vascular pole, this is reflected to become the parietal epithelium of Bowman’s capsule. At the interface between the glomerular capillaries and the mesangium on one side and the podocyte layer on the other side, the glomerular basement membrane (GBM) is developed. The space between both layers of Bowman’s capsule represents the urinary space, which, at the urinary pole, continues as the tubule lumen.

On entering the tuft, the afferent arteriole immediately divides into several primary capillary branches, each of which gives rise to an anastomosing capillary network representing a glomerular lobule. In contrast, the efferent arteriole is already established inside the tuft by

Microvasculature of the Kidney
Arterial vessels
and capillaries

MD

Venous
vessels

EA

AA
Cortical
radial artery

EGM

Afferent
arteriole
Cortex

Cortical
radial vein
Arcuate
vein

Outer
stripe

Outer
medulla
Inner
stripe

To
intrarenal
vein
Efferent
arteriole

PO
PE

Arcuate
artery
Descending
vasa recta
Ascending
vasa recta

Inner
medulla

P

Fig. 1.4 Longitudinal Section Through a Glomerulus (Rat). At the vascular pole, the afferent arteriole (AA), the efferent arteriole (EA), the extraglomerular mesangium (EGM), and the macula densa (MD) are seen. At the urinary pole, the parietal epithelium (PE) transforms into the proximal tubule (P). PO, podocyte. (Light microscopy; magnification ×390.)

Peripheral Portion of a Glomerular Lobule

Podocyte

Fig. 1.3 Microvasculature of the Kidney. Afferent arterioles supply the glomeruli and efferent arterioles leave the glomeruli and divide into the descending vasa recta, which, together with the ascending vasa recta, form the vascular bundles of the renal medulla. The vasa recta ascending from the inner medulla all traverse the inner stripe within the vascular bundles, whereas most of the vasa recta from the inner stripe of the outer medulla ascend outside the bundles. Both types traverse the outer stripe as wide, tortuous channels.

confluence of capillaries from each lobule.6 Thus the efferent arteriole has a significant intraglomerular segment located within the glomerular stalk. Glomerular capillaries are a unique type of blood vessel made up of nothing but an endothelial tube (Figs. 1.6 and 1.7). A small stripe of the outer aspect of this tube directly abuts the mesangium; the major part bulges toward the urinary space and is covered by the GBM and the podocyte layer. This peripheral portion of the capillary wall represents the filtration area. The glomerular mesangium establishes the axis of a glomerular lobule to which the GBM, together with the glomerular capillaries, are attached.

Glomerular Basement Membrane

The GBM serves as the skeleton of the glomerular tuft. This membrane is a complexly folded sack with an opening at the glomerular hilum

Glomerular
basement
membrane

Foot
processes
Capillary

Mesangial
angle

Capillary
endothelium
Microfilaments
Mesangium

Mesangial
matrix

Fig. 1.5 Peripheral Portion of a Glomerular Lobule. This part shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary-mesangial interface, the capillary endothelium directly abuts the mesangium.

GBM

MF

A

B

Fig. 1.6 Glomerular Capillary. (A) The layer of interdigitating podocyte processes and the glomerular basement membrane (GBM) do not completely encircle the capillary. At the mesangial angles (arrows), both deviate from a pericapillary course and cover the mesangium. Mesangial cell processes containing dense bundles of microfilaments (MF) interconnect the GBM and bridge the distance between the two mesangial angles. (B) Filtration barrier. The peripheral part of the glomerular capillary wall includes the endothelium with open pores (arrowheads), the GBM, and the interdigitating foot processes. The GBM shows a lamina densa bounded by the lamina rara interna and externa. The foot processes are separated by filtration slits bridged by thin diaphragms (arrows). (TEM; A, ×8770; B, ×50,440.)

(Fig. 1.8). The outer aspect of this GBM sack is completely covered with podocytes. The interior of the sack is filled with the capillaries and the mesangium. As a result, on its inner aspect, the GBM is in contact with either capillaries or the mesangium. At any transition between these two locations, the GBM changes from a convex pericapillary to a concave perimesangial course; the turning points are called mesangial angles. In electron micrographs, the GBM appears as a trilaminar structure, with a lamina densa bounded by two less dense layers, the lamina rara interna and lamina rara externa (see Fig. 1.6). Studies with freeze techniques reveal only one thick, dense layer directly attached to the bases of the epithelium and endothelium.[7]

The major components of the GBM include type IV collagen, laminin, and heparan sulfate proteoglycans similar to other basement membranes. Types V and VI collagen and nidogen (entactin) have also been demonstrated. Unique features of the GBM encompass a distinct spectrum of type IV collagen and laminin isoforms. The mature GBM consists of type IV collagen (with the major part made of α3, α4, and α5 chains, produced by podocytes, and the minor part made of α1, and α2 chains, produced by endothelial cells) and laminin 11, made of α5, β2, and γ1 chains.[8] Type IV collagen is the antigenic target in Goodpasture disease (see Chapter 25), and mutations in the genes of the α3, α4, and α5 chains of type IV collagen are responsible for Alport syndrome (see Chapter 48).

Current models depict the basic structure of the GBM as a threedimensional network of type IV collagen.[7] The type IV collagen monomer consists of a triple helix that is 400 nm in length, with a large, noncollagenous globular domain at its C-terminal end called NC1. At the N terminus, the helix possesses a triple helical rod 60 nm long: the 7S domain. Interactions between the 7S domains of two triple helices or the NC1 domains of four triple helices allow type IV collagen monomers to form dimers and tetramers. In addition, triple helical strands interconnect by lateral associations through binding of NC1 domains to sites along the collagenous region. This network is complemented by an interconnected network of laminin 11, resulting in a flexible, nonfibrillar polygonal assembly that provides mechanical strength and elasticity to the basement membrane and serves as a scaffold for alignment of other matrix components.[9,10]

The electronegative charge of the GBM mainly results from the presence of polyanionic proteoglycans. The major proteoglycans of the GBM are heparan sulfate proteoglycans, including perlecan and agrin. Proteoglycan molecules aggregate to form a meshwork that is kept well hydrated by water molecules trapped in the interstices of the matrix.

Mesangium

Three major glomerular cell types are all in close contact with the GBM: mesangial cells (MCs), endothelial cells, and podocytes. The mesangial/endothelial/podocyte cell ratio is 2:3:1 in the rat. The mesangial cells and mesangial matrix establish the glomerular mesangium.

Mesangial cells. MCs are irregular in shape, with many processes extending from the cell body toward the GBM (see Figs. 1.5 and 1.6). In these processes, dense assemblies of microfilaments are found, containing α-smooth muscle actin, myosin, and α-actinin.[11] The processes are attached to the GBM directly or through the interposition of microfibrils. The GBM represents the effector structure of mesangial contractility. MC-GBM connections are found throughout the mesangium-GBM interface, but they are especially prominent at the turning points of the GBM infoldings (mesangial angles). A new adhesion complex has been uncovered at these sites,[12] consisting of nephronectin deposited by podocytes into the GBM and α8 β1integrins enriched in the tips of MC processes inserting to the GBM.

The folding pattern of the GBM is permanently challenged by the expansile forces of the high intraglomerular perfusion pressure. Centripetal MC contraction balances the expansile forces. Thus the

Renal Corpuscle and
Juxtaglomerular Apparatus
FP
PP

Juxtaglomerular
AA
apparatus

MD

EGM
EA

N
Vascular pole

SMC

GC

PE
PO

A

Bowman
capsule

E

M

F
GBM

US
Urinary pole

B

Fig. 1.7 Branching Pattern of Podocyte Foot Processes (Rat). (A) Scanning electron micrograph (SEM) showing the urinary side of the podocyte cover of a glomerular capillary consisting of cell bodies, large primary processes (PP), and interdigitating foot processes (FP) separated by the filtration slits. (B) Drawing of the basal aspect of the FP-branching pattern as seen by block-face SEM. A fully homogenous branching pattern of foot processes attaches to the glomerular basement membrane (GBM), which may be compared with a pattern of interdigitating filopodia connected by adherens junctions. The high degree of branching (not seen from the luminal aspect) provides a high degree of adaptability to area changes of the underlying GBM. (From Ichimura K, Kakuta S, Kawasaki Y, et al. Morphological process of podocyte development revealed by block-face scanning electron microscopy. J Cell Sci. 2017;130:132–142.)

folding pattern of the GBM, including the complex convolutions of glomerular capillaries, are maintained by mesangial cells.
MCs possess a great variety of receptors, including those for angiotensin II (Ang II), vasopressin, atrial natriuretic factor, prostaglandins, and other growth factors (tumor growth factor [TGF]-β, plateletderived growth

factor [PDGF], epidermal growth factor [EGF], and connective tissue growth factor [CTGF]).13

Mesangial matrix. The mesangial matrix fills the highly irregular spaces between the mesangial cells and the perimesangial GBM, anchoring the mesangial cells to the GBM.6 Many common extracellular matrix proteins have been demonstrated within the mesangial matrix, including collagen types IV, V, and VI and microfibrillar protein components, such as fibrillin and microfibril-associated glycoprotein. The matrix also contains several glycoproteins, most abundantly fibronectin, and several types of proteoglycans.

Endothelium

Glomerular endothelial cells consist of cell bodies and peripherally located, attenuated, and highly porous cytoplasmic sheets (see Figs. 1.5 and 1.6). Glomerular endothelial pores lack diaphragms, which are encountered only in the endothelium of the final tributaries to the efferent arteriole.6 The round to oval pores have a diameter of 50 to 100 nm. A layer of membrane-bound and loosely attached molecules (called the glycocalyx) covers the entire luminal surface including, as sieve plugs, the endothelial pores.14 Because of a great variety of polyanionic glycoproteins (including podocalyxin), the endothelium has a strong negative charge, establishing an exit barrier for negatively

Proximal
tubule

AA
MD
EGM
EA
N
GC
SMC

Afferent arteriole
Macula densa
Extraglomerular mesangium
Efferent arteriole
Sympathetic nerve terminals
Granular cells
Vascular smooth muscle cells

PE
PO
M
E
F
GBM
US

Parietal epithelium
Podocyte
Mesangium
Endothelium
Foot process
Glomerular basement membrane
Urinary space

Fig. 1.8 Renal Corpuscle and Juxtaglomerular Apparatus. (Modified from Kriz W, Kaissling B. Structural organization of the mammalian kidney. In Seldin DW, Giebisch G, eds. The Kidney, 3rd ed. Lippincott Williams & Wilkins: 2000;587–654.)

charged macromolecules like albumin. Endothelial cells actively participate in processes controlling coagulation and inflammation and have receptors for vascular endothelial growth factor (VEGF), angiopoietins, and TGF-β1. They synthesize and release PDGF-B, endothelin-1, and nitric oxide, among others.15

Visceral Epithelium (Podocytes)

The visceral epithelium of Bowman's capsule includes highly differentiated cells called the podocytes (see Fig. 1.7; see also Fig. 1.5). In the developing glomerulus, podocytes have a simple polygonal shape. In humans, podocytes complete mitosis during prenatal life. Differentiated podocytes are unable to replicate; consequently, lost podocytes cannot be replaced in the adult. All efforts of the last decade to find progenitor cells that might migrate into the tuft and replace lost podocytes have failed.

Glomerular Filtration Barrier
Cl−
Actin
N

NSCC

Ca2+

M

AT1

PC

S
Ez

Ang II

TRPC6
Podocin

CD

α-Actinin 4
Laminin 11
Agrin

Nephrin
NEPH 1-3
P-Cadherin
FAT1

Ca2+
Z
Cat

U

Cas
FAK
TPV

β

ILK
TPV
β1

α

α3

Dystroglycan
Integrin

COLLAGEN IV (α3, α4, α5)

Capillary

endothelium

Capillary
endothelium

Fig. 1.9 Glomerular Filtration Barrier. Two podocyte foot processes bridged by the slit membrane, the glomerular basement membrane (GBM), and the porous capillary endothelium are shown. The surfaces of podocytes and of the endothelium are covered by a negatively charged glycocalyx containing the sialoprotein podocalyxin (PC). The GBM is mainly composed of type IV collagen (α3, α4, and α5), laminin 11 (α5, β2, and γ1 chains), and the heparan sulfate proteoglycan agrin. The slit membrane represents a porous proteinaceous membrane composed of (as far as is known) nephrin, NEPH 1-3, P-cadherin, and FAT1. The actin-based cytoskeleton of the foot processes connects to both the GBM and the slit membrane. Regarding the connections to the GBM, β1α3 integrin dimers specifically interconnect the TPV complex (talin, paxillin, vinculin) to laminin 11; the β- and α-dystroglycans interconnect utrophin to agrin. The slit membrane proteins are joined to the cytoskeleton by various adapter proteins, including podocin, zonula occludens protein 1 (ZO-1; Z), CD2-associated protein (CD), and catenins (Cat). Among the nonselective cation channels (NSCC), TRPC6 associates with podocin (and nephrin, not shown) at the slit membrane. Only the angiotensin II (Ang II) type 1 receptor (AT1) is shown as an example of the many surface receptors. Cas, p130Cas; Ez, ezrin; FAK, focal adhesion kinase; ILK, integrin-linked kinase; M, myosin; N, Na+-H+ exchanger regulatory factor (NHERF2); S, synaptopodin. (Modified from Endlich KH, Kriz W, Witzgall R. Update in podocyte biology. Curr Opin Nephrol Hypertens. 2001;10:331–340.)

Podocytes have a voluminous cell body that floats within the urinary space, separated from the GBM by a subpodocyte space.16 The cell bodies give rise to primary processes that fall apart into foot processes (FPs) that fix the cells to the capillaries (i.e., to the GBM). Sporadic FPs may also arise directly from the cell body. The FPs of neighboring podocytes regularly interdigitate with each other, leaving meandering slits (filtration slits) between them that are bridged by a complex extracellular structure known as the slit diaphragm (SD) that may be seen as a modified adherens junction (Fig. 1.9; see also Figs. 1.6 and 1.7). Traditional scanning electron micrograph (SEM) pictures (see Fig. 1.7A) do not convey the correct pattern of how FPs interdigitate and adhere to the GBM. As seen by block-face SEM (see Fig. 1.7B), individual FP may terminate with a final branching, and primary processes fall off into basal ridges that actually are also FPS.17 Thus the interdigitating FP pattern as it adheres to the GBM is completely homogenous, forming a uniform cover of interdigitating filopodia. This is of utmost importance to understand the adaptive mobility of this cover (see later).

The cell body contains a prominent endoplasmic reticulum and Golgi system and a well-developed endocytotic and autophagic machinery. A complex cytoskeleton accounts for the shape of the cells. In the cell body and the primary processes, microtubules and intermediate filaments (vimentin, desmin) dominate. Within the FPs, microfilaments (β-actin) form prominent U-shaped bundles arranged in the longitudinal axis of two successive FPs in an overlapping pattern. Above, the bends of these bundles are linked to the microtubules of the primary processes; peripherally, these bundles terminate in the dense cytoplasm associated with the sole plates, being part of the anchoring system of the FPs to the GBM (see later). In addition, the cell body and the FPs have a well-developed subplasmalemmal actin network that has intimate contact to the anchor line of the SD and diffusely to the actin bundles of FPs. Multiple actin-associated proteins, including α-actinin-4 and synaptopodin, establish the specific cytoskeleton in podocytes.18 FPs do not contain myosin II19; thus the actin fibers in FPs are not part of a contractile system. Instead, the complex cytoskeleton of FPs supports the attachment of FPs to the GBM and the maintenance of their interdigitating pattern.20

The luminal membrane contains a great variety of receptors (see later) and, together with the luminal surface of the SD, it is covered by a thick surface coat that is rich in sialoglycoproteins, including podocalyxin and podoendin, accounting for the high negative surface charge of the podocytes.

The abluminal cell membrane consists of a narrow band of lateral cell membrane extending from the SD to the GBM and, most importantly, the soles of the FPs abutting to the GBM. A complex anchoring system connects the cytoskeleton of the FPs to the GBM. Two systems are known: (1) α3β1 integrin dimers interconnect the cytoplasmic focal adhesion proteins vinculin, paxillin, and talin with the α3, α4, and α5 chains of type IV collagen and laminin 521; and (2) β-α-dystroglycans interconnect the cytoplasmic adapter protein utrophin with agrin and laminin α5 chains in the GBM.9

The junctional connection of podocyte FPs by the SD bridging the filtration slits is complex and unique. Filtration slits have a constant width of about 30 to 40 nm: thus SD has to connect the FPs over a considerable distance. By transmission electron microscopy (TEM), the SD shows up as a single dark line in cross sections and in an en-face view as a homogenous network of fibrillar structures interconnecting both membranes. Combined tannic acid and glutaraldehyde fixed tissue reveals, in en-face view, a zipper-like structure with a row of pores approximately 14 × 2 nm on either side of a central bar. The transmembrane proteins that establish the slit membrane and its connection to the actin cytoskeleton of the FPs include nephrin, P-cadherin, FAT1, NEPH 1-3, podocin, and CD2AP21 (see Fig. 1.9).

Podocytes contain many surface receptors and ion channels (see Fig. 1.9).21 Among the transient receptor potential (TRP) cation channels, TRPC5 and TRPC6 have received much attention.22–24 The major target of this signaling orchestra is the cytoskeleton (see later). Other receptors, such as for TGF-β, FGF-2, and other cytokines/chemokines, are involved in synthesis functions (GBM components) or in the development of podocyte diseases.21 Megalin is a multiligand endocytotic receptor and the major antigen of Heymann nephritis in the rat25 but is not present in humans.13 However, human podocytes express phospholipase A-2 receptor, which is the autoantigen targeted in the majority of patients with idiopathic membranous nephropathy.

Podocytes, by paracrine and autocrine signaling, regulate the interplay with endothelial cells and MCs; during development, they have the exclusive commandership in building a glomerulus. VEGF, angiopoietins, and PDGF, among others, are of crucial importance for the homeostatic maintenance of the tuft.26

Function and Maintenance of the Filtration Barrier

Filtration pressure and expansion. Traditionally, the high transmural hydrostatic pressure gradients necessary for filtration have been considered as the main challenge to the filtration barrier. Podocyte FPs were considered as pericyte processes that counteracted variations and derailments in perfusion pressures. This view has been challenged because of the discovery that podocytes are chiefly lost by detachment from the GBM as viable cells. It seems self-contradictory that FPs, which need their cytoskeleton to continually adapt their pattern of attachment to the GBM (see later), would simultaneously function as contractile pericyte-like processes, counteracting the expansion of the GBM by increasing their tone. This agrees with the finding that FPs do not contain any myosin.19 Consequently, the principal burden for counteracting transmural pressure gradients (i.e., for developing wall tension) falls instead on the GBM.27

As previously described, the GBM is an elastic membrane that expands or shrinks in surface area with increasing or decreasing transmural hydrostatic pressure, respectively. Its expansion decreases with increasing pressure and is limited. Thus podocytes situated downstream of the GBM are protected against sudden pressure rises. A situation in which the pressure is high enough to disrupt the GBM has never been reported.

Expansion of the GBM affords the immediate coordinated increase in the cover by interdigitated FPs, thus the FPs and the SD have to increase correspondingly (and vice versa when pressure decreases). The ability to make such acute adaptions has previously been shown in the isolated perfused kidney. It is suggested that the changes in FP length occur by actin polymerization/depolymerization; the mechanism underlying changes in SD length is unknown.20,27

Filtrate flow and shear stress. The flow of the filtrate through the filtration barrier represents by far the highest extravascular fluid flow in the body. It consists of the outflow from glomerular capillaries, through the GBM, and into Bowman’s space. This latter step creates a problem: in contrast to the exit of filtrate from capillaries, where flow presses the endothelium against the basement membrane, its entry into Bowman’s space tends to separate the podocytes from the GBM. This danger explains the high density of integrin-connections of FPs to the GBM.

The shear stress depends on the flow rate and the geometry of the channel; the narrower the channel or the higher the flow velocity, the higher the shear stress. In rats, the filtrate flow amounts to 30 nL/min, creating a shear stress to the FPs within the filtration slit as high as 8 Pa.28 Much lower values of shear stress to the podocyte cell bodies (0.5 Pas when they come to lie within the urinary orifice) lead to the detachment of podocytes from the GBM and loss with the urine flow as viable cells; this has repeatedly been shown by light microscopy (LM) and TEM in experimental disease models with podocyte loss.20 Moreover, a high sensitivity of podocytes to shear stress has been shown in cell culture studies.

This led to a new view of the relevance of the slit membrane (in addition to its barrier function; see later). Shear stress tends to lead to deformations of the lateral walls of FPs, thus widening the slit. The interconnection of both opposite FPs by the SD at the narrowest site of the slit is ideally positioned to counteract these destabilizing forces. The SD uses the shear stress against one side of the slit to balance the shear stress against the opposite site. This means that during filtrate flow the SD is permanently under tension, which counteracts the shear stress to both sides of the slit.20 This hypothesis is supported by the observation that the loss of the SD connection between adjacent FPs represents the earliest failure that starts the detachment of a podocyte (see Pathology).

Barrier function. Filtrate flow through the barrier occurs along an extracellular route, including the endothelial pores, GBM, and slit diaphragm (see Figs. 1.6 and 1.9). All these components are quite permeable for water, resulting in a high permeability for water, small solutes, and ions. On the other hand, the barrier is fairly tight for macromolecules and selective for size, shape, and charge.21 The charge selectivity of the barrier results from the dense accumulation of negatively charged molecules on the surface coat (glycocalyx) of endothelial cells. Because most plasma proteins, including albumin, are negatively charged, their entrance into the barrier is slowed but not eliminated. Albumin that penetrates the barrier is filtered and reabsorbed in the proximal tubule.

The size/shape selectivity seems to be established by the SD.14 Uncharged macromolecules up to an effective radius of 1.8 nm pass freely through the filter. Larger components are increasingly restricted and are totally excluded at effective radii of greater than 4 nm. The fate of components that are captured inside the SD is unknown; transcytosis through podocytes has been suggested.29 Plasma albumin has

an effective radius of 3.6 nm; without the repulsion from the negative charge, plasma albumin would pass through the filter in considerable amounts.

Moeller[30] has proposed an electrophoretic mechanism for the repulsion and exclusion of plasma proteins from the glomerular filter based on the flow of the filtrate through the charged filter, creating a streaming potential.[31] This electrical field is negatively charged on the urinary side of the glomerular filter compared with the capillary side by approximately −0.05 mV/10 mm Hg filtration pressure. Thus albumin molecules (and most plasma proteins, because virtually all are negatively charged) that approach the filter will be exposed to an electrophoretic force driving them back toward the capillary lumen.

The charm of this hypothesis consists of its independence from any structural impediment to filtration. The barrier actually consists of a filtration-dependent potential difference; without sufficient convective flow of filtrate, the barrier will become permeable.[31]

Pathology. The hypothesis that the mechanical interconnection of the FPs by the SD is critical for maintenance of an intact barrier and is vulnerable to the physical challenges of filtration is supported by the pathologic changes. The loss of the SD connection between adjacent FPs initiates the detachment of podocytes[20] and the loss of local control of filtrate flow.

Unchanneled filtrate flow through such leaks will exert unbalanced shear stress on the FPs starting local detachment of FPs. Repair of such leaks is difficult in the face of ongoing filtrate flow, accounting for the observation that the damage tends to progress.

Taken together, the layer of interdigitating FPs interconnected by the SD regulates the entry of the filtrate flow into Bowman’s space by channeling the flow through the filtration slits. The geometry of the slits is maintained against the shear forces to both opposite FPs through the interconnection of opposing FPS by the SD. Loss of the junctional connection is detrimental because it opens leaks for uncontrolled filtrate flow with the tendency to increase the leaks.[32] This situation also accounts for the fact that podocytes cannot undergo cytokinesis and, when lost, cannot be replaced by progenitors immigrating from outside.

Parietal Epithelium

The parietal epithelium of Bowman’s capsule consists of squamous epithelial cells resting on a basement membrane (see Figs. 1.4 and 1.8). The flat cells are filled with bundles of actin filaments running in all directions. In contrast to the GBM, the parietal basement membrane has several proteoglycan-dense layers that, in addition to type IV, contain type XIV collagen. The predominant proteoglycan of the parietal basement membrane is a chondroitin sulfate proteoglycan.[33] A niche of epithelial stem cells may reside within the parietal epithelium at the transition to the proximal tubule and/or to the visceral epithelium,[34,35] but unequivocal evidence is lacking.

Renal Tubule

The renal tubule consists of distinct segments: a proximal tubule (convoluted and straight portions), an intermediate tubule, a distal tubule (straight and convoluted portion), a connecting tubule (CNT), and the collecting duct (see Figs. 1.1 and 1.2; Table 1.1).[1,2,33] Henle’s loop includes the straight part of the proximal tubule (representing the thick descending limb), the thin descending and the thin ascending limbs (both thin limbs together represent the intermediate tubule), and the thick ascending limb (representing the straight portion of the distal tubule), which includes the macula densa. The CNT connects the nephron to the collecting duct system.

Tubular epithelium consists of a single layer of cells anchored to a basement membrane. The cells have multiple transport functions and show numerous structural adaptations to their special roles. They are connected apically by a junctional complex consisting of a beltlike tight junction (zonula occludens), a belt-like adherens junction (zonula adherens), and, at some sites, a desmosome. The tight junction represents a structural border between the luminal and the basolateral cell membrane domain, preventing movements of membraneassociated transport proteins between the two domains. Two different pathways through the epithelium exist (Fig. 1.10): a transcellular pathway, including the transport across the luminal and the basolateral cell membrane and through the cytoplasm, and a paracellular pathway through the junctional complex and the lateral intercellular spaces.

Tubular Epithelia
Luminal
Paracellular Transcellular
membrane
transport
transport

Tight
junction
Basolateral
membrane

Lateral
intercellular
space

Basement
membrane

Fig. 1.10 Tubular Epithelia. Transport across the epithelium may follow two routes: transcellular, across luminal and basolateral membranes, and paracellular, through the tight junction and intercellular spaces.

The functional characteristics of the paracellular transport are determined by the tight junction, which differs markedly in its elaboration in the various tubular segments. The tight junctional proteins responsible for the specific permeability properties are occludin and especially the claudins.[36] Transcellular transport is determined by apical and basolateral channels, carriers, and transporters. The various nephron segments differ markedly in function, distribution of transport proteins, and responsiveness to hormones and drugs such as diuretics.

The cell surface area of the plasmalemmal compartments carrying the transport systems is extensively enlarged in many tubule cells: namely, by microvilli at the luminal membrane domain, by lamellar folds of the basolateral membrane interdigitating with those of the neighboring cells (interdigitations), or by lamellar folds of the basal cell membrane invaginating into the own cell (invaginations).

Proximal Tubule

The proximal tubule reabsorbs the bulk of filtered water and solutes (Fig. 1.11) and is generally subdivided into three segments (known as S1, S2, S3) that differ considerably in cellular organization and, consequently, also in function.[37] The proximal tubule has a prominent brush border and extensive interdigitation by basolateral cell processes. These lateral cell interdigitations extend up to the leaky tight junction, thus considerably increasing the tight junctional belt in length and providing a greatly increased passage for the passive transport of ions. Proximal tubule cells have large prominent mitochondria intimately associated with the basolateral cell membrane where the Na^+,K^+–adenosine triphosphatase (ATPase) is located; this machinery is the molecular mechanism initiating numerous secondary transcellular transport processes. The luminal transporter for Na+

B

A

Fig. 1.11 Tubules of the Renal Cortex. (A) Proximal convoluted tubule is equipped with a brush border and a prominent vacuolar apparatus in the apical cytoplasm. The rest of the cytoplasm is occupied by a basal labyrinth consisting of large mitochondria associated with basolateral cell membranes. (B) Distal convoluted tubule also has interdigitated basolateral cell membranes intimately associated with large mitochondria. In contrast to the proximal tubule, however, the apical surface is amplified only by some stubby microvilli. (TEM; A, ×1530; B, ×1830.)

reabsorption specific for the proximal tubule is the Na^+-H^+ exchanger (NHE3) that is located in the plasma membrane of the apical microvilli and accounts for reabsorption of most of the filtered sodium. Other sodium coupled transporters in the microvillous membrane are the sodium-glucose cotransporters SGLT2 and SGLT1 and several sodium-phosphate cotransporters. The abundance of channel protein aquaporin 1 in the apical microvillous membrane and the basolateral cell membrane accounts for the high hydraulic permeability for water of this epithelium. An apical tubulovesicular compartment is part of the prominent endosomal-lysosomal system and is responsible for the reabsorption of macromolecules (active peptides, polypeptides, and proteins such as albumin) that have passed the glomerular filter. The S3 and portions of the S2 segments are engaged in many secretory processes of toxic substances and drugs via organic anion transporters and an organic cation transporter (OCT). Proximal tubule cells are electrically coupled by gap junctions (Nexus).

Intermediate Tubule

The intermediate tubule includes the thin portion of Henle’s loop, thin descending and (only in long loops) thin ascending limbs (Fig. 1.12; see also Fig. 1.2). Thin descending limbs of short loops and those of long loops are equipped with different epithelia. The thin descending limbs of short loops have an extremely flat epithelium that, in its beginning part, is permeable to water, and, in its distal part, contains the urea transporter UT-A2 responsible for the uptake of urea coming up from the inner medulla (urea recycling).[38] The thin descending limbs of long loops, in their initial parts within the inner stripe, are quite permeable to Na^+ and Cl (uptake from the interstitial space) and have a considerable Na^+,K^+-ATPase activity, the relevance of which is unknown. Along their course down through the inner medulla they lose their salt permeability becoming permeable to water. The transition to the ascending thin limb epithelium occurs already before the bend. The ascending thin limbs have a heavily interdigitated epithelium highly permeable for ions releasing them into the interstitial space but impermeable for water. The relevance of transport functions of the thin limbs for the generation of the osmotic medullary gradient is debated.

Distal Straight Tubule (Thick Ascending Limb of Henle’s Loop)

The thick ascending limb of Henle’s loop is often called the diluting segment. It is water impermeable but reabsorbs considerable amounts of sodium and chloride, resulting in the separation of salt from water. The salt is trapped in the medulla (see Fig. 1.12), whereas the water is carried away into the cortex, where it may return into the systemic circulation. The specific transporter for Na+ reabsorption in this segment is the Na+-K+-2Cl cotransporter 2 (NKCC2),39 which is specifically inhibited by loop diuretics such as furosemide. This transporter is inserted in the luminal membrane, which is amplified by only solitary microvilli. The tight junctions of the thick ascending limb are elongated by lateral interdigitation of the cells. They have a comparatively low overall permeability; however, they contain the protein Claudin 16 for paracellular reabsorption of divalent ions, notably of magnesium. The cells are heavily interdigitated by basolateral cell processes, which are associated with large mitochondria supplying the energy for the transepithelial transport. The cells synthesize the Tamm-Horsfall protein and release it into the tubular lumen. This protein may help prevent the formation of kidney stones. A short distance before the transition to the distal convoluted tubule, the thick ascending limb contains the macula densa, which adheres to the glomerulus of the same nephron (see Juxtaglomerular Apparatus).

Distal Convoluted Tubule

The epithelium exhibits the most extensive basolateral interdigitation of the cells and the greatest numerical density of mitochondria compared with all other nephron portions (see Fig. 1.11). Apically, the cells are equipped with numerous solitary microvilli. The specific Na+ transporter of the distal convoluted tubule is the luminal Na+-Cl cotransport system (NCC), which can be inhibited by the thiazide diuretics. Magnesium is reabsorbed via the transient receptor potential channel melastatin subtype 6 (TRPM6) in the luminal membrane40

P

IC

CD

F
CD

VR
AL

TL
F
C

DL

TL

C

A

VR

B

Fig. 1.12 Tubules in the Medulla. (A) Cross-section through the inner stripe of the outer medulla shows a descending thin limb of a long Henle loop (DL), the medullary thick ascending limbs of Henle (AL), and a collecting duct (CD) with principal cells (P) and intercalated cells (IC). (B) In the inner medulla cross-section, thin descending and ascending limbs (TL), a collecting duct (CD), and vasa recta (VR) are seen. C, Peritubular capillaries; F, fibroblast. (TEM; A, ×990; B, ×1120.)

and, along the paracellular route, through the tight junctional proteins Claudin 16 and 19.

COLLECTING DUCT SYSTEM

The collecting duct system (see Fig. 1.2) includes the CNT, cortical ducts, and medullary collecting ducts (CDs). The embryologic origin of the CNT, which is interposed between the distal convoluted tubule and the CD, is unclear whether it derives from the nephron anlage or the ureteral bud. Two nephrons may join at the level of the CNT, forming an arcade. Two types of cell establish the CNT: the CNT cell, which is specific to the CNT, and the intercalated (IC) cell, which is also present in varying amounts in the distal convoluted tubule and in the collecting duct. The CNT cells are similar to the CD cells in cellular organization. Both cell types share sensitivity to vasopressin (antidiuretic hormone [ADH]; see later). The amiloride-sensitive epithelial sodium channel, ENaC, and the epithelial calcium channel, TRPV5, are located in the apical membrane, being already present in the distal convoluted tubule and extending into the CNT.

Collecting Ducts

The CDs (see Fig. 1.12) may be subdivided into cortical and medullary ducts, and the medullary ducts into an outer and inner portion; the transitions are gradual. Like the CNT, the CDs are lined by two types of cell: CD cells (principal cells) and IC cells. The IC cells decrease in number as the CD descends into the medulla and are absent from the inner medullary CDs.

The CD cells (Fig. 1.13A) increase in size toward the tip of the papilla. The basal cell membrane amplifies by lamellar invaginations into the cell (basal infoldings). The tight junctions have a large apical-basal depth, and the apical cell surface has a prominent glycocalyx. These cells contain an apical shuttle system for aquaporin 2 under the control of vasopressin, allowing the water permeability of the CDs to switch from very low to permeable.41 A luminal amiloride-sensitive Na+ channel is involved in the responsiveness of cortical CDs to aldosterone. The terminal portions of the CD in the inner medulla express the urea transport system UT-A1, which, in an antidiuretic hormone (ADH)-dependent fashion, accounts for the recycling of urea, a process that is crucial in the urine-concentrating mechanism.42 43

The second cell type, the IC cell (see Fig. 1.13B), is present in both the CNT and the CD. There are at least two types of IC cells, designated A and B cells, distinguished on the basis of structural, immunocytochemical, and functional characteristics. Type A cells express a H+ ATPase at their luminal membrane; they secrete protons. Type B cells express the H+-ATPase at their basolateral membrane; they secrete bicarbonate ions and reabsorb protons.44

The CDs are the final regulators of fluid and electrolyte balance, playing important roles in the handling of Na+, Cl , and K+, as well as in acid-base homeostasis. The responsiveness of the CDs to vasopressin enables an organism to live in arid conditions, allowing it to produce a concentrated urine and, if necessary, a dilute urine.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus (JGA) includes the macula densa, the extraglomerular mesangium, the terminal portion of the afferent arteriole with its renin-producing granular cells (also often called

B

A

Fig. 1.13 Collecting Duct Cells. (A) Principal cell (collecting duct [CD] cell) of a medullary collecting duct. The apical cell membrane bears some stubby microvilli covered by a prominent glycocalyx; the basal cell membrane forms invaginations. Note the deep tight junction. (B) Intercalated cells, type A. Note the dark cytoplasm (dark cells) with many mitochondria and apical microfolds; the basal membrane forms invaginations. (TEM; A, ×8720; B, ×6970.)

GC

EGM

A

B

Fig. 1.14 Juxtaglomerular Apparatus. (A) Macula densa of a thick ascending limb of Henle. The cells have prominent nuclei and lateral intercellular spaces. Basally, they attach to the extraglomerular mesangium (EGM). (B) Afferent arteriole near the vascular pole. Several smooth muscle cells are replaced by granular cells (GC) containing accumulations of renin granules. (TEM; A, ×1730; B, ×1310.)

juxtaglomerular cells), and the beginning portions of the efferent arteriole (see Fig. 1.8).

The macula densa is a plaque of specialized cells in the wall of the thick ascending limb of Henle at the site where the limb attaches to the extraglomerular mesangium of the parent glomerulus (Fig. 1.14A; see also Fig. 1.4). The most obvious structural feature is the narrowly packed cells with large nuclei, which account for the name macula densa. The cells are anchored to a basement membrane, which blends with the matrix of the extraglomerular mesangium. The cells are joined by tight junctions with very low permeability and have prominent lateral intercellular spaces. The width of these spaces varies under different functional conditions.[1] The most conspicuous immunocytochemical difference between macula densa cells and other epithelial cells of the nephron is the high content of neuronal nitric oxide synthase and cyclooxygenase-2 in macula densa cells.[45,46]

The basal aspect of the macula densa is firmly attached to the extraglomerular mesangium, a solid complex of cells and matrix penetrated by neither blood vessels nor lymphatic capillaries. As with the mesangial cells proper, extraglomerular MCs are heavily branched. Their processes are interconnected by gap junctions, contain prominent bundles of microfilaments, and are connected to the basement membrane of Bowman’s capsule and to the walls of both glomerular arterioles. As a whole, the extraglomerular mesangium interconnects all structures of the glomerular entrance.[6]

The granular cells are assembled in clusters within the terminal portion of the afferent glomerular arteriole (see Fig. 1.14B), replacing ordinary smooth muscle cells. “Granular” refers to the specific cytoplasmic granules in which renin, the major secretion product of these cells, is stored. Granular cells are the main site of the body where renin is secreted. Renin release occurs by exocytosis into the surrounding interstitium. Granular cells are connected to extraglomerular MCs, adjacent smooth muscle cells, and endothelial cells by gap junctions and are densely innervated by sympathetic nerve terminals. Granular cells are modified smooth muscle cells; under conditions requiring enhanced renin synthesis (e.g., volume depletion, renal artery stenosis), additional smooth muscle cells located upstream in the wall of the afferent arteriole may transform into granular cells.

The JGA serves two different functions: it regulates the flow resistance of afferent arterioles in the so-called tubule-glomerular feedback mechanism, and it participates in the control of renin synthesis and release from granular cells in the afferent arteriole. Renin release from granular cells is the major source of systemic angiotensin II and thus plays an essential role in controlling extracellular volume and blood pressure, whereas the vasoconstriction of the afferent arteriole locally serves to modulate the filtration of concerned nephron.[47,48]

KIDNEY INTERSTITIUM

The interstitium of the kidney is comparatively sparse, occupying 5% to 7% of the volume of the renal cortex, with a tendency to increase with age. The interstitium increases across the medulla from cortex to papilla. In the outer stripe, it is 3% to 4%, the lowest value of all kidney zones; this is interpreted as forming a barrier to prevent loss of solutes from a hyperosmolar medulla into the cortex. The interstitium is 10% in the inner stripe and up to about 30% in the inner medulla. The cellular constituents of the interstitium include resident fibroblasts (roughly 50%), which establish the scaffold frame for renal corpuscles, tubules, and blood vessels. Furthermore, dendritic cells (also roughly 50%) and varying numbers of macrophages are present. The space between the cells is filled with extracellular matrix, namely, ground substance (proteoglycans, glycoproteins), fibrils, and interstitial fluid.[49]

Fibroblasts are interconnected by specialized contacts and adhere by specific attachments to the basement membranes surrounding the tubules, renal corpuscles, capillaries, and lymphatics. They are the key cells in driving tubulointerstitial fibrosis.[50]

Fig. 1.15 Renal Dendritic Cells. Dendritic cells (CX3CR1+ cells, green) surrounding tubular segments in the medulla of mice (three-dimensional reconstruction). (Modified from Soos TJ, Sims TN, Barisoni L, et al. CX3CR1+ interstitial dendritic cells form a contiguous network throughout the entire kidney. Kidney Int. 2006;70:591–596.)

Kidney fibroblasts are difficult to distinguish from interstitial dendritic cells on a morphologic basis because both may show a stellate cellular shape and both display substantial amounts of mitochondria and endoplasmic reticulum. However, kidney fibroblasts may easily be distinguished by immunocytochemical techniques and by their subplasmalemmal actin cytoskeleton. Dendritic cells constitutively express the major histocompatibility complex class II antigen and may express antigens such as CD11c. Dendritic cells may have an important role in maintaining peripheral tolerance in the kidney (Fig. 1.15).[51] In contrast, fibroblasts in the kidney cortex (not in the medulla) contain the enzyme ecto-5 -nucleotidase (5 -NT). A subset of 5 -NT–positive fibroblasts of the cortex synthesizes erythropoietin.[52] Under normal conditions, these fibroblasts are exclusively found within the juxtamedullary portions of the cortical labyrinth. When there is an increasing demand for erythropoietin, synthesizing cells are recruited from fibroblasts in superficial portions of the cortical labyrinth.[53] Fibroblasts within the medulla, especially within the inner medulla, have a particular phenotype known as lipid-laden interstitial cells. The cells are oriented strictly perpendicularly toward the longitudinal axis of the tubules and vessels (running all in parallel) and contain conspicuous lipid droplets. These fibroblasts of the inner medulla produce large amounts of glycosaminoglycans and, possibly related to the lipid droplets, vasoactive lipids, especially PGE2[51]

SELF-ASSESSMENT QUESTIONS

1. Which of the statements concerning the interstitium of the healthy kidney is incorrect?
The renal interstitium contains:
A. fibroblasts
B. myofibroblasts
C. dendritic cells
D. cells that produce erythropoietin
E. macrophages

2. Which of the statements concerning the podocyte foot processes is incorrect?
Podocyte foot processes:
A. contain an actin-based cytoskeleton
B. have contractile properties
C. are connected to the glomerular basement membrane (GBM) by integrins
D. are connected to the GBM by the dystroglycans
E. are connected to each other by the slit diaphragm

3. Which of the statements concerning the inner stripe of the renal medulla is incorrect?
The inner stripe of the outer medulla contains:
A. the thin descending limbs of short loops
B. the thin descending limbs of long loops
C. the thin ascending limbs of long loops
D. the thick ascending loops of short loops
E. venous vasa recta that originate in the inner medulla

REFERENCES

1. Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Seldin DW, Giebisch G, Philadelphia, eds. The Kidney. 3rd ed. Lippincott Williams and Wilkens; 2000:587–654.
2. Kriz W, Bankir L. A standard nomenclature for structure of the kidney. The renal commission of the International Union of Physiological Sciences (IUPS). Pflügers Arch. 1988;411:113–120.
3. Rollhäuser H, Kriz W, Heinke W. Das Gefässsystem der Rattenniere. Z Zellforsch Mikrosk Anat. 1964;64:381–403.
4. Barajas L. Innervation of the renal cortex. Fed Proc. 1978;37:1192–1201.
5. DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997;77:75–197.
6. Elger M, Sakai T, Kriz W. The vascular pole of the renal glomerulus of rat. Adv Anat Embryol Cell Biol. 1998;139:1–98.
7. Inoue S. Ultrastructural architecture of basement membranes. Contrib Nephrol. 1994;107:21–28.
8. Miner JH. Renal basement membrane components. Kidney Int. 1999;56:2016–2024.
9. Abrahamson DR. Role of the podocyte (and glomerular epithelium) in building the GBM. Semin Nephrol. 2012;32:342–349.
10. Miner JH. Glomerular basement membrane composition and the filtration barrier. Pediatr Nephrol. 2011;26:1413–1417.
11. Kriz W, Elger M, Lemley KV, Sakai T. Structure of the glomerular mesangium: a biomechanical interpretation. Kidney Int. 1990;38:S2–S9.
12. Zimmerman SE, Hiremath C, Tsunezumi J, Yang Z, Finney B, Marciano DK. Nephronectin regulates mesangial cell adhesion and behavior in glomeruli. J Am Soc Nephrol. 2018;29. epub ahead of print.
13. Schlöndorff D, Banas B. The mesangial cell revisited: no cell is an island. J Am Soc Nephrol. 2009;20:1179–1187.
14. Haraldsson B, Jeansson M. Glomerular filtration barrier. Curr Opin Nephrol Hypertens. 2009;18:331–335.
15. Obeidat M, Obeidat M, Ballermann BJ. Glomerular endothelium: a porous sieve and formidable barrier. Exp Cell Res. 2012;318:964–972.
16. Neal CR, Crook H, Bell E, Harper SJ, Bates DO. Three-dimensional reconstruction of glomeruli by electron microscopy reveals a distinct restrictive urinary subpodocyte space. J Am Soc Nephrol. 2005;16:1223–1235.
17. Ichimura K, Miyazaki N, Sadayama S, et al. Three-dimensional architecture of podocytes revealed by block-face scanning electron microscopy. Sci Rep. 2015;5:8993.
18. Faul C. The podocyte cytoskeleton: key to a functioning glomerulus in health and disease. Contrib Nephrol. 2014;183:22–53.
19. Suleiman HY, Roth R, Jain S, Heuser JE, Shaw AS, Miner JH. Injuryinduced actin cytoskeleton reorganization in podocytes revealed by superresolution microscopy. JCI Insight. 2017;2.
20. Kriz W, Lemley KV. Mechanical challenges to the glomerular filtration barrier: adaptations and pathway to sclerosis. Pediatr Nephrol. 2017;32:405–417.
21. Pavenstädt H, Kriz W, Kretzler M. Cell biology of the glomerular podocyte. Physiol Rev. 2003;83:253–307.
22. Reiser J, Polu KR, Moller CC, et al. TRPC6 is a glomerular slit diaphragmassociated channel required for normal renal function. Nat Genet. 2005;37:739–744.
23. Winn MP, Conlon PJ, Lynn KL, et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science. 2005;308:1801–1804.
24. Greka A, Mundel P. Calcium regultes podocyte actin dynamics. Semin Nephrol. 2012;32:319–326.
25. Kerjaschki D, Farquhar MG. Immunocytochemical localization of the Heymann antigen (gp 330) in glomerular epithelial cells of normal Lewis rats. J Exp Med. 1983;157:667–686.
26. Bartlett CS, Jeansson M, Quaggin SE. Vascular growth factors and glomerular disease. Annu Rev Physiol. 2016;78:437–461.
27. Kriz W, Lemley KV. A potential role for mechanical forces in the

detachment of podocytes and the progression of CKD. J Am Soc Nephrol. 2015;26:258–269.

28. Endlich N, Endlich KH. The challenge and response of podocytes to glomerular hypertension. Semin Nephrol. 2012;32:327–341.
29. Tojo A, Hatakeyama S, Kinugasa S, Fukuda S, Sakai T. Enhanced podocyte vesicle transport in the nephrotic rat. Med Mol Morphol. 2017;50:86–93.
30. Hausmann R, Kuppe C, Egger H, et al. Electrical forces determine glomerular permeability. J Am Soc Nephrol. 2010;21:2053–2058.
31. Moeller MJ, Tenten V. Renal albumin filtration: aternative models to the standard physical barriers. Nat Rev Nephrol. 2013;9:266–277.
32. Kriz W, Hähnel B, Hosser H, Rösener S, Waldherr R. Structural analysis of how podocytes detach from the glomerular basement membrane under hypertrophic stress. Front Endocrinol. 2014;5:207.
33. Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: Alpern RJ, Caplan MJ, Moe OW, eds. Seldin and Giebisch’s the Kidney: Physiology and Pathophysiology. 5th ed. Philadelphia: Elsevier; 2013:595–691.
34. Appel D, Kershaw DB, Smeets B, et al. Recruitment of podocytes from glomerular parietal epithelial cells. J Am Soc Nephrol. 2009;20:333–343.
35. Peired AJ, Melica ME, Molli A, Nardi C, Romagnani P, Lasagni L. Molecular mechanisms of renal progenitor regulation: how many pieces in the puzzle? Cells. 2021;10.
36. Yu AS. Claudins and the kidney. J Am Soc Nephrol. 2015;26:11–19.
37. Maunsbach AB. Functional ultrastructure of the proximal tubule. In: Windhager EE, ed. Handbook of Physiology: Section on Renal Physiology. 2nd ed. New York: Oxford University Press; 1992:41–108.
38. Wade JB, Lee AJ, Liu C, et al. UT-A2: a 55-kDa urea transporter in thin descending limb whose abundance is regulated by vasopressin. Am J Physiol Renal Physiol. 2000;278:F52–F62.
39. Marcoux AA, Tremblay LE, Slimani S, et al. Molecular characteristics and physiological roles of Na(+) -K(+) -Cl(-) cotransporter 2. J Cell Physiol. 2021;236:1712–1729.
40. Nie M, Bal MS, Liu J, et al. Uromodulin regulates renal magnesium homeostasis through the ion channel transient receptor potential melastatin 6 (TRPM6). J Biol Chem. 2018;293:16488–16502.
41. Sabolic I, Brown D. Water channels in renal and nonrenal tissues. News Physiol Sci. 1995;10:12–17.
42. Bankir L, Trinh-Trang-Tan MM. Urea and the kidney. In: Brenner BM, ed. The Kidney. 6th ed. Philadelphia: Saunders; 2000:637–679.
43. Geng X, Zhang S, He J, et al. The urea transporter UT-A1 plays a predominant role in a urea-dependent urine-concentrating mechanism. J Biol Chem. 2020;295:9893–9900.
44. Madsen KM, Verlander JW, Kim J, Tisher CC. Morphological adaptation of the collecting duct to acid-base disturbances. Kidney Int. 1991;40:S57–S63.
45. Mundel P, Bachmann S, Bader M, et al. Expression of nitric oxide synthase in kidney macula densa cells. Kidney Int. 1992;42:1017–1019.
46. Harris RC, McKanna JA, Akai Y, et al. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. J Clin Invest. 1994;94:2504–2510.
47. Kurtz A. Renin release: sites, mechanisms, and control. Annu Rev Physiol. 2011;73:377–399.
48. Schnermann JB, Briggs JD. Tubular control of renin synthesis and secretion. Pflugers Arch. 2013;465:39–51.
49. Kaissling B, Hegyi I, Loffing J, Le Hir M. Morphology of interstitial cells in the healthy kidney. Anat Embryol. 1996;193:303–318.
50. Kuppe C, Ibrahim MM, Kranz J, et al. Decoding myofibroblast origins in human kidney fibrosis. Nature. 2021;589(7841):281–286.
51. Krüger T, Benke D, Eitner F, et al. Identification and functional characterization of dendritic cells in the healthy murine kidney and in experimental glomerulonephritis. J Am Soc Nephrol. 2004;15:613–621.
52. Bachmann S, Le Hir M, Eckardt KU. Co-localization of erythropoietin

mRNA and ecto-5′-nucleotidase immunoreactivity in peritubular cells of rat renal cortex indicates that fibroblasts produce erythropoietin. J Histochem Cytochem. 1993;41:335–341.
53. Kaissling B, Spiess S, Rinne B, Le Hir M. Effects of anemia on the morphology of the renal cortex of rats. Am J Physiol. 1993;264:F608–F617.

2

Renal Physiology

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GLOMERULAR STRUCTURE AND ULTRASTRUCTURE

Urine formation begins with the production of an ultrafiltrate of plasma. Chapter 1 details glomerular ultrastructure, and the essentials are revisited here. The ultrafiltration pathway consists of the fenestrated capillary endothelium, the capillary basement membrane (the noncellular layer), and the visceral epithelial cell layer (podocytes) of Bowman’s capsule; the podocytes have large cell bodies and make contact with the basement membrane only by cytoplasmic foot processes.

Parietal epithelial cells lining the inside of Bowman’s capsule are highly proliferative and may provide a niche for replenishment of the podocyte pool, especially after injury.[1] Mesangial cells fill the intercapillary space and provide structural support for the glomerulus, including secretion of mesangial matrix. They are contractile and can affect glomerular capillary flow and the surface area for filtration.

Filtration is determined principally by the molecular size and shape of the filtered solute and to a lesser extent by its charge. The size cut-off is not absolute. Resistance to filtration begins at an effective molecular radius of approximately 2 nm, and substances with an effective radius greater than 4 nm are not filtered at all. The fenestrations between capillary endothelial cells have a diameter of 50 to 100 nm. The podocyte foot processes have gaps (filtration slits) with a diameter of 30 to 40 nm. These filtration slits are bridged by the slit diaphragms (SDs), which are themselves penetrated by small pores. The SDs likely constitute the main filtration barrier, although the endothelium (by preventing the passage of blood cells) and the basement membrane also contribute.[2] Furthermore, podocytes and endothelial cells are covered by a glycocalyx composed of negatively charged glycoproteins, glycosaminoglycans, and proteoglycans, and the basement membrane is rich in heparan sulfate proteoglycans. This accumulation of fixed negative charges restricts filtration of large negatively charged ions, mainly proteins (Fig. 2.1). Albumin is negatively charged and, with an effective radius of 3.6 nm (35 Å), is normally almost completely excluded from filtration. If the glomerular barrier loses fixed negative charge, as in some forms of early or mild glomerular disease (e.g., minimal change disease), albumin filterability increases and leads to proteinuria. It is possible that some albumin is normally filtered and is then almost completely reabsorbed along the proximal tubule, although this is controversial. Certainly proximal tubular cells can take up albumin via megalin and cubilin, transport proteins in the apical membrane.[3] However, deletion of this tubular transport system in mice causes only a small increase in albuminuria, suggesting that filtration of albumin is both normally low and the major determinant of urinary excretion.[4] Nonetheless, the filtration-to-reabsorption relationship is dynamic and physiologically regulated[5] and may change in diseases such as diabetic nephropathy, contributing to albuminuria.[6]

The glomerular barrier is not a passive unidirectional filter: filtration pressure generates a small potential difference across the filtration barrier, which may help clear the filter by driving negatively charged proteins out of the SD and back into the blood.[7]

GLOMERULAR FILTRATION RATE

The driving force for glomerular filtration (net ultrafiltration pressure) is determined by the sum of the hydrostatic and oncotic (colloid osmotic) pressure gradients between plasma and Bowman’s space.

Single-nephron glomerular filtration rate (SNGFR) is determined by the product of the net ultrafiltration pressure and the ultrafiltration coefficient, a composite of the surface area available for filtration (influenced by the contractile mesangium) and the hydraulic conductivity of the glomerular membranes, which is very high compared with other capillary beds. Thus, the SNGFR is calculated as:

$$Kf\ [(Pgc - Pbs) - (\pi gc - \pi bs)]$$

where Kf is the ultrafiltration coefficient, Pgc is the glomerular capillary hydrostatic pressure (~45 mm Hg), Pbs is the Bowman space hydrostatic pressure (~10 mm Hg), πgc is the glomerular capillary oncotic pressure (~25 mm Hg), and πbs is Bowman’s space oncotic pressure (0 mm Hg).

Net ultrafiltration pressure is approximately 10 mm Hg at the afferent end of the capillary tuft. As filtration of plasma from blood proceeds along the glomerular capillaries, proteins are concentrated and the glomerular capillary oncotic pressure (πgc) increases. Loss of fluid would also be expected to cause a reduction in glomerular capillary hydrostatic pressure. Theoretically, toward the efferent end of a glomerular capillary, πgc may equal the net hydrostatic pressure gradient, at which point ultrafiltration pressure would fall to zero. Filtration equilibrium is observed in a number of capillary beds (e.g., skeletal muscle). In the healthy glomerulus, however, net ultrafiltration pressure progressively declines and filtration equilibrium is never achieved for two reasons: first, the glomerular capillary bed flows into an arteriole, rather than a venous system, and efferent arteriole resistance limits the fall in capillary hydrostatic pressure (Fig. 2.2); second, progressive morphologic changes in the capillary endothelium reduce permeability toward the efferent end.

The total glomerular filtration rate (GFR) is the sum of the SNGFRs of functioning nephrons and the normal range is wide, typically cited at 120 mL/min per 1.73 m2 surface area. GFR can be measured with renal clearance techniques. The renal clearance of any substance not metabolized by the kidneys is the volume of plasma required to provide that amount of the substance excreted in the urine per unit time. This is a virtual volume that can be expressed mathematically as follows:

$$Cy = Uy / Py \times V$$

where Cy is the renal clearance of y; Uy and Py are the concentrations of y in the urine and plasma, respectively; and V is the urine flow rate.

If a substance is freely filtered by the glomerulus and is not reabsorbed

Size and Charge Barrier

Filterability (%)

100
75
50
25

Anions
Neutral molecules
Cations
1

2

3

4
Albumin
Effective molecular radius (nm)

Fig. 2.1 Effects of Size and Electrical Charge on Filterability. Filterability of 100% indicates the substance is freely filtered; that is, its concentration in Bowman’s space equals that in glomerular capillary plasma. For molecules and small ions (e.g., Na +, Cl−), charge has no effect on filterability; but for ions whose effective molecular radius exceeds 1.6 nm, anions are filtered less easily than neutral molecules or cations. Albumin is an anion with a radius of 3.6 nm, and insignificant amounts of albumin are normally filtered. If the fixed negative charges of the glomerular basement membranes are lost, as in early minimal change nephropathy, charge no longer influences filterability; consequently, significant albumin filtration occurs.

Glomerular Filtration Pressures

RENAL PLASMA FLOW

The kidneys are approximately 0.5% of total body mass but account for approximately 7% of whole-body oxygen consumption. The renal blood flow (RBF) of approximately 1200 mL/min (～20% of the cardiac output) is delivered into the renal cortex, maintaining a high partial pressure of oxygen sufficient to support aerobic respiration by the proximal tubule. Almost all of the blood arriving by the renal artery is delivered into glomerular capillaries to support ultrafiltration; the filtration fraction (i.e., the proportion of plasma that is filtered—GFR/RPF) is 20% to 25%.

The glomerular capillaries drain into the efferent arteriole (rather than into the venous system), after which a second set of capillaries is formed. Capillaries arising from efferent arterioles of cortical (superficial and short-looped) nephrons form the peritubular network entwined around proximal and distal nephron segments in the cortex to provide an exit route for the bulk reabsorption of glomerular filtrate. The efferent arterioles of juxtamedullary (deeper and longlooped) nephrons provide descending vasa recta capillaries and supply blood to the medulla.

RBF can be calculated from measurement of renal plasma flow (RPF; typically ~650 mL/min) and hematocrit. RPF is measured by the clearance technique using substances that undergo both glomerular filtration and almost complete (or effective) tubular secretion. Paraaminohippuric acid (PAH, hippurate) is widely used for this purpose. PAH is an organic acid filtered by the glomerulus and then actively secreted into the urine through organic anion transporters (OATs) in the proximal straight tubule. This method is limited because the renal extraction of PAH is always less than 100% and variably underestimates RPF. This effect is compounded in patients with liver or kidney failure, where production of toxins and weak organic acids can interfere with PAH secretion, or during treatment with certain drugs, such as probenecid, which compete with PAH for tubular secretion and reduce PAH clearance. Thus, in a variety of clinical settings, PAH clearance is influenced by the abundance/pharmacokinetics of the OAT pathway and may not accurately reflect true RPF. Given that PAH clearance is also invasive (requiring intravenous [IV] infusion), time consuming, and expensive, alternative imaging approaches are being refined to estimate RBF directly, including Doppler ultrasound8 and magnetic resonance imaging.9

AUTOREGULATION OF RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Fig. 2.2 Glomerular Filtration Pressures Along a Glomerular Capillary. Gating of flow by the efferent arteriole maintains a relatively constant hydrostatic pressure gradient ($\Delta P = Pgc - Pbs$) along the length of a capillary, whereas the opposing oncotic pressure gradient ($\Delta\pi = \pi gc$) increases as protein-free fluid is filtered. The net ultrafiltration pressure falls along the capillary but does not fall to zero, the point of filtration equilibrium.

or secreted by the tubule, its renal clearance equals the GFR; that is, renal clearance measures the volume of plasma filtered through the glomeruli per unit time. The various methods for measuring GFR and their pitfalls are discussed in Chapter 3

Acute physiologic variations in arterial blood pressure cause corresponding changes in RBF and GFR. These are short-lived because compensatory mechanisms return both RBF and GFR toward normal within seconds.10 In normal physiology, RBF and GFR are autoregulated and renal hemodynamics are largely independent of systemic blood pressure (Fig. 2.3). Autoregulation of RBF occurs throughout the preglomerular arterial system but is achieved primarily by the afferent arterioles. Autoregulation results from two main mechanisms:

Myogenic reflex: Increased renal perfusion pressure stretches arteries and afferent arterioles, depolarizing smooth muscle cells to promote constriction of the vessel wall.

Tubuloglomerular feedback (TGF): Increased renal perfusion pressure increases sodium chloride (NaCl) delivery to the macula densa and specialized cells at the junction of the loop of Henle and distal nephron. The macula densa senses increased delivery and responds by causing afferent arteriolar constriction, reducing SNGFR.

These mechanisms are tonically active and dynamic and combine to restore both RBF and Pgc toward normal, reversing the initial

Renal Autoregulation

Tubuloglomerular Feedback

Afferent
arteriole

5

Adenosine

Flow (mL/min/g kidney)

4

3

Macula
densa

Glomerulus

ATP

NaCl

?

Renal blood flow

Glomerular filtration rate

2

1

100

200

Mean arterial pressure (mm Hg)

Fig. 2.3 Renal Autoregulation of Renal Blood Flow and Glomerular Filtration Rate. If mean arterial blood pressure is in the range of 80 to 180 mm Hg, fluctuations in blood pressure have only marginal effects on renal blood flow and glomerular filtration rate. This is an intrinsic mechanism and can be modulated or overridden by extrinsic factors. The dashed lines indicate the upper and lower limit of the autoregulatory range.

change in SNGFR. The TGF system is controlled within the juxtaglomerular apparatus (see Chapter 1), which consists of the macula densa region, the adjacent glomerulus, and afferent and efferent arterioles (Fig. 2.4). Both myogenic and TGF mechanisms are dependent on extracellular adenosine triphosphate (ATP) signaling. ATP is released from cells during vascular stretch, inducing vasoconstriction via P2 purinoceptors.[11] ATP is also the primary mediator of TGF. Increased NaCl delivery to the macula densa leads to increased NaCl uptake by these cells through a furosemide-sensitive $Na^+,K^+,2Cl$ cotransporter, triggering ATP release into the surrounding extracellular space.[12] ATP can have a direct vasoconstrictor effect on the afferent arteriole, activating P2X1 purinoceptors to depolarize the smooth muscle cells. However, because the macula densa is anatomically separated from the afferent arteriole by the extraglomerular mesangium, the final signal for TGF is likely to be adenosine, rather than ATP, acting on afferent arteriolar A1 receptors to cause vasoconstriction.[12] The sensitivity of TGF is modulated by locally produced angiotensin II (Ang II), nitric oxide (NO), and certain eicosanoids (see later discussion).

The TGF regulation of GFR may be more complex than usually described, with evidence for regulatory cross-talk between the distal nephron and vasculature sites beyond the macula densa,13 as well as for synchronization of blood flow across networks of nephrons in response to changes in sodium delivery.14

Renal autoregulation is not perfect and renal hemodynamics are modulated by neural and humoral factors. Independent or unequal changes in the resistance of afferent and efferent glomerular arterioles, together with alterations in Kf (thought to result largely from mesangial cell contraction/relaxation), can result in disproportionate, or even contrasting, changes in RBF and GFR. In addition, changes in regional vascular resistance can alter the distribution of blood flow within the kidney. For example, contraction of pericytes in the descending vasa recta causes medullary vasoconstriction.15 Whole-kidney blood flow

Efferent
arteriole

Fig. 2.4 Tubuloglomerular Feedback. Changes in the delivery of NaCl to the macula densa region of the thick ascending limb of the Henle loop cause changes in the afferent arteriolar caliber. The response is mediated by adenosine triphosphate (ATP), either directly or after metabolism to adenosine, and modulated by other locally produced agents such as angiotensin II and nitric oxide. Increased macula densa NaCl delivery results in afferent arteriolar constriction, thereby reducing the glomerular filtration rate (GFR).

Glomerular Hemodynamics
Arteriolar
resistance

Glomerulus

Renal blood
Net
flow
ultrafiltration
pressure

Control
Afferent

Efferent

Increased
afferent

Decreased
afferent

Increased
efferent

Decreased
efferent

Fig. 2.5 Glomerular Hemodynamics. Changes in afferent or efferent arteriolar resistance will alter renal blood flow and (usually) net ultrafiltration pressure. The effect on ultrafiltration pressure, however, depends on the relative changes in afferent and efferent arteriolar resistance. The overall effect on the glomerular filtration rate will depend not only on renal blood flow and net ultrafiltration pressure but also on the ultrafiltration coefficient (Kf; see Table 2.1).

may not change because blood can be diverted through the cortex. Sustained vasa recta constriction renders the medulla vulnerable to ischemic injury.[16] Fig. 2.5 indicates how changes in afferent and efferent arteriolar resistance can affect net ultrafiltration. Table 2.1 lists some of the vasoactive factors that can alter renal hemodynamics (see Integrated Control of Renal Function). Damage to the afferent arteriole, as in patients with hypertension and progressive kidney disease, can impair renal autoregulatory mechanisms.

TABLE 2.1

Physiologic and Pharmacologic Influences on Glomerular Hemodynamics
ARTERIOLAR RESISTANCE

Renal sympathetic nerves
Epinephrine
Adenosine
Cyclosporine
NSAIDs
Angiotensin II
Endothelin-1
High-protein diet
Nitric oxide
ANP (high dose)
PGE2/PGI2
Calcium channel blockers
ACE inhibitors, ARBs

Afferent

Efferent

Renal Blood Flow

Net Ultrafiltration
Pressure
Kf

↑↑

↑

↓

↓

↑

↑

↑

→

↑↑

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GFR
↓

↓

↓

↓

↓

↓→

↓

↑

↑

↑ (?)

?

↑

↑

?
↑

↑

↑
?[a]

The overall effect on GFR will depend on renal blood flow, net ultrafiltration pressure, and the ultrafiltration coefficient (K_f), which is controlled by mesangial cell contraction and relaxation. The effects shown are those seen when the agents are applied (or inhibited) in isolation; the actual changes that occur are dose dependent and are modulated by other agents.

[a] In clinical practice, GFR is usually either decreased or unaffected.

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ANP, atrial natriuretic peptide; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE2/PGI2, prostaglandins E2 and I2.

TUBULAR TRANSPORT

Vectorial transport is the net movement of substances from tubular fluid to blood (reabsorption) or vice versa (secretion). The cell membrane facing the tubular fluid (luminal or apical) must have different properties from the membrane facing the blood (peritubular or basolateral). Such epithelia are “polarized,” allowing the net movement of substances across the cell (transcellular route).

The tight junction, which is a contact point close to the apical side of adjacent cells, limits water and solute movement between cells (paracellular route).

Solute transport across cell membranes uses either passive or active mechanisms.

Passive Transport

Simple diffusion occurs down an electrochemical gradient, which is a composite of the concentration and electrical gradients (electrochemical gradient). With an undissociated molecule, only the concentration gradient is relevant; for a charged ion, the electrical gradient must also be considered. Simple diffusion does not require a direct energy source, although active transport is usually necessary to establish and maintain the electrochemical gradient.

Facilitated diffusion (coupled or carrier-mediated diffusion) depends on an interaction of the molecule or ion with a specific membrane carrier protein that facilitates its passage across the cell membrane’s lipid bilayer. In almost all cases of carrier-mediated transport in the kidney, two or more ions or molecules share the carrier: one moiety moves down its electrochemical gradient and the other(s) is transported “uphill,” against the gradient.

Diffusion through a membrane channel (or pore) formed by specific integral membrane proteins is a form of facilitated diffusion because it allows charged, polar, and lipophobic molecules to pass through the membrane at a high rate.

Active Transport

Ion movement directly against an electrochemical gradient requires a source of energy and is known as active transport. In cells, this energy is derived from ATP production and its hydrolysis. The most important active cell transport mechanism is the sodium pump, which extrudes sodium ions (Na+) from inside the cell in exchange for potassium ions (K+) from outside the cell. In the kidney, this process is confined to the basolateral membrane. The Na pump derives energy from the enzymatic hydrolysis of ATP and is more correctly named Na+,K+-ATPase.

It exchanges 3Na+ for 2K+ and is electrogenic because it extrudes a net positive charge from the cell; Na+,K+-ATPase is an example of a primary active transport mechanism. Other well-defined primary active transport processes in the kidney are the H+-ATPase, important in proton secretion in the distal nephron, and the Ca2+-ATPase, partly responsible for calcium reabsorption.

Activity of the basolateral Na+,K+-ATPase underpins all of the passive transport processes outlined earlier. It keeps intracellular Na+ concentration low (10–20 mmol/L) and K+ concentration high (~150 mmol/L), compared with their extracellular concentrations (~140 and 4 mmol/L, respectively). The pump-leak model of sodium transport uses the electrochemical gradient established and maintained by the Na pump to allow “leak” of Na+ into the cell through a variety of membrane transport proteins, ranging from Na+ channels to carrier proteins that couple Na+ entry to the influx (symport or cotransport) or efflux (antiport or countertransport) of other molecules or ions. In various parts of the nephron, glucose, phosphate, amino acids, K+, and chloride ions (Cl) are all cotransported with Na+; moreover, H2+ and Ca2+ can be countertransported against Na+ entry. In each case, the non-Na molecule or ion is transported against its electrochemical gradient, using energy derived from the “downhill” movement of Na+.

Their ultimate dependence on the Na+,K+-ATPase makes them secondary active transporters.

Major Transport Mechanisms Along the Nephron

DCT
Lumen

Principal cells
Interstitium

Lumen

Na+

Na+

Cl

K+

Na+
Na+

K+

K+
K+

K+

Cl

Ca2+

Interstitium

Ca2+

o

Ca2+
Na+

Intercalated cells
PCT
Lumen
Na+
Glucose
Na+
Amino acids
Na+
Phosphate
Na+
Citrate
Cl
Formate/Oxalate
Na+
H+

Alpha
Interstitium
Glucose
Amino acids

Na+
K+
K+
Cl
K+

H+
H+
K+

HCO3
Cl
Cl

Beta
HCO3
Cl
Na+
HCO3
Cl

H+
Cl

Cl
Na+
HCO3

Fig. 2.6 Major Transport Mechanisms Along the Nephron. Major transport proteins for solutes in the apical and basolateral membranes of tubular cells in specific regions of the nephron. Stoichiometry is not indicated; it is not 1:1 in all cases. Red circles represent primary active transport; white circles represent carrier-mediated transport (secondary active); cylinders represent ion channels. In the proximal convoluted tubule (PCT), Na+ enters the cell through an Na+-H+ exchanger and a series of cotransporters. In the distal convoluted tubule (DCT), Na+ enters the cell through the thiazide-sensitive Na +-Cl− cotransporter. In the principal cells of the cortical collecting duct, Na + enters through the epithelial sodium channel (ENaC). In all cases, Na+ is extruded from the cells through the basolateral Na +,K+-ATPase. Transporters in the thick ascending limb of Henle are dealt with separately (see Fig. 2.10).

TRANSPORT IN SPECIFIC NEPHRON SEGMENTS

In total, 180 L of plasma (largely protein free) is filtered each day, necessitating massive reabsorption by the nephron. Fig. 2.6 shows major transport mechanisms along the nephron; the loop of Henle is discussed separately.

Proximal Tubule

Proximal tubule cells are adapted for bulk reabsorption of the glomerular filtrate. The apical membrane have microvilli (brush border) to provide a large absorptive area, and the basolateral membrane has folds, also increasing its surface area. Abundant mitochondria are concentrated at the basolateral membrane to supply the Na+,K+-ATPase with ATP. Proximal tubule transport is heavily reliant on oxidative phosphorylation (aerobic metabolism) and is susceptible to hypoxia and mitochondrial dysfunction. Drugs that are toxic to mitochondria (e.g., tenofovir) can cause Fanconi syndrome (see Chapter 50), and mitochondrial protection strategies may have potential to improve function in some forms of acute kidney injury.17

The proximal convoluted tubule (PCT, pars convoluta) makes up the first two-thirds of the proximal tubule, and the final third is the proximal straight tubule (pars recta). The proximal tubular epithelium can also be subdivided into three segments based on subtle structural and functional differences: S1 is the initial short segment of the PCT; S2, the remainder of the PCT and the cortical segment of the pars recta; and S3, the medullary segment of the pars recta.

The NHE3 isoform of the Na^+-H^+ exchanger (antiporter) is the main route of Na^+ entry into proximal tubular cells. A battery of specialized transporters is also expressed in the apical membrane, coupling Na^+ entry to other solutes. The proximal tubule accounts for the bulk of Na^+, K^+, Cl^-, and bicarbonate (HCO_3^-) reabsorption and the almost complete reabsorption of amino acids and low-molecularweight proteins (e.g., retinol binding protein, α- and β-microglobulin) that have passed the filtration barrier. The proximal tubule reabsorbs almost all the filtered glucose via the sodium-glucose cotransporters (the SGLTs). SGLT1, which is also expressed in the small intestine, localizes to the apical membrane of the S3 proximal tubule, reabsorbing approximately 10% of the filtered glucose. Exclusive to the kidney, SGLT2 is expressed predominantly in the brush border of S1 and S2 and is the dominant pathway for glucose reabsorption. SGLT2 inhibitors (gliflozins) cause glycosuria and polyuria and lower blood glucose levels and, to a small extent, blood pressure in diabetics. In animal models of diabetes, gliflozins reduce glomerular hyperfiltration by inhibiting TGF, reduce autophagy of renal tubule cells, and lower albuminuria. SGLT2 inhibitors may also preserve mitochondrial function, contributing to their renoprotection.[18] SGLT2 inhibitors are an important new class of antidiabetic and nephroprotective drug used mainly to treat type 2 diabetes, and recent clinical trials have demonstrated a wider benefit in nondiabetic kidney disease and in heart failure.

Many other filtered solutes are also reabsorbed in the proximal tubule (e.g., ~60% of calcium, ~80% of phosphate, and 50% of urea). Constitutive expression of aquaporin 1 (AQP1) water channels in both membranes confers a large hydraulic permeability to cells. Furthermore, the protein junctional complexes (such as Claudin 1 and Zonula Occludens 1) connecting tubular cells are “leaky,” facilitating the reabsorption of large amounts of sodium, potassium, and water. The substantial hydraulic permeability requires only a very small osmotic driving force (<5 mOsm/kg/H_2O), and the osmolality of the tubular fluid changes little along the proximal tubule, referred to as “isosmotic” reabsorption.

In the final section of the proximal tubule (late S2 and S3), there is efficient secretion of weak organic acids and bases, including most diuretics, PAH (see Renal Blood Flow), nonsteroidal antiinflammatory drugs (NSAIDs), antiretroviral drugs, and some antibiotics. The molecular machinery for secretion is complex, mediated by 13 members of the SLC22 family of transport proteins.[19]

Loop of Henle

Anatomically, the loop of Henle includes the pars recta of the proximal tubule, the thin descending and ascending limbs (thin ascending limbs are present only in long-looped nephrons), the thick ascending limb, and the macula densa. In addition to its role in further reabsorption of solutes (Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}), the loop of Henle is responsible for the kidney’s ability to generate a concentrated or dilute urine, described in detail later. The thick limb of Henle also produces uromodulin (Tamm-Horsfall protein), normally the most abundant protein in urine. Mutations in the encoding gene (UMOD) cause rare autosomal dominant kidney diseases with medullary cyst formation, hyperuricemia, and progressive loss of renal function. Several polymorphisms have been associated with an increased risk for hypertension and chronic kidney disease. A recent mendelian randomization study to assess causality reported that increased urinary levels are causally linked to CKD and increased blood pressure.19a The role of uromodulin is not fully understood, but studies in mice suggest that it activates Na+,K+,2Cl− cotransport to promote sodium reabsorption in the thick limb of Henle. Uromodulin may also be a constitutive urinary inhibitor of calcium stone formation and can protect the kidney from ascending urinary tract infections.20

Distal Nephron

The distal tubule involves three segments. The distal convoluted tubule (DCT) reabsorbs NaCl via a thiazide-sensitive NaCl cotransporter (NCC) in the apical membrane.21 The connecting tubule (CNT) is a functional intermediate between the DCT and the initial cortical collecting duct (CD; see Fig. 2.6), which is formed of principal cells (i.e., the main cell type) and intercalated cells (i.e., inserted between). Principal cells are responsible for Na+ reabsorption, K+ secretion,22 and regulated water reabsorption (see later discussion). Na+ enters the principal cell through apical epithelial sodium channels (ENaC) and exits by the basolateral Na+,K+-ATPase. This process is electrogenic and establishes a lumen-negative transepithelial potential difference. K+ enters the principal cell by the same basolateral Na+,K+-ATPase and leaves by K+ transport pathways in both membranes; however, the relative depolarization of the apical membrane (caused by Na+ entry through ENaC) favors K+ secretion into the lumen, the major route for which is through renal outer medullary potassium (ROMK) channels.

Intercalated (IC) cells contribute to acid-base homeostasis. Type A (or α) IC cells secrete H+ into the tubular fluid via H+-ATPase and H+,K+-ATPase. Type B (or β) IC cells mediate HCO3− secretion into the final urine, in exchange for Cl−. An exchanger called pendrin, encoded by SLC26A4, mediates this process. Type B IC cells also express a Na+-dependent chloride-bicarbonate exchanger (NDCBE; SLC4A8). Functionally coupled with pendrin, NDCBE achieves electroneutral sodium transport across the type B cell (see Fig. 2.6).23

In the medullary CD there are increasingly fewer IC cells, whereas the principal-like cells are modified such that they reabsorb Na+ but, lacking apical K+ channels, do not secrete K+.

Figs. 2.7 and 2.8 show the sites of Na+ and K+ reabsorption and secretion along the nephron. Table 2.2 outlines the pathophysiologic consequences of known genetic defects in some of the major transporters in the nephron (see Chapter 49 for details).

GLOMERULOTUBULAR BALANCE

The proportion of filtered Na+ that is excreted in the urine is so small (normally <1%) that even small changes in the filtered load would cause potentially major changes in the amount excreted in the final urine. For example, if GFR were to increase by 10%, and the rate of reabsorption remained unchanged, Na+ excretion would increase more than 10-fold. An intrinsic feature of tubular function, however, is that the extent of Na+ reabsorption in a given nephron segment is proportional to the Na+ delivery to that segment. This process is called glomerulotubular balance. In perfect balance, both the reabsorption and the excretion of Na+ would change in exactly the same proportion as the change in GFR, but glomerulotubular balance is usually less than perfect. Most studies have focused on the proximal tubule where glomerulotubular balance stabilizes delivery of Na+ and fluid to the distal nephron, permitting efficient secretion of K+ and H+. However, Na+ reabsorption in the thick limb of Henle and distal tubule is also delivery-dependent. This partly explains why diuretics acting on the proximal tubule are less effective compared with those acting more distally: with distal-acting diuretics, there is less scope further downstream for compensatory Na+ reabsorption. This also explains why combining two diuretics (acting at different nephron sites) can cause a more striking diuresis and natriuresis.

Renal Sodium Handling
Distal convoluted tubule

8%
Cortex

5%

Proximal
convoluted
tubule
50%
Proximal
straight
tubule 15%
Outer
medulla

3%

Collecting duct

Connecting
tubule
20%
Thick
ascending
limb

35%

7%
Inner
medulla

Thin
ascending
limb

Thin
descending
limb

,1%

Fig. 2.7 Renal Sodium Handling Along the Nephron. Figures outside the nephron represent the approximate percentage of the filtered load reabsorbed in each region. Figures within the nephron represent the percentages remaining. Most filtered sodium is reabsorbed in the proximal tubule and loop of Henle; normal day-to-day control of sodium excretion is exerted in the distal nephron.

Renal Potassium Handling
Distal convoluted tubule

10%
Cortex
Proximal
convoluted
tubule
45%
Proximal
straight
tubule
Outer

medulla

Inner
medulla

Connecting
tubule

Collecting duct

Thick
ascending
limb

Thin
descending
limb

Thin
ascending
limb
1%–100%

Fig. 2.8 Renal Potassium Handling Along the Nephron. Figures are not given for percentages reabsorbed or remaining in every region because quantitative information is incomplete, but most filtered potassium is reabsorbed in the proximal convoluted tubule and thick ascending limb of Henle; approximately 10% of the filtered load reaches the early distal tubule. Secretion by connecting tubule cells and principal cells in the late distal tubule–cortical collecting duct is variable and is the major determinant of potassium excretion.

TABLE 2.2 Genetic Defects in Transport
Proteins Resulting in Renal Disease a
Transporter

Consequence of Mutation

Proximal Tubule
Apical Na+-cystine cotransporter
Apical Na+-glucose cotransporter
(SGLT2)

Lumen

Cystinuria
Renal glycosuria

Na+-HCO3

Proximal renal tubular acidosis

H+-Cl

Dent disease

Basolateral
cotransporter
Intracellular
(CIC5)

Peritubular Capillaries Modulate
Fluid Reabsorption

exchanger

Thick Ascending Limb
Apical Na+-K+-2Cl cotransporter

Bartter syndrome type 2

Basolateral Cl channel

Bartter syndrome type 3

Basolateral Cl channel accessory
protein

Bartter syndrome type 4

Collecting Duct
Apical Na+ channel (principal
cells)

Na+
+
H2O Na+ K
Paracellular
backflux

Peritubular
capillary

P_{pc}
(low)
π_{pc}
(high)
Fluid
reabsorbed

Bartter syndrome type 1

Apical K^+ channel

Distal Convoluted Tubule
Apical Na^+-Cl cotransporter

Normal
Proximal tubule Interstitial
fluid

Gitelman syndrome
Overexpression: Liddle syndrome
Underexpression:
pseudohypoaldosteronism type 1b

Aquaporin 2 channel (principal cells)

Nephrogenic diabetes insipidus

Basolateral Cl /HCO_3 exchanger (intercalated cells)

Distal renal tubular acidosis

Apical H^+-ATPase (intercalated cells)

Distal renal tubular acidosis (with or without deafness)

[a] For more detailed coverage of these clinical conditions, see Chapter 49

ATP, Adenosine triphosphate.

The mechanism of glomerulotubular balance is not fully understood. In the proximal tubule, physical factors (Starling forces) operating across peritubular capillary walls may be involved. Glomerular filtration of an essentially protein-free fluid means that the plasma leaving the glomeruli in the efferent arterioles and supplying the peritubular capillaries has a relatively high oncotic pressure, favoring reabsorption of fluid from the proximal tubules. If GFR were reduced in the absence of a change in RPF, the filtration fraction would fall. Peritubular capillary oncotic pressure would also be reduced, and the tendency of the peritubular vasculature to take up fluid reabsorbed from the proximal tubule would be diminished. Backflux of this fluid is thought to occur through the leaky tight junctions, reducing net reabsorption (Fig. 2.9). This mechanism could only work, however, if GFR changed in the absence of a corresponding change in RPF; if the two changed in parallel, filtration fraction would stay constant, with no change in oncotic pressure.

A second contributory factor to glomerulotubular balance in the proximal tubule could be the filtered loads of glucose and amino acids:

if more is filtered, the rates of Na^+-coupled glucose and amino acid reabsorption in the proximal tubule will also increase. It has been proposed that the brush border microvilli of the proximal tubule serve a “mechanosensing” function, transmitting changes in torque (caused by altered tubular flow rates) to the tubular cells’ actin cytoskeleton

Reduced peritubular capillary oncotic pressure
Na^+
+
H_2O Na^+ K
Increased
paracellular
backflux

↓ πpc

Raised
Less fluid
interstitial
reabsorbed
pressure

Fig. 2.9 Physical Factors and Proximal Tubular Reabsorption. Influence of peritubular capillary oncotic pressure on net reabsorption in proximal tubules. Uptake of reabsorbate into peritubular capillaries is determined by the balance of hydrostatic and oncotic pressures across the capillary wall. Compared with those in systemic capillaries, the peritubular capillary hydrostatic (Ppc) and oncotic (πpc) pressures are low and high, respectively, so that uptake of proximal tubular reabsorbate into the capillaries is favored. If peritubular capillary oncotic pressure decreases (or hydrostatic pressure increases), less fluid is taken up, interstitial pressure increases, and more fluid may leak back into the lumen paracellularly; net reabsorption in proximal tubules would therefore be reduced.

and thereby modulating transporter activity.24 The mechanisms are unknown, but the release of paracrine mediators such as ATP, dopamine, or Ang II into the lumen fluid may contribute.25

Although renal sympathetic nerves and certain hormones can influence reabsorption in the proximal tubule and loop of Henle, under normal conditions, the combined effects of autoregulation and glomerulotubular balance ensure a relatively constant load of glomerular filtrate is delivered to the distal tubule, which exert normal dayto-day control of Na^+ excretion. Evidence indicates important roles for the late DCT21 and the CNT,26 in addition to the CD.22 Aldosterone, secreted from the adrenal cortex, activates mineralocorticoid receptors within CNT cells and in principal cells, leading to generation and activation by phosphorylation of the regulatory protein serum- and glucocorticoid-inducible kinase 1 (SGK1). SGK1 increases the density of apical ENaC (see Fig. 2.6) and enhances the basolateral Na^+,K^+ ATPase. Overall, Na^+ transport across the principal cell stimulated and the maximal depolarization of the apical membrane drives K^+ secretion into the tubular fluid. The electrophysiologic coupling of Na^+ reabsorption to K^+ secretion explains why aldosterone promotes antinatriuresis and kaliuresis. Under conditions of volume depletion, however, aldosterone promotes sodium retention without promoting urinary potassium excretion. The mechanism underlying this aldosterone paradox relates to the major stimulus for aldosterone production.

During hypovolemia, the renin-angiotensin system drives aldosterone synthesis. The combination of high aldosterone and Ang II engages the WNK4 kinase network and activates NCC in the DCT, promoting potassium-sparing sodium reabsorption, while also inhibiting ROMK channels to limit potassium secretion.21 Ang II also activates NDBCE and pendrin in the type B IC cell to promote potassium-sparing sodium reabsorption. Conversely, when hyperkalemia is the major stimulus for aldosterone release, then NCC is inhibited, pushing sodium reabsorption downstream where it is coupled to potassium secretion in the principal cell. Even modest increases in plasma potassium inhibit NCC activity, accounting for the natriuretic and blood pressure–lowering effects of high dietary potassium intake.27

Mineralocorticoid receptors have equal affinity in vitro for aldosterone and cortisol. The circulating concentrations of cortisol vastly exceed those of aldosterone, and in vivo specificity for aldosterone along the distal nephron is conferred by the enzyme 11β-hydroxysteroid dehydrogenase 2, which inactivates cortisol in the vicinity of the receptor.28 Mutations in the encoding gene, or inhibition of the enzyme by derivatives of glycyrrhetinic acid (found in licorice), cause hypokalemic hypertension because of excessive and unregulated stimulation of Na+ transport29 and salt appetite30 by cortisol (see also Chapter 49).

COUNTERCURRENT SYSTEM

The loop of Henle generates and maintains the interstitial osmotic gradient from the renal cortex (~290 mOsm/kg) to the tip of the medulla (~1200 mOsm/kg). As indicated in Chapter 1, the loops of Henle of superficial nephrons turn at the junction between outer and inner medulla, whereas those of deep nephrons (long-looped nephrons) penetrate the inner medulla to varying degrees. The loops of Henle as a whole reabsorb approximately 40% of filtered Na+, mostly in the proximal straight tubule and the thick ascending limb, and approximately 25% of filtered water in the proximal straight tubule and the thin descending limbs of deep nephrons. Evidence suggests that the thin descending limb of superficial nephrons is relatively impermeable to water.31 Both the thin ascending limb (found only in deep nephrons) and the thick ascending limb are essentially impermeable to water.

Both segments reabsorb Na+. In the thin ascending limb, this is passive. The thick ascending limb operates an active pump-leak system: the basolateral Na+,K+-ATPase maintains the electrochemical driving force for passive Na+ entry from the lumen through the Na+,K+,2Cl cotransporter (NKCC2) and, to a smaller extent, the NHE3 (Fig. 2.10). NKCC2 is directly inhibited by loop diuretics such as furosemide and bumetanide. Na+ exits the cell through the Na+,K+-ATPase, and Cl and K+ exit via basolateral ion channels, and a K+-Cl cotransporter. K+ can also recycle back across the apical membrane through ion channels and this sustains operation of NKCC2 because the availability of K+ is a limiting factor for the transporter (K+ concentration in tubular fluid being lower than Na+ and Cl). Potassium recycling helps to generate a lumen-positive transepithelial potential difference in the thick ascending limb, which drives additional Na+ reabsorption through the paracellular pathway; for each Na+ reabsorbed by the transcellular route, another is reabsorbed paracellularly (see Fig. 2.10). Other cations (K+, Ca2+, Mg2+) are also reabsorbed by this route. The reabsorption of NaCl along the thick ascending limb in the absence of significant water reabsorption means that the tubular fluid leaving this segment is hypotonic; the thick ascending limb is also known as the diluting segment for this reason.

The reabsorption in the thick ascending limb of solute without water generates a “horizontal” osmotic gradient of about 200 mOsm/kg between the tubular fluid and interstitium. This separation is the single osmotic effect. The U-shaped arrangement of the loop of Henle,

Transport Mechanisms in
the Thick Ascending Limb
Lumen

Cells of thick ascending limb

Interstitial fluid
Na+

K+

Na+
H+
Na+
K+
Ca2+
Mg2+ +

K+
K+
2Cl−
Na+

K+
K+
Cl−
Cl−

Paracellular
diffusion

Lumen-positive
potential difference

Fig. 2.10 Transport Mechanisms in the Thick Ascending Limb of Henle. The major cellular entry mechanism is the Na +-K+-2Cl− cotransporter. The transepithelial potential difference drives paracellular transport of Na+, K+, Ca2+, and Mg2+.

in which flow in the descending limb is opposite to that in the ascending limb, multiplies the single effect to generate a much larger vertical (corticomedullary) osmotic gradient. This process is countercurrent multiplication (Fig. 2.11). Fluid entering the descending limb from the proximal tubule is isosmotic (~290 mOsm/kg). On encountering the hypertonicity of the medullary interstitial fluid (caused by NaCl reabsorption in the water-impermeable ascending limb), the fluid in the descending limb comes into rapid osmotic equilibrium, either by solute entry into the descending limb (superficial nephrons) or by water exit by osmosis (deep nephrons). These events, combined with continuing NaCl reabsorption in the ascending limb, result in a progressive increase in medullary osmolality from the corticomedullary junction to the papillary tip. A similar osmotic gradient exists in the thin descending limb, and at any level in the ascending limb, the osmolality of the tubule fluid is approximately 200 mOsm/kg less than in the surrounding tissue. The fluid that exits the loop of Henle has an osmolarity of approximately 100mOsm/kg. Further sodium is reabsorbed as the fluid traverses the distal nephron and CD, allowing for the formation of a very dilute urine (~50 mOsm/kg) if required for fluid balance.

Role of Urea

The thin limbs of the loop of Henle are relatively permeable to urea (ascending more permeable than descending), but the thick ascending limb and beyond are urea-impermeable up to the final section of the inner medullary CD. During antidiuresis, water reabsorption from the CDs concentrates urea, such that in the terminal inner medullary CD there is a large concentration gradient between the luminal fluid and interstitium. This section of the inner medullary CD expresses urea transporters (UT-A1 and UT-A3), allowing passive reabsorption of urea into the inner medullary interstitium. These processes are under the control of vasopressin (AVP, also known as antidiuretic hormone).[32] The interstitial urea exchanges with vasa recta capillaries (see next section) and some urea enters the S3 segment of the pars recta and the descending and ascending thin limbs; it is then returned to the inner medullary CDs to be reabsorbed. The net result of this urea recycling process is to add urea to the inner medullary interstitium, thereby

Countercurrent Multiplication

Cortex
NaCl
H2O
NaCl
290
Outer
medulla

NaCl

H2O

100

290

290
NaCl

600

H2O

Inner
medulla

900

H2O

Papilla

1200

400

600

NaCl

NaCl

600
NaCl

700

900

1200

900

1200

Fig. 2.11 Countercurrent Multiplication by the Loop of Henle. The nephron drawn represents a deep
(long-looped) nephron. Figures represent approximate osmolarities (mOsm/kg).

Osmotic equilibration occurs in the thin descending limb of Henle, whereas NaCl is reabsorbed in the water-impermeable ascending limb; hypotonic fluid is delivered to the distal tubule. In the absence of vasopressin, this fluid remains hypotonic during its passage through the distal tubule and collecting duct, despite the large osmotic gradient favoring water reabsorption. A large volume of dilute urine is therefore formed. During maximal vasopressin secretion, water is reabsorbed down the osmotic gradient, so that tubular fluid becomes isotonic in the cortical collecting duct and hypertonic in the medullary collecting duct. A small volume of concentrated urine is formed.

increasing interstitial osmolality. The high urea concentration within the medullary CD is balanced by a similarly high urea concentration in the medullary interstitium. This renders urea in the CD osmotically inactive and permits large quantities of urea to be excreted without osmotic diuresis. Moreover, the high urea concentration in the medullary interstitium should also increase osmotic water abstraction from the thin descending limbs of deep nephrons, thus raising the intraluminal Na^+ concentration within the thin descending limbs. Although until recently this process was thought to drive passive Na^+ reabsorption along the thin ascending limbs, mice with genetic deletion of the urea transporters UT-A1 and UT-A3 have a greatly reduced urea concentration in the inner medullary interstitium but a normal interstitial NaCl gradient.32 Therefore, the mechanisms responsible for the inner medullary electrolyte gradients are still unclear. It is worth emphasizing, however, that the ultimate driving force for countercurrent multiplication is active Na^+ reabsorption in the thick ascending limb. For this reason, loop diuretics disrupt the osmotic gradient, and genetic mutations in the pathways contributing to efficient Na^+ reabsorption in the thick ascending limb cause saltwasting Bartter syndrome (see Chapter 49).

Role of the Vasa Recta

The blood supply into the medulla arrives and leaves via the cortex. This U-shaped arrangement of the vasa recta prevents the dissipation of the medullary osmotic gradient by equilibration with the isotonic capillary blood. Solute enters and water leaves the vasa recta as it descends into the medulla, and this is almost entirely offset by the opposite fluxes as the vasa recta ascends back to the cortex and drains into the arcuate vein. This passive process, called countercurrent exchange (Fig. 2.12), preserves medullary hypertonicity. Most solutes remain in the interstitium and any water reabsorbed from the collecting duct is swiftly removed, which results in a blood flow rate that is higher in the ascending than in the descending vasa recta.

Renal Medullary Hypoxia

Oxygen also undergoes countercurrent exchange by the medullary capillaries, diffusing from descending to ascending vasa recta and bypassing the deeper regions. This phenomenon, combined with ongoing energy-dependent Na^+ transport in the (outer medullary) thick ascending limb, renders medullary tissue relatively hypoxic. Thus, the partial pressure of oxygen normally decreases from about 50 mm Hg in the cortex to 10 mm Hg in the inner medulla.33 Medullary cells are adapted to this relatively hypoxic environment, having a higher capacity for glycolysis than cortical cells. Moreover, a number of heat shock proteins are expressed in the medulla, which assist cell survival by restoring damaged proteins and by inhibiting apoptosis.33 The degree of medullary hypoxia depends on the balance between medullary blood flow, influenced by contractile pericytes that surround the descending vasa recta, and oxygen consumption in the thick ascending limb (e.g., inhibition of NKCC2 by furosemide increases medullary oxygenation). In health, this balance is modulated by a variety of autocrine/paracrine agents (e.g., NO, eicosanoids, ATP, adenosine; see later

Countercurrent Exchange
290

290

300

H_2O

290

Solute
600

600
H_2O

900

Solute

900

H_2O

1200

1190

1200

Fig. 2.12 Countercurrent Exchange by the Vasa Recta. Figures represent approximate osmolarities (mOsm/kg). The vasa recta capillary walls are highly permeable, but the U-shaped arrangement of the vessels minimizes the dissipation of the medullary osmotic gradient. Nevertheless, because equilibration across the capillary walls is not instantaneous, a certain amount of solute is removed from the interstitium.

discussion) and by renal nerves, which can alter medullary oxygenation by simultaneously regulating pericyte contraction and thick ascending limb Na^+ transport. Some cases of radiocontrast-induced nephropathy result from a disturbance in the balance between oxygen supply and demand, with consequent hypoxic medullary injury in which the normal cellular adaptations are overwhelmed, with subsequent apoptotic and necrotic cell death.

VASOPRESSIN (ANTIDIURETIC HORMONE) AND WATER REABSORPTION

Vasopressin is a nonapeptide synthesized in specialized neurons of the supraoptic and paraventricular nuclei. Vasopressin is transported from these nuclei to the posterior pituitary and released in response to increases in plasma osmolality and decreases in blood pressure. Osmoreceptors are found in the hypothalamus, and there is also input to this region from arterial baroreceptors and atrial stretch receptors. The actions of vasopressin are mediated by three receptor subtypes: V1a, V1b, and V2. The V1a receptors are found in vascular smooth muscle and are coupled to the phosphoinositol pathway; they cause an increase in intracellular Ca^{2+} resulting in contraction. V1a receptors also have been identified in the apical membrane of several nephron segments; activation by luminal vasopressin can influence Na^+ transport in these segments. V1b receptors are found in the anterior pituitary, where vasopressin modulates adrenocorticotropic hormone release. V2 receptors are found in the basolateral membrane of principal cells in the late distal tubule and the whole length of the CD; they are coupled by a Gs protein to cyclic adenosine monophosphate generation, which ultimately leads to the insertion of aquaporin 2 (AQP2) water channels into the apical membrane of this otherwise water-impermeable segment (Fig. 2.13). In the X-linked form of nephrogenic diabetes insipidus, the most common inherited form, the V2 receptor is defective.[34]

Several aquaporins have been identified in the kidney.[35] AQP1 is found in apical and basolateral membranes of all proximal tubules and of thin descending limbs of long-looped nephrons, conferring high basal water permeability to these segments. AQP3 is constitutively expressed in the basolateral membrane of CNT cells and cortical and outer medullary principal cells. AQP4 is constitutively expressed in the basolateral membrane of outer medullary principal cells and inner medullary CD cells. The variable water permeability of the late distal tubule and CD is determined by AQP2. Acute vasopressin release causes shuttling of AQP2 from intracellular vesicles to the apical membrane, whereas chronically raised vasopressin levels increase transcription and translation of the gene encoding AQP2. Apical insertion of AQP2 allows reabsorption of water, driven by the high interstitial osmolality. Vasopressin also contributes directly to the gradient by stimulating Na^+ reabsorption in the thick ascending limb and urea reabsorption through the UT-A1 and UT-A3 transporters in the inner medullary CD. In the (rare) autosomal recessive and (even rarer) autosomal dominant forms of nephrogenic diabetes insipidus, AQP2 is abnormal and/or fails to translocate to the apical membrane.[34]

More frequently, defects in AQP2 shuttling contribute to the urine-concentrating defects associated with both hypokalemia and hypercalcemia. With chronic hypokalemia, AQP2 expression in the CD is reduced, possibly reflecting the generalized suppression of proteins central to urine concentration[36] and a reduction in the medullary osmotic gradient. With hypercalcemia, an elevated concentration of Ca^{2+} in tubular fluid activates the calcium-sensing receptor in the apical membrane of the principal cell, preventing insertion of AQP2. This is thought to be a protective mechanism to hinder kidney stone formation.[37] In addition, stimulation of the calcium receptor in the basolateral membrane of the thick ascending limb (a receptor similar to that in the parathyroid glands) reduces transcellular solute flux by inhibiting NKCC2 and ROMK channels and also by direct inhibition of paracellular permeability.[37] Overall, this reduces the medullary osmotic gradient for water reabsorption.

INTEGRATED CONTROL OF KIDNEY FUNCTION

The kidneys regulate blood volume by controlling the sodium content of the body and thus the effective circulating volume, a conceptual volume reflecting the degree of fullness of the vasculature. Chapter 8 details the regulation of effective circulating volume, and this chapter now introduces some of the key mediator systems. The list is not exhaustive, and it is important to recognize that these systems are not static and do not operate in isolation. Rather, kidney salt and water transport (and indeed blood pressure) has circadian rhythmicity[38] and is influenced by a dynamic web of interlocking control systems operating at whole-body and local, intrarenal levels.

Pressure Natriuresis

Acute increases in arterial blood pressure induce natriuresis. This is the pressure natriuresis phenomenon and is considered important for long-term stability of effective circulating volume[25] Pressure natriuresis occurs because autoregulation of RBF is not perfect, and a rise in renal perfusion pressure increases flow in the medullary vasa recta. Kidney volume is constrained by the renal capsule: elevated flow in the medulla causes a proportionate rise in renal interstitial hydrostatic pressure (RIHP), which reduces net reabsorption in the proximal tubule by increasing paracellular backflux through the tight junctions of the tubular wall (see Fig. 2.9) and by inactivating apical membrane sodium transport proteins. Increased RIHP also stimulates the production of nitric oxide (NO) and ATP to inhibit sodium reabsorption in the thick limb of Henle and distal nephron.[39]

Another renal action of NO results from the presence of inducible (type II) nitric oxide synthase (iNOS) in glomerular mesangial cells. Local NO production counteracts the mesangial contractile response

Renin-Angiotensin-Aldosterone System

Action of Vasopressin
Lumen

Cells

Interstitium

H_2O
H_2O
Vesicles
containing
AQP2

AQP4
AQP3

Protein kinase A
ATP

AQP2
H_2O

cAMP

A
C

V2 receptor
Vasopressin
H_2O
H_2O

Fig. 2.13 Mechanism of Action of Vasopressin (Antidiuretic Hormone). Vasopressin binds to V2 receptors on the basolateral membrane of collecting duct principal cells and increases intracellular cyclic adenosine monophosphate (cAMP) production, causing insertion of preformed aquaporin 2 (AQP2) water channels into the apical membrane through intermediate reactions involving protein kinase A. The water permeability of the basolateral membrane, which contains aquaporins 3 and 4, is permanently high. Therefore, vasopressin secretion allows transcellular movement of water from lumen to interstitium. AC, Adenylate cyclase; ATP, adenosine triphosphate.

to agonists such as Ang II and endothelin (see later discussion). Furthermore, NO may contribute to the regulation of medullary blood flow. Locally synthesized NO offsets the vasoconstrictor effects of other agents on the pericytes of the descending vasa recta, and it reduces Na^+ reabsorption in the thick ascending limb; both actions help protect the renal medulla from hypoxia.

Renal Sympathetic Nerves

Reductions in arterial pressure and/or central venous pressure suppress afferent signaling from arterial baroreceptors and atrial volume receptors, eliciting a reflex increase in renal sympathetic nervous discharge. This reduces urinary Na^+ excretion in at least three ways: (1) constriction of afferent and efferent glomerular arterioles (predominantly afferent), directly reducing RBF and GFR, and indirectly reducing RIHP; (2) direct stimulation of Na^+ reabsorption in the proximal tubule and the thick ascending limb of the Henle loop; and (3) stimulation of renin secretion by afferent arteriolar cells (see later discussion). Renal sympathetic overactivity has long been associated with Na+ retention and experimental hypertension. The Symplicity-HTN trials initially indicated that bilateral sympathetic efferent denervation caused long-lasting reductions in blood pressure in patients with resistant hypertension. However, this early promise from small studies was not supported in a larger single-blind, sham-controlled trial, and enthusiasm for renal denervation to treat resistant hypertension waned. With advances in technology and refined study design, however, clinical trials such as SPYRAL-pivotal have shown reproducible and sustained reductions in ambulatory blood pressure, establishing confidence in the underlying concept. The next step is to identify those patients for whom renal denervation is clinically indicated and effective.

The renin-angiotensin-aldosterone system (RAAS) is central to the control of extracellular fluid volume (ECFV) and blood pressure. Renin is synthesized and stored in specialized afferent arteriolar cells that form part of the juxtaglomerular apparatus and is released into the circulation in response to (1) increased renal sympathetic nervous discharge, (2) reduced stretch of the afferent arteriole after a reduction in renal perfusion pressure, and (3) reduced delivery of NaCl to the macula densa region of the nephron (see Fig. 2.4).

Renin catalyzes the production of the decapeptide Ang I from circulating angiotensinogen (synthesized in the liver). Ang I is converted by angiotensin-converting enzyme (ACE) to the octapeptide Ang II, which acts via AT1 receptors to regulate ECFV and blood pressure by:

✓•✓ Inducing arteriolar vasoconstriction, including renal afferent and (particularly) efferent arterioles, thereby increasing arterial pressure but reducing RBF. The tendency of Pgc to increase is offset by Ang II–induced mesangial cell contraction, and reduced Kf and the overall effect on the GFR is unpredictable.

✓•✓ Directly stimulating sodium reabsorption in the proximal tubule and distal tubule thiazide-sensitive NaCl cotransport.27

✓•✓ Stimulating aldosterone secretion from the zona glomerulosa of adrenal cortex. Aldosterone stimulates distal nephron sodium reabsorption.

Many tissues, including kidney, express a homologue of ACE called ACE2. This membrane-bound protein converts Ang II to Ang(1-7), thereby regulating local Ang II bioactivity. Ang(1-7) also activates the Mas receptor, causing vasodilation, natriuresis, and diuresis. ACE2 operates locally as a RAAS counterregulatory system and the balance between these two pathways determines the net effect on fluid-volume and blood pressure. ACE2 was also identified as a route for SARSCOV2 entry into cells.

Eicosanoids

Eicosanoids are a family of metabolites of arachidonic acid (AA) produced enzymatically by three systems: cyclooxygenase, with two isoforms, COX-1 and COX-2, both expressed in the kidney; cytochrome P-450 (CYP-450); and lipoxygenase. The lipoxygenase system is activated (in leukocytes, mast cells, and macrophages) during inflammation and injury and is not considered further here.

The major renal eicosanoids produced by the COX system are the prostaglandins E2 (PGE2) and I2 (PGI2), both of which are renal vasodilators and buffer the effects of renal vasoconstrictor agents (e.g., Ang II, norepinephrine) and the vasoconstrictor thromboxane A2. PGE2 and PGI2 normally have minimal effects on renal hemodynamics, but during stressful situations such as hypovolemia, they help protect the kidney from excessive functional changes. Consequently, NSAIDs, which are COX inhibitors, can cause significant falls in GFR. PGE2 also has tubular effects, inhibiting Na+ reabsorption in the thick ascending limb of the Henle loop and both Na+ and water reabsorption in the

CD.40 The action of PGE2 in the thick ascending limb, together with a dilator effect on vasa recta pericytes, is another paracrine regulatory mechanism that helps protect the renal medulla from hypoxia. This may explain why inhibition of COX-2 can reduce medullary blood flow and cause apoptosis of medullary interstitial cells.

The metabolism of AA by renal CYP-450 enzymes yields epoxyeicosatrienoic acids (EETs), 20-hydroxyeicosatetraenoic acid (20-HETE), and dihydroxyeicosatrienoic acids (DHETs). These compounds appear to have multiple autocrine/paracrine/second messenger effects on the renal vasculature and tubules still to be fully unraveled. As with prostaglandins, EETs are vasodilator agents, whereas 20-HETE is a potent renal arteriolar constrictor and may be involved in the vasoconstrictor effect of Ang II and of the TGF mechanism. 20-HETE also constricts vasa recta pericytes and may be involved in the control of medullary blood flow. Some evidence suggests that locally produced 20-HETE and EETs can inhibit sodium reabsorption in the proximal tubule and thick ascending limb. Indeed, CYP-450 metabolites of AA may contribute to the reduced proximal tubular reabsorption seen in pressure natriuresis.41

COX-2 is present in macula densa cells and has a critical role in the release of renin from juxtaglomerular cells (granular cells) in response to reduced NaCl delivery to the macula densa.41 A low-sodium diet increases COX-2 expression in the macula densa and simultaneously increases renin secretion; the renin response is virtually abolished in COX-2 knockout mice or during pharmacologic inhibition of COX-2. Therefore, it is likely that the low renin observed during administration of NSAIDs is largely a consequence of COX-2 inhibition. In addition to COX-2, the enzyme PGE synthase is expressed in macula densa cells, and the principal COX-2 product responsible for enhancing renin secretion is PGE2, acting on specific receptors identified in juxtaglomerular cells. It is not clear whether PGI2 is also synthesized in macula densa cells. nNOS (type I isomer) is also present in macula densa cells and produces NO that blunts TGF. NO also has a permissive role in renin secretion, although the mechanism is not understood. The increase in macula densa COX-2 expression induced by a low-sodium diet is attenuated during administration of selective nNOS inhibitors, which has led to speculation that NO is responsible for the increase in COX-2 activity and the resulting increase in juxtaglomerular renin secretion. Fig. 2.14 shows the established and proposed roles of COX-2 and nNOS in the macula densa.

Atrial Natriuretic Peptide

If blood volume increases significantly, the resulting atrial stretch stimulates the release of atrial natriuretic peptide (ANP) from atrial myocytes. This hormone increases sodium excretion by suppressing renin and aldosterone release and through a direct inhibitory effect on sodium reabsorption in the medullary CD. ANP may also increase GFR because high doses cause afferent arteriolar vasodilation and mesangial cell relaxation (thus increasing Kf; see Table 2.1).

Endothelins

The kidney is a rich source of endothelins, predominantly paracrine peptides acting via ETA and ETB receptors: endothelin-1 (ET-1) is the major isoform.42 ETA activation causes sustained vasoconstriction and mesangial contraction, meaning that ET-1 can significantly reduce RBF and GFR (see Table 2.1). ETA also reduces medullary blood flow and polarizes resident immune cells to a proinflammatory phenotype. In combination, these effects of ETA activation explain why chronically elevated ET-1 may contribute to kidney diseases. Activation of ETB inhibits ENaC-mediated sodium reabsorption, causing natriuresis, and mice with CD-specific knockout of ETB receptors exhibit saltsensitive hypertension. There is mounting evidence that NO mediates the natriuretic and diuretic effects of medullary ETB stimulation,42 highlighting the potential importance of ET-1/NO interactions in the control of Na+ and water excretion. ETA antagonists reduce albumin excretion in diabetic kidney disease43 and are being investigated in other forms of kidney disease with proteinuria. Selective ETA antagonists were thought to avoid the sodium/water retention and edema seen in trials with nonselective endothelin antagonists; however, they still seem to show this effect, especially at higher doses, suggesting that both ETB and ETA play a role in collecting duct sodium excretion.44

ATP and Other Metabolic Intermediates

Paracrine signaling is firmly established as a key aspect of renal regulation.

Multiple systems form an interlocking network of control that

Interactions Between Macula Densa
and Afferent Arteriole
Renin
Vasoconstriction

Afferent arteriolar
granular cell
+
Adenosine

+

+
o

?

o

NO

ATP

+

Macula densa cell

+ PGE2
?
+

nNOS

ATP
+

?
Na+

COX-2
o

o

K+
K+

Tubular lumen

2Cl−
Fig. 2.14 Interactions Between Macula Densa and Afferent Arteriole: Proposed Mediators of Renin Secretion and Tubuloglomerular Feedback. Both cyclooxygenase-2 (COX-2) and neuronal nitric oxide synthase (nNOS) enzyme systems are present in macula densa cells. Increased NaCl delivery to the macula densa stimulates NaCl entry into the cells through the Na+-K+-2Cl− cotransporter. This causes afferent arteriolar constriction through adenosine or adenosine triphosphate (ATP) and also inhibits COX-2 activity; the latter effect might be mediated partly through inhibition of (nNOS-mediated) nitric oxide (NO) production. Generation of prostaglandin E2 (PGE2) by COX-2 stimulates renin release. PGE2 also modulates vasoconstriction, as does NO.

can rapidly adjust hemodynamic and tubular function; such systems support and interact with classical endocrine and neural control mechanisms. One of the most powerful paracrine regulators are the extracellular purines, ATP, adenosine diphosphate (ADP) and adenosine that alter cell function via specific cell surface receptors.[12] Purinoceptors are subdivided into P1 and P2 receptors. P1 receptors are responsive to adenosine and are more usually known as adenosine receptors (A1, A2a, A2b, and A3). P2 receptors are responsive to nucleotides (e.g., ATP, ADP) and are further subdivided into P2X (ligand-gated ion channel) and P2Y (G-protein coupled) receptors, each category having a number of subtypes.[45] As indicated earlier, A1 and P2X1 receptors are found in afferent arterioles and mediate vasoconstriction. Purinoceptors are also found in the apical and basolateral membranes of renal tubular cells. Stimulation of A1 receptors enhances proximal tubular reabsorption and inhibits CD Na^+ reabsorption, whereas stimulation of P2 receptors generally has an inhibitory effect on tubular transport.[45] Thus, luminally applied nucleotides, acting on a variety of P2 receptor subtypes, can inhibit Na^+ reabsorption in the proximal tubule, distal tubule, and CD, and stimulation of P2Y2 receptors in the CD inhibits vasopressin-sensitive water reabsorption.

Other metabolic intermediates regulate kidney function, and our understanding of their roles often relies on assigning a cognate ligand to an “orphan” G-protein coupled receptor. The Kreb’s cycle intermediate succinate stimulates renin release via GPR91, which may contribute to RAAS activation in type 2 diabetes.[46] Lactate, which accumulates in the kidney after ischemic injury, is the ligand for GPR81, which is expressed in the renal vasculature. Activation of GPR81 stimulates ET-1 release, causing renal vasoconstriction.47

Extracellular Vesicles and other Luminal Factors

All kidney cells release vesicles (including exosomes) and contain proteins, mRNA, and microRNA specific to their cell of origin and have generated much interest as a reservoir for kidney disease biomarker discovery. Vesicles released from one renal cell can be carried in the urine and taken up under hormonal control by downstream cells, influencing their function.48 Vesicles from distant organs, such as the liver and heart, are also able to transfer microRNA to kidney cells in vivo, but the full implications of this novel organ-to-organ communication system for health and disease are still unknown.49 Finally, recent studies have also shown the importance and potential clinical relevance of enzymes (serine proteases) in urine that can activate ENaC and thereby affect Na^+ reabsorption, particularly in proteinuric diseases such as the nephrotic syndrome when plasma proteases can be filtered and enter the glomerular filtrate.50

SELF-ASSESSMENT QUESTIONS

1. Filtration at the glomerulus is a passive process. Which of the following statements are true?
A. Albumin is too large to be freely filtered.
B. Albumin is not filtered because the glomerular barrier has a net positive charge.
C. Hydrostatic pressure in the glomerular capillaries is the only force influencing filtration rate.
D. Dilation of the afferent arteriole, but not the efferent arteriole, can increase filtration rate.
E. Mesangial cells do not influence filtration rate.
2. Fanconi syndrome is a disorder of the proximal tubule. Patients can present with glycosuria, polyuria, hypercalciuria, hyperphosphaturia, and low-molecular-weight proteinuria. These features can be explained by which of the following actions of the proximal tubule?
A. It reabsorbs about 100% of the filtered glucose.
B. It reabsorbs approximately 65% of the filtered water because of a large transepithelial osmotic gradient.
C. It actively reabsorbs calcium through Ca^{2+}-ATPase in the apical membrane.
D. It secretes phosphate through the organic anion transporter system.
E. It is a tight epithelium, impermeable to paracellular movement of proteins.
3. The corticomedullary osmotic gradient is required for urine concentration. Which of the following would diminish this gradient?
A. Increased circulating vasopressin.
B. Increased blood flow through the renal medulla.
C. Activation of the sympathetic nervous system.
D. Activation of the renin-angiotensin-aldosterone system.
E. Increased urea recycling through the collecting duct system.

REFERENCES

1. Kaverina NV, Eng DG, Freedman BS, et al. Dual lineage tracing shows that glomerular parietal epithelial cells can transdifferentiate toward the adult podocyte fate. Kidney Int. 2019;96(3):597–611.
2. Scott RP, Quaggin SE. The cell biology of renal filtration. J Cell Biol. 2015;209(2):199–210.
3. Amsellem S, Gburek J, Hamard G, et al. Cubilin is essential for albumin reabsorption in the renal proximal tubule. J Am Soc Nephrol. 2010;21(11):1859–1867.
4. Edwards A, Christensen EI, Unwin RJ, Anthony G, Norden W. Predicting the protein composition of human urine in normal and pathological states: quantitative description based on Dent1 disease (CLCN5 mutation). J. Physiol. 2021;599(1):323–341.
5. Wagner MC, Campos-Bilderback SB, Chowdhury M, et al. Proximal tubules have the capacity to regulate uptake of albumin. J Am Soc Nephrol. 2016;27(2):482–494.
6. Mori KP, Yokoi H, Kasahara M, et al. Increase of total nephron albumin filtration and reabsorption in diabetic nephropathy. J Am Soc Nephrol. 2017;28(1):278–289.
7. Hausmann R, Kuppe C, Egger H, et al. Electrical forces determine glomerular permeability. J Am Soc Nephrol. 2010;21:2053–2058.
8. Becker AS, Rossi C. Renal arterial spin labeling magnetic resonance imaging. Nephron. 2016.
9. Wan L, Yang N, Hiew C-Y, et al. An assessment of the accuracy of renal blood flow estimation by Doppler ultrasound. Intensive Care Med. 2008;34:1503–1510.
10. Cupples WA. Interactions contributing to kidney blood flow autoregulation. Curr Opin Nephrol Hypertens. 2007;16:39–45.
11. Kauffenstein G, Tamareille S, Prunier F, et al. Central role of P2Y6 UDP receptor in arteriolar myogenic tone. Arterioscler Thromb Vasc Biol. 2016;36:1598–1606.
12. Vallon V, Unwin R, Inscho EW, et al. Extracellular nucleotides and P2 receptors in renal function. Physiol Rev. 2020;100:211–269.
13. Holstein-Rathlou NH, Sosnovtseva OV, Pavlov AN, et al. Nephron blood flow dynamics measured by laser speckle contrast imaging. Am J Physiol Renal Physiol. 2011;300:F319–F329.
14. Komlosi P, Bell PD, Zhang ZR. Tubuloglomerular feedback mechanisms in nephron segments beyond the macula densa. Curr Opin Nephrol Hypertens. 2009;18:57–62.
15. Peppiatt-Wildman CM. The evolving role of renal pericytes. Curr Opin Nephrol Hypertens. 2013;22:10–16.
16. Regner KR, Roman RJ. Role of medullary blood flow in the pathogenesis of renal ischemia-reperfusion injury. Curr Opin Nephrol Hypertens. 2012;21:33–38.
17. Hall AM, Schuh CD. Mitochondria as therapeutic targets in acute kidney injury. Curr Opin Nephrol Hypertens. 2016;25:355–362.
18. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr Opin Nephrol Hypertens. 2020;29:190–198.
19. Koepsell H. The SLC22 family with transporters of organic cations, anions and zwitterions. Mol Aspects Med. 2013;34:413–435.
19a. Ponte B, Pruijm M, Ackermann D, et al. Uromodulin, salt, and 24hour blood pressure in the general population. Clin J Am Soc Nephrol. 2021;16(5):787–789.
20. Scolari F, Izzi C, Ghiggeri GM. Uromodulin: from monogenic to multifactorial diseases. Nephrol Dial Transplant. 2015;30:1250–1256.
21. Subramanya AR, Ellison DH. Distal convoluted tubule. Clin J Am Soc Nephrol. 2014;9:2147–2163.
22. Pearce D, Soundararajan R, Trimpert C, et al. Collecting duct principal cell transport processes and their regulation. Clin J Am Soc Nephrol. 2015;10:135–146.
23. Wall SM, Lazo-Fernandez Y. The role of pendrin in renal physiology. Annu Rev Physiol. 2015;77:363–378.
24. Weinbaum S, Duan Y, Satlin LM, et al. Mechanotransduction in the renal tubule. Am J Physiol Renal Physiol. 2010;299:F1220–F1236.

25. Ivy JR, Bailey MA. Pressure natriuresis and the renal control of arterial blood pressure. J Physiol. 2014;592:3955–3967.

26. Loffing J, Korbmacher C. Regulated sodium transport in the renal connecting tubule (CNT) via the epithelial sodium channel (ENaC). Pflugers Arch. 2009;458:111–135.
27. Hoorn EJ, Gritter M, Cuevas CA, Fenton RA. Regulation of the renal NaCl cotransporter and its role in potassium homeostasis. Physiol Rev. 2020;100:321–356.
28. Hunter RW, Bailey MA. Glucocorticoids and 11beta-hydroxysteroid dehydrogenases: mechanisms for hypertension. Curr Opin Pharmacol. 2015;21:105–114.
29. Bailey MA, Paterson JM, Hadoke PW, et al. A switch in the mechanism of hypertension in the syndrome of apparent mineralocorticoid excess. J Am Soc Nephrol. 2008;19:47–58.
30. Evans LC, Ivy JR, Wyrwoll C, et al. Conditional Deletion of Hsd11b2 in the brain causes salt appetite and hypertension. Circulation. 2016;133:1360–1370.
31. Zhai XY, Fenton RA, Andreasen A, et al. Aquaporin-1 is not expressed in descending thin limbs of short-loop nephrons. J Am Soc Nephrol. 2007;18:2937–2944.
32. Klein JD, Sands JM. Urea transport and clinical potential of urearetics. Curr Opin Nephrol Hypertens. 2016;25:444–451.
33. Neuhofer W, Beck FX. Cell survival in the hostile environment of the renal medulla. Ann Rev Physiol. 2005;67:531–555.
34. Noda Y, Sohara E, Ohta E, Sasaki S. Aquaporins in kidney pathophysiology. Nat Rev Nephrol. 2010;6(3):168–178.
35. Knepper MA, Kwon TH, Nielsen S. Molecular physiology of water balance. N Engl J Med. 2015;373(2):196.
36. Jeon US, Han KH, Park SH, et al. Downregulation of renal TonEBP in hypokalemic rats. Am J Physiol Renal Physiol. 2007;293:F408–F415.
37. Riccardi D, Valenti G. Localization and function of the renal calciumsensing receptor. Nat Rev Nephrol. 2016;12:414–425.
38. Ivy JR, Bailey MA. Non-dipping blood pressure: predictive or reactive failure of renal sodium handling? Physiology. 2021;36:21–34.
39. Garvin JL, Herrera M, Ortiz PA. Regulation of renal NaCl transport by nitric oxide, endothelin, and ATP: clinical implications. Annu Rev Physiol. 2011;73:359–376.
40. Nasrallah R, Hassouneh R, Hebert RL. PGE2, kidney disease, and cardiovascular risk: beyond hypertension and diabetes. J Am Soc Nephrol. 2016;27:666–676.
41. Hao CM, Breyer MD. Physiological regulation of prostaglandins in the kidney. Annu Rev Physiol. 2008;70:357–377.
42. Davenport AP, Hyndman KA, Dhaun N, et al. Endothelin. Pharmacol Rev. 2016;68:357–418.
43. Heerspink HJ, Parving H-H, Andress DL, et al. On behalf of the SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019;393:1937–1947.
44. Lynch J, Welch AK, Kohan DE et al. Endothelin-1 inhibits sodium reabsorption by ETA and ETB receptors in the mouse cortical collecting duct.
45. Menzies RI, Tam FW, Unwin RJ, Bailey MA. Purinergic signaling in kidney disease. Kidney Int. 2017;91(2):315–323.
46. Peti-Peterdi J. High glucose and renin release: the role of succinate and GPR91. Kidney Int. 2010;78:1214–1217.
47. Jones NK, Stewart K, Czopek A, et al. Endothelin-1 mediates the systemic and renal hemodynamic effects of GPR81 activation. Hypertension. 2020;75:1213–1222.
48. Morrison EE, Bailey MA, Dear JW. Renal extracellular vesicles: from physiology to clinical application. J Physiol. 2016;594:5735–5748.
49. Matthews O, Morrison EE, Tranter JD, et al. Transfer of hepatocellular microRNA regulates cytochrome P450 2E1 in renal tubular cells. EBioMedicine. 2020;62:103092.

50. Svenningsen P, Andersen H, Nielsen LH, Jensen BL. Urinary serine proteases and activation of ENaC in kidney: implications for physiological renal salt handling and hypertensive disorders with albuminuria. Pflugers Arch. 2015;467:531–542.

SECTION II Investigation of Renal Disease

3

Assessment of Glomerular Filtration Rate

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The level of glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. GFR decline is correlated with decline in other excretory functions of the kidney, such as tubular reabsorption and secretion, and with decline in endocrine and metabolic functions of the kidney. Decreased GFR is strongly associated with complications of acute kidney diseases and disorders (AKD) and chronic kidney disease (CKD), and decreased GFR is one criterion in the definition and staging of AKD and CKD. GFR estimating equations are now recommended for routine use in clinical practice, and estimated GFR (eGFR) is routinely reported when serum creatinine is measured.

GLOMERULAR FILTRATION RATE

GFR is the product of the average filtration rate of each nephron, the filtering unit of the kidneys, multiplied by the number of nephrons in both kidneys. The normal level for GFR is approximately 130 mL/min/1.73 m^2 for men and 120 mL/min/1.73 m^2 for women, with considerable variation among individuals according to age, sex, body size, physical activity, diet, blood pressure, glycemia, pharmacotherapy, and physiologic states such as pregnancy. To standardize GFR for differences in kidney size, which is proportional to body size, GFR is indexed for body surface area (BSA), computed from height and weight, and expressed per 1.73 m^2 BSA. Even after adjustment for BSA, GFR is approximately 8% higher in young men than in women and declines with age; the mean rate of decline is approximately 0.75 mL/min/yr after 40 years of age, but the variation is wide and the sources of variation are poorly understood. During pregnancy, GFR increases by about 50% in the first trimester and returns to normal immediately after delivery. GFR has a diurnal variation and is 10% lower at midnight compared with the afternoon. In an individual, GFR is relatively constant over short intervals of time but varies considerably among people, even after adjustment for the known variables.

Reductions in GFR may result from reduced nephron number from prematurity, nephrectomy or kidney disease, or reduced singlenephron (SN) GFR from physiologic or hemodynamic alterations. An increase in SNGFR caused by increased glomerular capillary pressure or glomerular hypertrophy can compensate for a decrease in nephron number; therefore the level of GFR may not reflect the loss of nephrons. As a result, there may be substantial kidney damage before GFR decreases.

MEASUREMENT AND ESTIMATION OF THE GLOMERULAR FILTRATION RATE

The GFR cannot be measured directly in humans. Instead, it is assessed from clearance measurements or serum levels of filtration markers, which are exogenous or endogenous solutes that are mainly eliminated by glomerular filtration. Both measured GFR (mGFR) and eGFR are associated with systematic and random error (bias and imprecision, respectively) in their determination and thus may differ from the “true GFR.”[1]

The classic method for GFR measurement described by Homer Smith is the urinary clearance of inulin and remains the reference (gold standard) against which other clearance methods and filtration markers are evaluated.[2] However, this technique is cumbersome in practice. Therefore many alternative clearance methods and filtration markers are used in clinical centers and as research tools (Table 3.1).[3] As discussed later, newer methods to measure GFR using plasma clearance of fluorescent tracer agents have been developed to shorten the measurement protocol, which might enable point-of-care GFR determination.

The GFR is generally estimated from serum levels of endogenous filtration markers to simplify GFR assessment without requiring administration of exogenous filtration markers and without performing clearance measurements.[4] The principles of GFR estimation are similar in adults and children.

CLEARANCE MEASUREMENTS

Concept of Clearance

Clearance of a substance is defined as the volume of plasma cleared of a marker per unit of time. The clearance of substance x (C_x) can be calculated as $C_x = A_x/P_x$, where A_x is the rate of elimination of x from the plasma, P_x is the average plasma concentration, and C_x is expressed in units of volume per time. Clearance does not represent an actual volume; rather, it is a virtual volume of plasma that is completely cleared of the substance per unit of time. The value for clearance is related to the efficiency of elimination: the greater the efficiency of elimination, the higher the clearance. Clearance of substance x is the sum of the urinary (renal) and nonurinary (extrarenal) clearance; for substances that are eliminated by both renal and extrarenal routes, plasma clearance exceeds urinary clearance.

By convention we refer to concentration of the substance in plasma when discussing physiologic principles and serum when discussing

TABLE 3.1

Exogenous Filtration Markers for Estimation of Glomerular Filtration Rate

Marker	Clearance Method	Comments
Inulin	Urinary or plasma clearance during continuous IV infusion	Gold standard.
Iothalamate	Urinary or plasma clearance after bolus IV injection. Urinary clearance after subcutaneous bolus injection	Can be administered as radioactive compound with iodine 125 (125I) as the tracer or in nonradioactive form, with assay using HPLC or MS methods in plasma and whole blood. In radioactive form, potential problem of thyroid uptake of 125I. Iothalamate is secreted, leading to overestimation of GFR.
99mTc-DTPA	Urinary or plasma clearance after bolus IV injection	Dissociation of 99mTc leads to plasma protein binding and underestimation of GFR.
51Cr-EDTA	Urinary or plasma clearance after bolus IV injection	10% lower clearance than inulin.
Iohexol	Plasma clearance after bolus IV injection	Low incidence of adverse effects; assay using HPLC or MS methods in plasma and whole blood. Research studies have used capillary blood spots. Iohexol may have extrarenal clearance, leading to overestimation of GFR.
Novel engineered markers conjugated to fluorescein[a]	Plasma clearance or transdermal fluorescence after bolus IV injection	Requires less time than plasma clearance of filtration marker alone. Neither are FDA approved for clinical use as of yet. Initial studies in small samples show strong correlation with iohexol plasma clearance.

[a] The

two novel markers include relmapirazin (Lumitrace), a novel agent that has been engineered to not interact with the body and be excreted by the kidney, and visible fluorescent injectate (VFI), which consists of a 150-kDa rhodamine derivative, used to assess plasma volume, and a 5-kDa fluorescein carboxymethylated dextran, used to assess GFR.

^{51}Cr-EDTA, Chromium 51–labeled ethylenediaminetetraacetic acid; GFR, glomerular filtration rate; HPLC, high-performance liquid chromatography; IV, intravenous; MS, mass spectrophotometric; ^{99m}Tc-DTPA, technetium 99m–labeled diethylenetriaminepentaacetic acid.

clinical measures. In practice, laboratory measurements of markers of glomerular filtration are similar in plasma and serum and are generally referred to as serum concentrations.

(A_x) divided by the average plasma concentration (P_x), which can be computed from the area under the curve of plasma concentration versus time.

$$C_x = A_x / P_x$$

Urinary Clearance

The rate of urinary excretion of substance x can be calculated as the product of the urinary flow rate (V) and the urinary concentration (U_x). Therefore urinary clearance is defined as follows:

$$C_x = (U_x \times V)/P_x$$

The rate of urinary excretion of a substance depends on the rates of filtration, tubular secretion, and tubular reabsorption. Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers because their urinary clearance can be used as a measure of GFR. For substances that are filtered and secreted, urinary clearance exceeds GFR, and for substances that are filtered and reabsorbed, urinary clearance is less than GFR.

Measurement of urinary clearance requires a timed urine collection for measurement of urine flow rate, as well as urine and plasma concentrations of the filtration marker. The classic protocol of Smith[2] used a continuous intravenous infusion to achieve a steady state and bladder catheterization with multiple timed urine collections. Alternative protocols to assess urinary clearance have been validated, including bolus intravenous or subcutaneous administration rather than continuous intravenous infusion and spontaneous bladder emptying rather than bladder catheterization.[3] Bolus administration of the marker results in declining plasma levels of the filtration markers during the clearance measurement, which may cause errors in determining the average plasma concentration during the clearance measurement.

Plasma Clearance

Measurement of plasma clearance avoids the need for a timed urine collection. GFR is calculated from plasma clearance (C_x) after bolus intravenous administration of an exogenous filtration marker, with the clearance (C_x) computed from the amount of the marker administered

The decline in the plasma level is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component).

Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually two or three time points until 60 minutes) and late (one to three time points from 120 minutes onward).[5] Novel methods are under investigation to shorten the time required for clearance measurements.[6,7] As with urinary clearance, plasma clearance of a substance depends on filtration, tubular secretion, and tubular reabsorption, but, in addition, extrarenal elimination and the time course for equilibration of the filtration marker between plasma and its volume of distribution. Edematous conditions prolong the distribution from plasma to extracellular fluid and may cause error in GFR. Extrarenal elimination has been demonstrated for several filtration markers.

Accuracy of Clearance Measurements

Sources of errors in measuring GFR include biologic variation in GFR, “nonideal” handling of the filtration marker by the kidney (incomplete filtration, nonzero tubular reabsorption or secretion), measurement error in the serum or urine assays for filtration markers, and measurement error in serum or urine collections. By definition, the classic method of Smith is unbiased, but it may be imprecise. The coefficient of variation (CV) for repeated measurements in individuals using this method is approximately 7%. For other procedures, the smallest reported within-person CVs for repeated measures on different days range from approximately 5% to 15%, with larger values for urinary clearance than for plasma clearances. For a measurement method without bias compared with true GFR, a CV of 10% is equivalent to approximately 90% of measures being within 15% of true GFR (P15 of 90%).

Relationship of GFR and Non-GFR Determinants to Serum Levels

G (cells)

G (diet)

P

$U \times V$
(kidney)

$U \times V =$
$GFR \times P - TR + TS$
$G - E =$
$GFR \times P - TR + TS$
$GFR =$
$(G + TR - TS - E) / P$

E (gut, liver)

Fig. 3.1 Relationship of GFR and non-GFR Determinants to Serum Levels. G, Generation; GFR, glomerular filtration rate; E, extrarenal elimination; P, plasma; TR, tubular reabsorption; TS, tubular secretion. (Modified from Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis. 2014;63[5]:820-834.)

ESTIMATION OF THE GLOMERULAR FILTRATION RATE

Fig. 3.1 shows the relationship of plasma concentration of substance x to its generation (G_x) by cells and dietary intake, urinary excretion ($U_x \times V$), and extrarenal elimination (E_x) by gut and liver. The plasma level is related to the reciprocal of the level of GFR, but it is also influenced by generation, tubular secretion and reabsorption, and extrarenal elimination, collectively termed non-GFR determinants of the plasma level.[4]

In the steady state, a constant plasma level of substance x is maintained because the rate of generation is equal to the sum of the rates of urinary excretion and extrarenal elimination. Estimating equations incorporate demographic and clinical variables as surrogates for the non-GFR determinants and provide a more accurate estimate of GFR than the reciprocal of the plasma level alone. Most GFR estimating equations have been developed using linear regression to relate observed values of mGFR and serum concentration of the filtration marker, modified by demographic or clinical variables. Another method, as exemplified by the Full Age Spectrum (FAS) equations (see below), is based on hypothetical relationships based on assumptions about age- and sex-adjusted normal values for endogenous filtration markers, age-adjusted normal values for mGFR, and reciprocal changes in mGFR for deviations in observed filtration marker concentrations.[8] Recently, equations have been developed using some features of both methods.

Irrespective of the method for equation development, eGFR in an individual may differ from mGFR if a discrepancy exists between the true and average values of the surrogates for the non-GFR determinants of the filtration marker. Other sources of errors include measurement error in the filtration marker (e.g., failure to calibrate assay for filtration marker to assay used in development of equation), measurement error in mGFR method used in development of the equation, and regression to the mean. In principle, the absolute magnitude of these errors is likely to be greater at higher values for GFR, although such errors may be more clinically significant at lower mGFR. Accuracy of eGFR, as assessed as the percent of eGFR within 30% of mGFR (P30) of 80% to 90%, is generally considered adequate for many clinical circumstances;

P30 greater than 90% would be optimal.

For application to general populations, GFR estimating equations should be developed and validated in diverse populations including a wide range in age, race-ethnicity, and clinical conditions. To facilitate best practices and communication among patients, providers, and public, a single equation should be used for each filtration marker or combination of filtration markers, and clinical laboratories should automatically report eGFR whenever the filtration marker is measured.

Filtration Markers

Solutes with molecular weight less than approximately 20,000 Da and not bound to plasma proteins are freely filtered by the glomeruli and are candidate filtration markers.

Exogenous Filtration Markers

Iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid, often chelated to radioisotopes for ease of detection, are commonly used alternatives to inulin (see Table 3.1).[3] Deviations from ideal behavior of the filtration marker can be inferred from differences from inulin clearance during simultaneous clearance measurements. The most common methods used in the United States are urinary clearance of iothalamate after subcutaneous bolus administration and plasma clearance of iohexol after intravenous bolus administration.[9] Of note, the doses of iothalamate and iohexol that are used to measure GFR are far below the doses used for contrast imaging that have been associated with kidney toxicity and acute kidney injury. The challenge with both methods is assay of the exogenous marker using high performance liquid chromatography for iohexol in plasma samples or capillary blood spots, ^{125}I-labeling for iothalamate, or mass spectroscopy (for both).[10]

Endogenous Filtration Markers

Endogenous filtration markers are substances generated in the body at a relatively constant rate and eliminated largely by glomerular filtration. The plasma level correlates highly with mGFR after accounting for the non-GFR determinants. Currently identified endogenous filtration markers include metabolites (such as creatinine and urea) and low-molecular-weight plasma proteins (such as cystatin C) (Table 3.2). Filtered metabolites may undergo reabsorption or secretion, which may be assessed by comparing their urinary clearance to urinary clearance of exogenous filtration markers. By contrast, filtered plasma proteins are reabsorbed and degraded within the tubule with minimal appearance in the urine. For metabolites excreted in the urine, urinary clearance can be computed from a timed urine collection and a single measurement of serum concentration. If the serum concentration is not constant during the urine collection, as in acute kidney disease or when residual kidney function is assessed in patients undergoing intermittent dialysis, it is necessary to obtain additional blood samples during the urine collection to estimate the average serum concentration.

CREATININE

Metabolism and Excretion

Creatinine is a 113 Da end product of muscle catabolism. Advantages of creatinine include its ease of measurement and the low cost and widespread availability of assays (see Table 3.2). Disadvantages include the large number of conditions affecting its non-GFR determinants, leading to a wide range of GFR for a given serum creatinine level (Table 3.3). For example, a serum creatinine level of 1.5 mg/dL (132 µmol/L) may correspond to a GFR from approximately 20 to 90 mL/min/1.73 m^2

Creatinine is derived by the metabolism of phosphocreatine in muscle, as well as from dietary meat intake or creatine supplements. Creatinine generation is proportional to muscle mass, which can be estimated from age, sex, and body size, but many other factors can affect creatinine generation. Creatinine is distributed in total body water, not protein bound, and freely filtered across the glomerulus and secreted by

TABLE 3.2

Creatinine, Cystatin C, and Urea as Endogenous Filtration Markers

Variable

Creatinine

Cystatin C

Molecular Properties
Weight (Da)

113

13,000

60

Structure

Amino acid derivative

Nonglycosylated basic protein

Organic molecular product of protein metabolism

Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women

Varies, according to dietary protein intake and catabolism

Physiologic Determinants of Serum Level
Generation
Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and Whites

Urea

Handling by kidney

Filtered, secreted, and excreted in urine

Filtered, reabsorbed, and catabolized

Filtered, reabsorbed, and excreted in urine

Extrarenal elimination

Yes; increases at reduced GFR

Preliminary evidence of increases at reduced GFR

Yes; increases at reduced GFR

Age, sex

Not applicable

Use in Estimating Equations for GFR
Demographic and clinical
Age, sex, and race; related to muscle
variables as surrogates for
mass
physiologic determinants
Accuracy

Accurate for GFR <60 mL/min/1.73 m2

Unknown

Not applicable

Assay
Method

Colorimetric or enzymatic

PENIA, PETIA, or ELISA

Direct measurement, enzymatic
colorimetric, and electrochemical

Assay precision

Very good except at low range

Precise throughout range, but difficult to
standardize

Precise throughout range

Clinical laboratory practice

Multiple assays; widely used
nonstandard calibration

Not on most autoanalyzers; not
standardized

Multiple assays; enzymatic and
colorimetric more common

Standardized recommendation
materials (SRMs)

SRM 967

ERM-DA471/IFCC

SRM 912a

Reference assay

IDMS

PENIA, PETIA, or ELISA

IDMS

ELISA, Enzyme-linked immunosorbent assay; GFR, glomerular filtration rate; IDMS, isotope-dilution–mass spectroscopy; PENIA, particle-enhanced nephelometric immunoassay; PETIA, particle-enhanced turbidimetric immunoassay.

the tubules. Several medications, such as cimetidine, trimethoprim, and fenofibrate, competitively inhibit creatinine secretion, leading to a rise in the serum creatinine concentration without an effect on GFR.

In addition, creatinine is contained in intestinal secretions and can be degraded by bacteria; gastrointestinal elimination of creatinine is increased at higher levels of serum creatinine but can be reduced by changes in gut flora due to antibiotic use. Clinically, it can be difficult to distinguish a rise in serum creatinine concentration caused by inhibition of tubular secretion or extrarenal elimination of creatinine from a decline in GFR.

Creatinine clearance (Clcr) is usually computed from the creatinine excretion in a 24-hour urine collection and single measurement of serum creatinine in the steady state. Creatinine excretion rates vary with age and sex with mean levels of approximately 20 to 25 mg/kg/d and 15 to 20 mg/kg/d in a complete collection in healthy young men and women, respectively. Deviations from estimated creatinine excretion (based on age, sex, weight, and other variables)[11] can indicate errors in timing or completeness of urine collection but cannot be relied on because of wide variability in creatinine generation.

Creatinine Assay

Historically, the most common assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine can interfere with the assay, causing errors of up to 20% in normal individuals. Enzymatic methods are less susceptible to interference, and their use is increasing. Reference materials traceable to an isotope-dilution–mass spectrometry (IDMS) are now available to standardize creatinine measurements, and most manufacturers have now calibrated their instruments using these reference materials.[12,13] Standardization has reduced but not eliminated the error in estimating GFR at higher levels.

Estimated Glomerular Filtration Rate From Serum Creatinine

GFR can be estimated from serum creatinine (eGFRcr) by equations that use demographic factors or body size as surrogates for the non-GFR determinants, principally creatinine generation. Despite ongoing refinements in recent years, GFR estimates remain imprecise; none of the equations is expected to work as well in patients with extreme levels for creatinine generation, such as large or small individuals, amputees, bodybuilders, patients with muscle-wasting conditions, or people with an atypical pattern of meat consumption (see Table 3.3). As discussed later, further improvements will probably require additional filtration markers.

Equations Currently Recommended for Use

The Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) 2009 and 2021 creatinine equations were developed from a large

Factors Affecting Serum Creatinine and Cystatin C Concentrations Independent From Glomerular Filtration Rate

TABLE 3.3

Factors	Effect on Creatinine (Direction/Mechanism)	Effect on Cystatin C (Direction/Mechanism)
Age	Decrease Lower creatinine generation presumed due to decline in muscle mass. Effect on tubular secretion and extraelimination unknown.	Decrease Presumed lower cystatin C generation caused by decreased cellular mass, smaller influence than creatinine. Effect on extraelimination unknown.
Female sex	Decrease Lower creatinine generation presumed due to lower muscle mass. Effect on tubular secretion and extraelimination unknown.	Decrease Presumed lower cystatin C generation caused by lower cellular mass, smaller influence than creatinine. Effect on extraelimination unknown.
	Increase Cause unknown; higher creatinine generation and lower tubular secretion of creatinine observed in some studies, but not consistent. Effect on extraelimination unknown. Factors less well known for race and ethnic groups other than African Americans or Whites.	No effect
	Decrease Lower creatinine generation.	No effect
	Increase Transient increase in creatinine generation, although this may be blunted by transient increase in GFR.	No effect
	Increase Higher muscle generation caused by increased muscle mass and/or increased protein intake.	No effect

Smaller muscle mass (e.g., amputation, anorexia)

Decrease
Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake.

No effect

Malnutrition, muscle wasting, in context of chronic illness

Decrease
Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake.

Possible increase
Presumed higher cystatin C generation in conditions associated with inflammation.

Obesity

No change
Excess fat mass, not muscle mass, which does not contribute to creatinine generation.

Increase
Presumed higher cystatin C generation by excess fat mass.

Increase
Reduced tubular secretion of creatinine.

No known effects, not studied

Interference with alkaline picrate assay for creatinine.

No known effects, not studied

Race
Self-identified African American or Black in US or European studies, or African ancestry

Diet
Vegetarian
Ingestion of cooked meats and creatinine supplements
Body Habitus
Larger muscle mass

Medications
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil, dolutegravir, and cobicistat PARP inhibitors,a tyrosine kinase inhibitorsb
Ketoacids, some cephalosporins
aSuch

as olaparib and rucaparib.
as imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, and pazopanib.
GFR, Glomerular filtration rate; PARP, poly-ADP ribose polymerase.

bSuch

database of adults, including those with and without kidney disease, with and without diabetes, and with and without a history of organ transplantation.14 The 2009 equation includes age, sex, and race (categorized as African American vs. non–African American), and standardized serum creatinine. It estimates mGFR assessed from urinary clearance of iothalamate. It uses a two-slope “spline” for serum creatinine and is accurate across the full range of eGFR. It has been

extensively validated and is accurate across a wide range of patient characteristics, including age, sex, race, body mass index (BMI), and presence or absence of diabetes or history of organ transplantation. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that clinical laboratories use CKD-EPI creatinine equations to report eGFR in adults in North America, Europe, and Australia whenever serum creatinine is measured or to use other

Relevant Guidelines, GFR Calculators, and Other Information About Assessment of GFR

BOX 3.1

KDIGO Guideline 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease15: http://kdigo.org/guidelines/ckd-evaluation-andmanagement/
Guideline for Acute Kidney Injury74: http://kdigo.org/guidelines/acute-kidneyinjury/
KDIGO Clinical Practice Guideline on the Evaluation and Follow-Up Care of Living Kidney Donors78: http://kdigo.org/guidelines/living-kidney-donor/
KDIGO Controversy Conference on Drug Prescribing in Kidney Disease: Initiative for Improved Dosing82: https://kdigo.org/conferences/drug-prescribingin-ckd/
U.S. Department of Health and Human Services—Food and Drug Administration: Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing: https://www.fda.gov/media/78573/download
Chronic Kidney Disease Epidemiology Collaboration (CKP-EPI): https://www.tuftsmedicalcenter.org/CKDEPI

equations if they are shown to be superior to CKD-EPI equations in other populations (Box 3.1).15

The 2021 equation was developed from the same dataset used for development of the 2009 equation without inclusion of a term for Black race, in response to the call to remove race from clinical algorithms in medicine.16–19 It is less accurate than the 2009 equation but sufficiently accurate for use in clinical practice and more accurate than prior equations. Importantly, it avoids potential for misclassification by race in a multiracial population.20–22 The 2021 equation is now recommended for use by the American Society of Nephrology and National Kidney Foundation.23

There is insufficient information on racial and ethnic groups other than African-American and White individuals to be certain about the accuracy of GFR estimates in these populations.

The Chronic Kidney Disease in Children (CKiD) 2009 creatinine equation was developed from a moderate-sized study of children with CKD and decreased GFR.24 The equation uses height and standardized serum creatinine to estimate mGFR assessed from plasma clearance of iohexol. It underestimates mGFR at higher eGFR. The 2012 KDIGO guidelines recommend its use for children with kidney disease but do not recommend reporting eGFR whenever serum creatinine is measured in children. An updated and more accurate equation (CKiD 2021) is based on a larger sample size with age up to 25 years, and uses age and sex in addition to height and recalibrated iohexol measurements.25 Of note, the CKD-EPI and CKiD creatinine equations often give different results in the transition years from adolescence to young adulthood, reflecting their development in separate study populations.

Equations Previously Recommended for Use

The Cockcroft-Gault equation for adults, developed in 1976, estimates measured Clcr from serum creatinine, age, sex, and body weight, in addition to serum creatinine.26 Comparison to normal values for Clcr requires computation of BSA and adjustment to 1.73 m^2. The Cockcroft-Gault formula has several limitations. First, it is not precise, in particular in the GFR range above 60 mL/min. Second, it estimates Clcr rather than GFR and thus is expected to overestimate mGFR. Third, the formula was derived by older assay methods for serum creatinine, which cannot be calibrated to newer assay methods and would be expected to lead to variable systematic bias in estimating Clcr (generally an overestimate). Fourth, it systematically overestimates measured Clcr in edematous or obese patients. Fifth, the large age term

means that all older adults will have lower levels of estimated GFR.

The Schwartz equation for children, developed in 1976, estimates measured Clcr using serum creatinine and height.27 When using standardized creatinine, it overestimates mGFR.

The Modification of Diet in Renal Disease (MDRD) study equation for adults was developed in 199928 and updated for use with standardized serum creatinine in 2006.29 It is more accurate than the CockcroftGault equation.30 However, it was derived from a study population with CKD, so it underestimates the mGFR in populations with higher levels of GFR, and numeric values should not be reported for GFR levels greater than 60 mL/min/1.73 m2 31

Other Equations That Could Be Considered for Use in Selected Populations

The Lund-Malmo Revised (LMR) equation for adults and the Berlin Initiative Study (BIS) equation for the elderly (age ≥70 years) use standardized creatinine and were developed in European and US populations that predominantly included White participants.32 33 The FAS 2016 creatinine equation is based on hypothetical relationships rather than linear regression, which overcomes the limitation of discontinuity at the transition from adolescence to young adulthood.34 Variations of the FAS equations combined with features of equations derived from linear regression have also been proposed.35–37 These equations were derived from data on White persons from North America and Europe and appear as accurate as the CKD-EPI equation in White persons but less accurate in African-American persons.38–41 Other equations have been developed in Asian and African populations that improve the accuracy of GFR estimates in the study population; however, the equations do not generalize well to other populations.42–47

CYSTATIN C

Metabolism and Excretion

Cystatin C is a 122–amino acid protein with molecular weight of 13 kDa (see Table 3.2).48 Cystatin C is produced in all nucleated cells and is distributed in extracellular fluid. In health, approximately 99% of the filtered cystatin C is reabsorbed by the proximal tubular cells, where it is almost completely catabolized, with the remainder eliminated in the urine largely intact; in kidney disease, tubular uptake may be impaired, leading to an increase in urinary excretion.49

Some evidence suggests the existence of tubular secretion and extrarenal elimination. Smoking, inflammation, adiposity, thyroid diseases, certain malignant neoplasms, and use of glucocorticoids appear to be associated with higher cystatin C levels independent of mGFR.50 51 Therefore factors other than GFR must be considered in interpreting cystatin C levels.

Cystatin C Assay

Several assays are available (all more expensive than those for creatinine). Reference materials for standardization of cystatin C from the International Federation of Clinical Chemists (IFCC) are now available, and standardization across clinical laboratories is improving.52–54

Estimated Glomerular Filtration Rate From Serum Cystatin C

Cystatin C is less affected by muscle than creatinine and is less affected by age, sex, and race than creatinine. However, eGFR based on serum cystatin C (eGFRcys) is not more accurate than eGFRcr, because of variation in other conditions affecting non-GFR determinants of serum cystatin C. Equations combining both these filtration markers (eGFRcrcys) appear to be more precise than equations using either marker alone.

The 2012 CKD-EPI cystatin C and creatinine–cystatin C equations for adults were developed from a large database of adults, including those with and without kidney disease or diabetes, are expressed for use with standardized serum creatinine and cystatin C and are recommended by the 2012 KDIGO guidelines (see Box 3.1).15 55 The creatinine–cystatin C equation uses age, sex, and race, whereas the cystatin C uses age and sex without race. The 2021 creatinine–cystatin C equation was derived from the same dataset as the 2012 equation and is almost as accurate but does not use race. In patients with reduced muscle mass (e.g., neuromuscular or liver disease, low BMI) or in patients with diabetes, eGFRcys may be more accurate than eGFRcr. Other recent equations using cystatin C have been developed; most but not all studies show that regional modifications appear to be less important for eGFRcys than for eGFRcr 33 56–58

Some studies show that a lower eGFRcys is a better predictor of the risk for cardiovascular disease and total mortality than is a lower eGFRcr 59 In our view, this is likely due to confounding by non-GFR determinants of cystatin C and creatinine. Because of better accuracy and risk prediction, eGFRcr-cys is recommended as a confirmatory test for CKD, but full implementation will require standardization, greater availability, and cost reductions of cystatin C assays, as well as better understanding of non-GFR determinants of serum cystatin C (see Box 3.1).

The CKiD creatinine–cystatin C equation (also including urea nitrogen) for children was developed in 2009 and updated in 2012 but is not expressed for use with standardized cystatin C assays.24 60 A CKiD 2021 cystatin C equation estimates mGFR and uses standardized cystatin C, age, sex, and height and recalibrated iohexol measurements.25 Several equations are available for use in children and adults.

The Caucasian Asian Pediatric and Adult (CAPA) equation, developed in 2014, estimates mGFR using variety of methods and includes only age and standardized serum cystatin C; the FAS 2017 cystatin C equation includes age, sex, and standardized serum cystatin C and performs similarly to the CKD-EPI 2012 cystatin C equation; and the FAS 2017 creatinine–cystatin C equation performs similarly to the CKD-EPI 2012 creatinine–cystatin C equation.53 61

UREA AND OTHER METABOLITES

The serum urea level has limited value as an index of GFR, in view of widely variable non-GFR determinants, primarily urea generation and tubular reabsorption (see Table 3.2).

Urea is a 60 Da end product of protein catabolism by the liver. Factors associated with the increased generation of urea include protein loading from hyperalimentation and absorption of blood after a gastrointestinal hemorrhage. Catabolic states caused by infection, corticosteroid administration, or chemotherapy also increase urea generation. Decreased urea generation is seen in patients with severe malnutrition and liver disease.

Urea is freely filtered by the glomerulus and then passively reabsorbed in both proximal and distal nephrons. As a result of tubular reabsorption, urinary clearance of urea underestimates GFR. Reduced kidney perfusion in the patient with volume depletion and states of antidiuresis are associated with increased urea reabsorption. This leads to a greater decrease in urea clearance than the concomitant decrease in GFR. At mGFR of less than about 20 mL/min/1.73 m2, the overestimation of mGFR by measured Clcr resulting from creatinine secretion approximates the underestimation of measured GFR by measured urea clearance from urea reabsorption; thus the average of measured creatinine and urea clearance approximates the mGFR.

Recent advances in assays for metabolites have revealed a number of compounds that are highly correlated with mGFR and could be used for GFR estimation.62 An eGFR from a panel of four novel metabolites (pseudouridine, acetylthreonine, phenylacetylglutamine, and tryptophan) without demographic factors was as accurate as eGFRcr and eGFRcys but not more accurate than eGFRcr-cys; the most accurate equation included the four novel metabolites, creatinine, cystatin C, and demographic characteristics.[63] Assays for the four novel metabolites are not available.

OTHER LOW-MOLECULAR-WEIGHT SERUM PROTEINS

β2-Microglobulin (β2M) and β-trace protein (βTP) are low-molecularweight serum proteins being evaluated as filtration markers for estimating GFR and for their role in prognosis. As with cystatin C, β2M and βTP are freely filtered by the glomerulus and extensively reabsorbed and degraded by the proximal tubule, with only small amounts excreted in the urine under normal conditions.

Serum β2M and βTP levels are more strongly correlated with mGFR than serum creatinine and, like cystatin C, they are less influenced by age and sex than creatinine. The CKD-EPI 2020 eGFR from a panel of all four markers, age, and sex without race is as accurate as the CKDEPI 2012 creatinine–cystatin C equation that requires race.[64] In addition, studies have shown that β2M and βTP are better predictors of adverse health outcomes than creatinine and are potentially as accurate as cystatin C in the general population and in patients with CKD.[65] A recent study shows that serum β2M and βTP can be used to estimate residual kidney function in patients on dialysis.[66,67] The likely explanation is that they are too large to be filtered by conventional hemodialysis membranes or the peritoneum, so their serum concentrations reflect residual kidney function rather than the dialysis dose. β2M and βTP assays are not standardized across clinical laboratories, and further study of the usefulness of these equations in clinical practice is required.

CLINICAL APPLICATION OF ESTIMATED GLOMERULAR FILTRATION RATE

Chronic Kidney Disease

CKD is a heterogeneous group of disorders characterized by abnormalities in kidney structure or function for more than 3 months with implications for health. Estimation of GFR is necessary for the detection, evaluation, and management of patients with CKD. GFR less than 60 mL/min/1.73 m^2 for 3 months or longer is one of the criteria for the definition of CKD (see Box 3.1).[15] Guidelines recommend testing of patients at increased risk for CKD for decreased GFR and albuminuria, as a marker of kidney damage, and recommend staging of kidney disease severity and estimating prognosis using levels of albuminuria and GFR (see Box 3.1).[15] The Kidney Failure Risk Equation uses age, sex, GFR, and urine albumin-to-creatinine ratio to predict the risk for onset of kidney replacement therapy (KRT) within 2 or 5 years.[68]

Use of serum creatinine alone as an index of GFR is not recommended and can lead to delays in detection of CKD and misclassification of the severity of CKD. Use of estimating equations allows reporting of eGFR by clinical laboratories whenever serum creatinine is measured. Current estimating equations are less accurate in people with variation in non-GFR determinants of serum creatinine concentration (see Table 3.3). In these patients, more accurate GFR estimates require additional testing, such as measurement of cystatin C, measured Clcr, or mGFR. The KDIGO CKD guidelines recommend use of eGFRcr as an initial test followed by eGFRcr-cys or a clearance measurement for confirmation in conditions in which eGFR may be inaccurate (Fig. 3.2).[1] Examination of the consistency of GFR estimates and clearance measurements is recommended. If the results are inconsistent, clinicians should consider possible explanations, such as differences between observed and expected creatinine excretion for measured Clcr and non-GFR determinants of creatinine and cystatin C for eGFR, then eliminate the inconsistent value from consideration, repeat the measurement, or determine mGFR using an exogenous marker.

Approach to the Evaluation of GFR

Initial test: eGFRcr

Assessment of GFR
15 30 45 60

90

120

eGFR P30 ~90%
±30%
21–39

Consider sources of error and need
for more accurate assessment

±30%
42–78
Assessment of GFR

No

Yes

Perform confirmatory tests
and assess their consistency

15

30

45

±15%
24.5–34.5

60

90

120

±15%
51–69
mGFR P15 ~90%

Assessment of GFR
15 30 45 60

90

120

Clinical application
Fig. 3.2 An Approach to the Evaluation of GFR. Our approach is to use initial and confirmatory testing to
develop a final assessment of true glomerular filtration rate (GFR) and to apply it in individual decision-making.

Left, We would initially estimate GFR using serum creatinine (eGFR cr)—the findings from this assessment must be interpreted in light of its limitations. Estimation of GFR based on serum cystatin C (eGFR cys), both creatinine and cystatin C (eGFRcr-cys), and measured creatinine clearance (Clcr) are useful confirmatory tests in some circumstances, and measured GFR (mGFR) is an appropriate confirmatory test if available and performed using an accurate procedure. We recommend using the most convenient confirmatory test that will enable clinical decision-making, recognizing that more than one confirmatory test might be required. Clinical application of the findings requires additional clinical information, for example, a clinical action plan based on chronic kidney disease GFR categories, drug-dosing recommendations, or use in predictive instruments.
Right, It is important to determine how accurate an assessment of GFR needs to be for clinical decisionmaking. If accuracy within 30% is acceptable, eGFR may be sufficient, provided that there are not large deviations in non-GFR determinants of creatinine or cystatin C. If greater accuracy is needed, mGFR is recommended, and some methods can provide accuracy of within 15%. At a GFR of 60 mL/min/1.73 m 2, 30% accuracy for eGFR corresponds to an eGFR of 42 to 78 mL/min/1.73 m 2, and 15% for mGFR corresponds to 51 to 69 mL/min/1.73 m2. At a GFR of 30 mL/min/1.73 m2, 30% accuracy for eGFR corresponds to eGFR of 21 to 39 mL/min/1.73 m2, and 15% for mGFR corresponds to 25.5 to 34.5 mL/min/1.73 m 2. (Modified from Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol. 2020;16[1]:51–64.)

Change in serum creatinine is routinely used to assess the progression of kidney disease in populations, and quantitative associations with risk for KRT are now available. Changes in eGFR over 1 to 3 years were associated with higher risk for developing KRT in the subsequent time period compared with a stable eGFR for people at high and lower levels of eGFR.69 70 The current level of eGFR was more strongly associated with risk of KRT than the rate of decline.71 Similar results were observed for associations with mortality. A meta-analysis and statistical simulation from clinical trials demonstrates conditions in which an eGFR decline could be a valid surrogate endpoint for kidney disease progression.72 73

Acute Kidney Disease

AKD is a heterogeneous group of disorders characterized by abnormalities in kidney structure or function for 3 months or less with implications for health. Acute kidney injury (AKI) is a subset of AKD

in which the decline in GFR is sufficient to cause an increase in serum creatinine by 0.3 mg/dL over 48 hours or by 50% over 7 days (see Box 3.1).74 Change in GFR induces a nonsteady state in the serum levels of endogenous filtration markers (Fig. 3.3). After a decline in GFR, there is a lag before the rise in serum level because of the time required for retention of an endogenous filtration marker. Conversely, after recovery of GFR, there is a lag before the excretion of the retained marker.
During the nonsteady state, neither the serum level nor the GFR estimated from the serum level accurately reflects the mGFR. Nonetheless, a change in the eGFR in the nonsteady state can be a useful indication of the magnitude and direction of the change in mGFR. If the eGFR is decreasing, the decline in eGFR is less than the decline in mGFR. Conversely, if the eGFR is increasing, the rise in eGFR is greater than the rise in mGFR. The more rapid the change in eGFR, the greater is the change in measured GFR. When eGFR reaches a new steady state, it more accurately reflects mGFR. A GFR estimating equation for use

Effect of a Sudden Decrease in Glomerular Filtration Rate
on Endogenous Marker
Acute GFR Decline
120

120
90

90

GFR

60

60

Marker Generation

Marker Filtration
and Excretion

Time
0
1.5
2.0
2.5
3.0

Smarker eGFR
1.0
135
1.6
79
1.8
69
1.9
65
2.0
60

Cumulative
marker balance

2.0

2.0
1.5

1.5
Serum Marker
Concentration

1.0

0

1.0

1

2
3
4
Time

Fig. 3.3 Change in Serum Creatinine and eGFR after a Sudden Decrease in GFR. Graphs show the effect of acute GFR decline (top) on generation, filtration and excretion, balance of endogenous marker (middle), and concentration of serum marker (Smarker) (bottom).

in the nonsteady state has been proposed (“kinetic eGFR”), but has not yet been validated compared with change in mGFR.75

Simulations of creatinine kinetics after an abrupt GFR decline shows that the absolute and proportionate increase in serum creatinine are influenced by the baseline GFR and the magnitude of decline in GFR.76 In patients with AKI, serum cystatin C appears to increase more rapidly than serum creatinine.77 More data are required to establish whether changes in serum cystatin C are a more sensitive indicator of rapidly changing kidney function than changes in serum creatinine. In addition, similar to CKD, eGFRcr might be inappropriate in patients with differences in muscle mass or dietary protein intake, and in such patients it would be possible to confirm the change in eGFRcr with changes in eGFRcys or clearance measures (see Fig. 3.2).

LIVING KIDNEY DONOR CANDIDATES

KDIGO guidelines for the evaluation of the living kidney donor state that eGFR could be used in the evaluation of living kidney donor candidates (see Box 3.1).78 In the United States, where evaluation of living

kidney donor candidates requires a measured clearance, eGFR could be used as a first test with measured clearance as a confirmatory test.79 80 Performance of multiple tests and assessment of the consistency of their results is helpful to identify possible sources of error. Elsewhere, if a clearance measurement is not required, eGFR could be used to accept or decline donor candidates if the probability is very high that mGFR is above or below, respectively, the thresholds for decision-making.81

DRUG DOSING

Pharmacokinetic properties of many drugs are affected by acute and chronic kidney disease. Drug dosing must be adjusted in patients with alterations in GFR to ensure therapeutic levels. The Cockcroft-Gault formula has been widely used to assess pharmacokinetic properties of drugs in patients with impaired kidney function, but, because of the limitations described previously, the KDIGO Controversies Conference Report recommended that GFR, as it is best evaluated in an individual patient, be used to assess kidney function for drug dosing, rather than a specific equation (see Box 3.1).82 Using the MDRD Study or CKD-EPI equation led to more accurate classification of mGFR categories for drug dosing adjustment than estimated Clcr using the Cockcroft-Gault equation.83 In AKI, use of the kinetic eGFR may provide additional benefit.84 Studies of predicted and observed vancomycin kinetics suggest that eGFRcr or eGFRcys using the CKD-EPI equations is more accurate than estimated Clcr using the Cockcroft-Gault equation.85–87 The most recent update from the FDA acknowledges the importance of accurate GFR estimates for drug dosing and recommends eGFR using the MDRD Study or CKD-EPI equations rather than estimated Clcr using the Cockcroft and Gault equation for pharmacokinetic studies for drug development.88 For drug dosing, GFR should be expressed without indexing for BSA for patients in whom BSA differs substantially from the index value of 1.73 m2; to convert from mL/min/1.73 m2 to mL/min, multiply by BSA/1.73 m2. The accuracy of nonindexed eGFR compared with nonindexed mGFR is similar to the accuracy of indexed eGFR compared with indexed mGFR.89

SELF-ASSESSMENT QUESTIONS

1. A 59-year-old, 100-kg, 193-cm-tall man has a serum creatinine concentration of 1.5 mg/dL. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation and standardized serum creatinine is 53 mL/min/1.73 m2, but measured GFR (mGFR) is 90 mL/min/1.73 m2. What factor most likely explains the underestimation of mGFR?
A. Nonsteady state of serum creatinine.
B. Drug-induced inhibition of tubular secretion of creatinine.
C. Decreased extrarenal elimination of creatinine.
D. Increased creatinine generation from large muscle mass or diet.
2. An 80-year-old woman has a serum creatinine concentration of 1.0 mg/dL for 3 months. Her eGFR using the CKD-EPI creatinine equation and standardized serum creatinine is 57 mL/min/1.73 m2. She has no chronic kidney disease risk factors. What laboratory tests could be performed to confirm the diagnosis of chronic kidney disease?
A. Measure urine albumin-to-creatinine ratio.
B. Measure GFR using an exogenous filtration marker.
C. Measure serum cystatin C and calculate estimation of GFR based on serum cystatin C (eGFRcys).
D. Image the kidneys and urinary tract.
E. Examine the urine sediment.
F. Any or all of the above.
3. A 40-year-old man with type 1 diabetes mellitus and urine albuminto-creatinine ratio of 450 mg/g begins angiotensin-converting enzyme (ACE) inhibitor therapy to slow the progression of kidney disease. Within 2 weeks, estimate GFR using serum creatinine (eGFRcr) declines from 75 to 65 mL/min/1.73 m2. What is the most likely cause for decline in eGFR?
A. Effect of ACE inhibitor on serum creatinine assay.
B. Effect of ACE inhibitor on GFR.
C. Effect of ACE inhibitor on tubular secretion of creatinine.
D. Effect of ACE inhibitor on muscle mass.

REFERENCES

1. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol. 2020;16(1):51–64.
2. Smith HW. The Kidney: Structure and Function in Health and Disease. New York: Oxford University Press; 1951.
3. Soveri I, Berg UB, Bjork J, et al. Measuring GFR: a systematic review. Am J Kidney Dis. 2014;64(3):411–424.
4. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis. 2014;63(5):820–834.
5. Sapirstein LA, Vidt DG, Mandel MJ, Hanusek G. Volumes of distribution and clearances of intravenously injected creatinine in the dog. Am J Physiol. 1955;181(2):330–336.
6. Molitoris BA, George AG, Murray PT, et al. A novel fluorescent clinical method to rapidly quantify plasma volume. Cardiorenal Med. 2019;9(3):168–179.
7. Rizk DV, Meier D, Sandoval RM, et al. A novel method for rapid bedside measurement of GFR. J Am Soc Nephrol. 2018;29(6):1609–1613.
8. Hoste L, Dubourg L, Selistre L, et al. A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. Nephrol Dial Transplant. 2014;29(5):1082–1091.
9. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol. 2009;20(11):2305–2313.
10. Seegmiller JC, Eckfeldt JH, Lieske JC. Challenges in measuring glomerular filtration rate: a clinical laboratory perspective. Adv Chronic Kidney Dis. 2018;25(1):84–92.
11. Ix JH, Wassel CL, Stevens LA, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin J Am Soc Nephrol. 2011;6(1):184–191.
12. Miller WG, Myers GL, Ashwood ER, et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. Arch Pathol Lab Med. 2005;129(3):297–304.
13. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the laboratory working group of the National kidney disease Education Program. Clin Chem. 2006;52(1):5–18.
14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612.
15. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.
16. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight - reconsidering the use of race correction in clinical algorithms. N Engl J Med. 2020;383(9):874–882.
17. Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimate kidney function. JAMA. 2019;322(2):113–114.
18. Diao JA, Inker LA, Levey AS, Tighiouart H, Powe NR, Manrai AK. In search of a better equation - performance and equity in estimates of kidney function. N Engl J Med. 2021;384(5):396–399.
19. Inker LA, Eneanya ND, Coresh J, et al. Chronic kidney disease epidemiology collaboration. New creatinine- and cystatin Cbased equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–1749.
20. Diao JA, Wu GJ, Taylor HA, et al. Clinical implications of removing race from estimates of kidney function. JAMA. 2021;325(2):184–186.
21. Powe NR. Black kidney function matters: use or misuse of race? JAMA. 2020;324(8):737–738.
22. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney disease, race, and GFR estimation. Clin J Am Soc Nephrol. 2020;15(8):1203–1212.
23. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on Reassessing the inclusion of race in diagnosing kidney disease. J Am Soc Nephrol. 2021.
24. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629–637.

25. Pierce CB, Munoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ. Ageand sex-dependent clinical equations to estimate glomerular filtration

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rates in children and young adults with chronic kidney disease. Kidney Int. 2020.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Schwartz GJ, Haycock GB, Edelmann Jr CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259–263.

Modification of Diet in Renal Disease (MDRD) Study Group (prepared by Levey AS; Bosch JP; Lewis JB; Greene T; Rogers N; Roth D). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–470.

Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247–254.

Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis. 2010;56(3):486–495.

Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med. 2012;156(11):785–795.

Bjork J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmo Study cohort. Scand J Clin Lab Invest. 2011;71(3):232–239.
Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157(7):471–481.
Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant. 2016;31(5):798–806.
Bjork J, Nyman U, Delanaye P, et al. A novel method for creatinine adjustment makes the revised Lund-Malmo GFR estimating equation applicable in children. Scand J Clin Lab Invest. 2020;80(6):456–463.
Bjork J, Nyman U, Larsson A, Delanaye P, Pottel H. Estimation of the glomerular filtration rate in children and young adults by means of the CKD-EPI equation with age-adjusted creatinine values. Kidney Int. 2020.
Pottel H, Bjork J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate : a cross-sectional analysis of pooled data. Ann Intern Med. 2021;174(2):183–191.
Fan L, Levey AS, Gudnason V, et al. Comparing GFR estimating equations using cystatin C and creatinine in elderly individuals. J Am Soc Nephrol. 2015;26(8):1982–1989.
Levey AS, Tighiouart H, Simon AL, Inker LA. Comparing newer GFR estimating equations using creatinine and cystatin C to the CKD-EPI equations in adults. Am J Kidney Dis. 2017;70(4):587–589.
Björk J, Grubb A, Gudnason V, et al. Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort. Nephrol Dial Transplant. 2017;33(8):1380–1388.
Levey AS, Tighiouart H, Inker LA. Improving glomerular filtration rate estimation-across the age and diversity spectrum. Ann Intern Med. 2020.
Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2937–2944.
Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD Epidemiology Collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis. 2010;56(1):32–38.
van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. Clin Chem. 2008;54(7):1197–1202.
Praditpornsilpa K, Townamchai N, Chaiwatanarat T, et al. The need for robust validation for MDRD-based glomerular filtration rate estimation

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References

in various CKD populations. Nephrol Dial Transplant. 2011;26(9):2780–2785.
Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982–992.
Jessani S, Levey AS, Bux R, et al. Estimation of GFR in South Asians: a study from the general population in Pakistan. Am J Kidney Dis. 2014;63(1):49–58.
McMahon GM, Waikar SS. Biomarkers in nephrology: core curriculum 2013. Am J Kidney Dis. 2013;62(1):165–178.
Tenstad O, Roald AB, Grubb A, Aukland K. Renal handling of radiolabelled human cystatin C in the rat. Scand J Clin Lab Invest. 1996;56(5):409–414.
Liu X, Foster MC, Tighiouart H, et al. Non-GFR determinants of lowmolecular-weight serum protein filtration markers in CKD. Am J Kidney Dis. 2016;68(6):892–900.
Keddis MT, Amer H, Voskoboev N, Kremers WK, Rule AD, Lieske JC. Creatinine-based and cystatin C-based GFR estimating equations and their non-GFR determinants in kidney transplant recipients. Clin J Am Soc Nephrol. 2016;11(9):1640–1649.

Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I. First certified reference material for cystatin C in human serum ERMDA471/IFCC. Clin Chem Lab Med. 2010;48(11):1619–1621.
Grubb A, Horio M, Hansson LO, et al. Generation of a new cystatin Cbased estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. Clin Chem. 2014;60(7):974–986.
Eckfeldt JH, Karger A. College of American Pathologist: CYS-A 2019 Discussion; 2019. https://documents.cap.org/documents/CYS-A-2019discussion.pdf.
Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–29.
Levey AS, Fan L, Eckfeldt JH, Inker LA. Cystatin C for glomerular filtration rate estimation: coming of age. Clin Chem. 2014;60(7):916–919.
Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. GFR estimation using standardized serum cystatin C in Japan. Am J Kidney Dis. 2013;61(2):197–203.
Wang X, Vrtiska TJ, Avula RT, et al. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. Kidney Int. 2014;85(3):677–685.
Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369(10):932–943.
Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445–453.
Pottel H, Delanaye P, Schaeffner E, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrol Dial Transplant. 2017;32(3):497–507.
Coresh J, Inker LA, Sang Y, et al. Metabolomic profiling to improve glomerular filtration rate estimation: a proof-of-concept study. Nephrol Dial Transplant. 2019;34(5):825–833.
Freed TA, Coresh J, Inker LA, et al. Validation of a metabolite panel for a more accurate estimation of glomerular filtration rate using quantitative LC-MS/MS. Clin Chem. 2019;65(3):406–418.
Inker LA, Couture SJ, Tighiouart H, et al. A new panel estimated GFR, including beta2-microglobulin and beta-trace protein and not including race, developed in a diverse population. Am J Kidney Dis. 2020.
Inker LA, Coresh J, Sang Y, et al. Filtration markers as predictors of ESRD and mortality: individual participant data meta-analysis. Clin J Am Soc Nephrol. 2017;12(1):69–78.
Steubl D, Fan L, Michels WM, et al. Development and validation of residual kidney function estimating equations in dialysis patients. Kidney Medicine. 2019;1(3):104–114.
Shafi T, Parekh RS, Jaar BG, et al. Serum beta-trace protein and risk of mortality in incident hemodialysis patients. Clin J Am Soc Nephrol. 2012;7(9):1435–1445.

68. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315(2):164–174.
69. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518–2531.
70. Grams ME, Shafi T, Rhee EP. Metabolomics research in chronic kidney disease. J Am Soc Nephrol. 2018;29(6):1588–1590.
71. Grams M, Brunskill NJ, Ballew S, et al. Development and validation of prediction models of adverse kidney outcomes in the population with and without diabetes mellitus. Diabetes Care. In progress.
72. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of randomized controlled trials. J Am Soc Nephrol. 2019;30(9):1735–1745.

73. Greene T, Ying J, Vonesh EF, et al. Performance of GFR slope as a surrogate end point for kidney disease progression in clinical trials: a statistical simulation. J Am Soc Nephrol. 2019;30(9):1756–1769.

74. Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. J Am Soc Nephrol. 2013;24(6):877–888.

75. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.

76. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol. 2009;20(3):672–679.

77. Herget-Rosenthal S, Marggraf G, Husing J, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int. 2004;66(3):1115–1122.

78. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation. 2013;101(8S):1–115.

79. Levey AS, Inker LA. GFR evaluation in living kidney donor candidates. J Am Soc Nephrol. 2017;28(4):1062–1071.

80. Inker LA, Huang N, Levey AS. Strategies for assessing GFR and albuminuria in the living kidney donor evaluation. Curr Transplant Rep. 2017;4(1):13–23.

81. Huang N, Foster MC, Lentine KL, et al. Estimated GFR for living kidney donor evaluation. Am J Transplant. 2016;16(1):171–180.

82. Matzke GR, Aronoff GR, Atkinson Jr AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80(11):1122–1137.

83. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis. 2009;54(1):33–42.

84. Kwong YD, Chen S, Bouajram R, et al. The value of kinetic glomerular filtration rate estimation on medication dosing in acute kidney injury. PloS One. 2019;14(11):e0225601.

85. Peters BJ, Rule AD, Kashani KB, et al. Impact of serum cystatin C-based glomerular filtration rate estimates on drug dose selection in hospitalized patients. Pharmacotherapy. 2018;38(10):1068–1073.

86. Pai MP, DeBacker KC. Modeling kinetic glomerular filtration rate in adults with stable and unstable kidney function: vancomycin as the motivating example. Pharmacotherapy. 2020;40(9):872–879.

87. Kim DJ, Lee DH, Ahn S, et al. A new population pharmacokinetic model for vancomycin in patients with variable renal function: therapeutic drug monitoring based on extended covariate model using CKD-EPI estimation. J Clin Pharm Ther. 2019;44(5):750–759.

88. US Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing. Center for Drug Evaluation and Research (CDER); 2020. https://www.fda.gov/media/78573/download.

89. Titan S, Miao S, Tighiouart H, et al. Performance of indexed and nonindexed estimated GFR. Am J Kidney Dis. 2020;76(3):446–449.

4
Urinalysis
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DEFINITION

Urinalysis is critical for evaluation of kidney and urinary tract disease. When a patient is first seen by a nephrologist, urinalysis must always be performed. Reagent strips are still the most widely used method for urinalysis to supply physicochemical information, but the nephrologist should be aware of their limitations and order more sensitive and specific measurements by other methods in the case of reagent strip abnormalities (e.g., the accurate measurement of proteinuria in case of reagent strip positivity for albumin).1 Urine sediment examination is an integral part of urinalysis.2 3 For kidney patients, urine sediment examination should ideally be performed by nephrologists, who may be able to attribute clinical relevance to findings that may escape laboratory personnel.4

URINE SAMPLE

The use of an early morning urine sample is suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline,1 especially for the measurement of albumin (see later).

However, the 24-hour urine collection is still widely used for the measurement of multiple parameters, even though errors caused by improper timing and missed samples can lead to overcollection or undercollection of urine. Errors can be minimized by giving the patient clear written instructions (e.g., at 7:00 am discard the first urine of the morning, then collect in a capacious—of at least 2.5 L—and graduated container all the urine produced, including that passed at 7:00 am of the day after; measure the volume of urine carefully and record it).

Written instructions should also be provided for other types of urine samples (e.g., when testing for orthostatic proteinuria, one sample produced while the patient has been recumbent for some hours and another sample produced while the patient has been standing).

Strenuous physical exercise (e.g., running, soccer) should be avoided for at least 24 hours before the urine sample delivery to avoid exercise-induced proteinuria and hematuria or urinary casts. In women, urinalysis must be avoided during menstruation because of the high probability of blood contamination.

For urine microscopy, a midstream sample of the first morning urine is recommended by some international guidelines because this urine is the most concentrated and acidic and theoretically the best for the preservation of particles.5 On the other hand, the prolonged persistence in the bladder may favor the lysis of cells and casts, which may lead to false-negative results. For this reason, we use a combined dipstick and urine microscopy on the second morning urine.6

After handwashing, the external genitalia are washed and wiped dry with a paper towel. Then, women should spread the labia of the vagina and men withdraw the foreskin of the glans and collect the midstream urine after the first portion is discarded. The same procedures can be used for children. For small infants, bags for urine are often used, even though these carry a high probability of contamination. A suprapubic bladder puncture may occasionally be necessary. In special situations, urine can also be collected through a bladder catheter, although this procedure may cause hematuria. Permanent indwelling catheters are almost invariably associated with bacteriuria, leukocyturia, hematuria, and candiduria.

The container for urine should be clean and have a capacity of at least 50 mL. It should have a wide base to avoid accidental spillage and should be capped. The label should identify the patient and the hour of urine collection.5

Several elements (but especially leukocytes) can lyse rapidly after collection; thus ideally the sample should be handled and examined as soon as possible. We recommend analysis within 3 hours from collection. If this is not possible, refrigeration of specimens at 4°C to 8°C assists preservation but may cause precipitation of phosphates or urates, which can hamper examination. Alternatively, chemical preservatives such as formaldehyde or glutaraldehyde can be used but can modify the urine pH, with consequent changes in urinary findings, and so cannot be universally recommended.

PHYSICAL CHARACTERISTICS

Color

The color of normal urine ranges from pale to dark yellow and amber, depending on the concentration of the urochrome. Abnormal changes in color can be caused by pathologic conditions, drugs, or foods (Table 4.1).

The most frequent pathologic conditions that can cause color changes of the urine are gross hematuria, hemoglobinuria, or myoglobinuria (pink, red, brown, or black urine); bilirubinuria (dark yellow to brown urine); and massive uric acid crystalluria (pink urine).

Less frequent causes are urinary infection, mainly from Klebsiella spp., Proteus mirabilis, Escherichia coli, Providencia stuartii, or Enterococcus spp. in patients with permanent bladder catheter (purple urine, nowadays known as “purple urine bag syndrome”), chyluria (white milky urine), porphyrinuria (associated with the excretion in the urine of porphobilinogen), and alkaptonuria (red urine turning black over time).

The main drugs responsible for abnormal urine color are rifampin (yellow-orange to red urine); desferrioxamine (pinkish urine); phenytoin (red urine); chloroquine and nitrofurantoin (brown urine); triamterene, propofol, and blue dyes of enteral feeds (green urine); methylene blue (blue urine); and metronidazole, methyldopa, and imipenem-cilastatin (urine darkening on standing).

Among the foods responsible are beetroot (red urine), senna and rhubarb (yellow to brown or red urine), and carotene (brown urine).

Abnormal Changes in Urine Color and its Causes

TABLE 4.1

Urine Color	Causes
Pink	Conditions: massive uric acid crystalluria, hematuria, hemoglobinuria, myoglobinuria Drugs: desferrioxamine
Purple	Conditions: urinary tract infection
Blue	Drugs: methylene blue
Green	Drugs: triamterene, propofol, blue dyes of enteral feeds
Orange	Conditions: bilirubinuria Drugs: rifampin
Red	Conditions: hematuria, hemoglobinuria, myoglobinuria, porphyrinuria Drugs: rifampin, phenytoin, phenazopyridine Foods: beetroot, senna, rhubarb
Brown	Conditions: hematuria, hemoglobinuria, myoglobinuria, bilirubinuria Drugs: chloroquine, nitrofurantoin Foods: carotene, senna, rhubarb
Black	Conditions: hematuria, hemoglobinuria, myoglobinuria, porphyrinuria, and alkaptonuria (red urine turning black over time) Drugs: metronidazole, methyldopa, imipenem-cilastatin (urine darkens over time)
White	Conditions: chyluria

Turbidity

Normal urine is transparent. Urine can be turbid because of a high concentration of any urine particle, especially cells, crystals, and bacteria. The most frequent causes of turbidity are urinary tract infection

(UTI), heavy hematuria, and genital secretions. Importantly, pathologic urine can be transparent.

Odor

A change in urine odor may be caused by the ingestion of some foods, such as asparagus. A pungent odor, caused by the production of ammonia, is typical of most bacterial UTIs, whereas there is often a sweet or fruity odor with ketones in the urine. Some rare conditions confer a characteristic odor to the urine. These include maple syrup urine disease (maple syrup odor), phenylketonuria (musty odor), isovaleric acidemia (sweaty feet odor), and hypermethioninemia (rancid butter or fishy odor).

Relative Density

Relative density can be measured by specific gravity or osmolality.
Specific gravity (SG) refers to the weight of a volume of urine compared with the weight of the same volume of distilled water and depends on the mass and number of the dissolved particles. SG is most frequently evaluated by reagent strip (see discussion of chemical characteristics), which measures the ionic concentration of urine; alternatively, SG can be measured by refractometry. With reagent strip underestimation occurs with urine of pH above 6.5, whereas overestimation is found with urine protein concentration above 7.0 g/L.

For SG, we suggest refractometry for everyday practice because refractometers are inexpensive, simple to use, require only one drop of urine, and are more accurate than reagent strips. SG of 1.000 to 1.003 is seen with marked urinary dilution, as observed in patients with diabetes insipidus or water intoxication. SG of 1.010 is often called isosthenuric urine because it is of similar SG (and osmolality) to plasma, so it is often observed in conditions in which urinary concentration is impaired, such as acute tubular necrosis (ATN) and chronic kidney disease (CKD) with reduced glomerular filtration rate (GFR). SG above 1.040 almost always indicates the presence of some extrinsic osmotic agent, such as radiocontrast.

Osmolality is measured by an osmometer and depends only on the number of particles present and is not influenced by urine temperature or protein concentrations. Measurement of osmolality is hence more reliable than SG by either reagent strip or refractometry, although it can be influenced by high glucose concentrations.

CHEMICAL CHARACTERISTICS

Chemical characteristics of urine are most frequently evaluated by reagent strips. These plastic strips bear several pads (the most used are SG, pH, glucose, hemoglobin, albumin, leukocyte esterase, nitrites, bile pigments, and ketones), each pad being impregnated with chemical reagents meant to detect a specific urine feature. In clinical laboratories of wealthier countries, the reagent strip reading is performed by automated reader devices, using reflectance spectrometry, which supply highly reproducible results. Alternatively, the reading is performed manually, which is simple and quick but is exposed to subjectivity and incorrect procedures. Correct procedures imply rapid plunging of the strip in the urine; removal of the urine in excess on the pads to avoid color carryover from one pad to the close ones; adherence to the time interval between removal of the strip from urine and the reading of results as indicated by the manufacturer; and matching of the color developed in the pad with the color scale reported on the strip box under adequate light conditions.

Reagent strips have the advantages of simplicity and low cost and supply a full urinary profile within 2 to 3 minutes. Disadvantages include semiquantitative results only, susceptibility to interference by substances and urine discoloration. Sensitivity and specificity of reagent strips greatly differ across studies, which partly depend on the brand used (there is no standardization across manufacturers). Table 4.2 summarizes the main causes of false-negative and false-positive results that can occur with strip reagent testing.

pH

The pH is determined by a strip that covers the pH range of 5.0 to 8.5 or to 9.0, with intervals of only 0.5, which limits precision. Moreover, significant deviations from true pH are observed for values below 5.5 and above 7.5. In the presence of formaldehyde, the strip supplies reduced pH values. When an accurate measurement of pH is necessary, a pH meter with a glass electrode is mandatory.

Urine pH reflects the presence of hydrogen ions (H+), but this does not necessarily reflect the overall acid load in the urine because most of the acid is excreted as ammonia. Low pH is often observed with metabolic acidosis (in which acid is secreted), highprotein meals (which generate more acid and ammonia), and volume depletion (in which aldosterone is stimulated, resulting in an acid urine). High pH is often observed with renal tubular acidosis, vegetarian diets (caused by minimal nitrogen and acid generation), and infection because of urease-positive organisms that generate ammonia from urea.

Measurement of urine pH is also needed for a correct interpretation of other urine parameters (e.g., specific gravity, albumin) and several urine sediment findings, particularly for the evaluation of crystalluria.

TABLE 4.2

Urine Reagent Strip Testing

Constituent

False-Negative Results

Specific gravity (SG)

Urine pH > 6.5

False-Positive Results
Urine protein > 7.0 g/L

pH

Reduced values in presence of formaldehyde

—

Hemoglobin

High urine specific gravity
Ascorbic acid
Formaldehyde (0.5 g/L) used to preserve samples

Myoglobin
Microbial peroxidases

Glucose

Ascorbic acid
Bacteria

Very acidic urine pH
Oxidizing detergents

Albumin

Low urine specific gravity
Albumin < 0.25–0.30 g/L
Low urine
Tubular proteins
Monoclonal heavy/light chains

Urine SG ≥ 1.030
Urine pH > 8.0
Quaternary ammonium detergents
Chlorhexidine
Polyvinylpyrrolidone

Leukocyte esterase

High urine specific gravity
Ascorbic acid
Glucose ≥ 20 g/L
Protein >5.0 g/L
Cephalothin (strong inhibition)
Tetracycline (strong inhibition)

Cephalexin (moderate inhibition)
Tobramycin (mild inhibition)

Formaldehyde (0.4 g/L)
Imipenem
Meropenem
Clavulanate
Abnormally colored urine

Nitrites

Bacteria that do not reduce nitrates to nitrites
Lack of vegetables in diet
Short bladder incubation time

Abnormally colored urine

Ketones

Improper storage

Free sulfhydryl groups (e.g., captopril)
Levodopa
Abnormally colored urine

Main causes of false-negative and false-positive results of urine reagent strips. False results also may occur when time-expired strips are used.

Hemoglobin

Hemoglobin is detected by a dipstick based on the pseudoperoxidase activity of the heme moiety of hemoglobin, which catalyzes the reaction of a peroxide and a chromogen to form a colored product.

False-negative results are most frequently caused by high SG or by ascorbic acid, a strong reducing agent, which can result in low-grade microhematuria being completely missed. Some reagent strips also include a vitamin C pad to reduce these false-negative results.7

The most important causes of false-positive results are myoglobinuria, resulting from rhabdomyolysis, and a high concentration of bacteria with pseudoperoxidase activity (Enterobacteriaceae, Staphylococcus spp., and Streptococcus spp.).8

that physiologic proteinuria does not exceed 150 mg/24 hours for adults1 and 140 mg/m2 for children,9 in whom, however, the normal values do vary by age.1 Three different approaches can be used for the evaluation of proteinuria, as described next.

Albumin Reagent Strip

By reagent strip, with glucose oxidase as catalyst, glucose is first oxidized to gluconic acid and hydrogen peroxide. Through the catalyzing activity of a peroxidase, hydrogen peroxide then reacts with a reduced colorless chromogen to form a colored product. The reagent strip detects glucose concentrations of 0.5 to 20 g/L. When more precise quantification of urine glucose is needed, enzymatic methods such as hexokinase must be used. False-negative results for glucose occur in the presence of ascorbic acid and bacteria. False-positive findings may be observed in the presence of oxidizing detergents and very acidic urine pH.

The albumin reagent strip test is based on the effect of albumin on a buffer (tetrabromophenol blue), which causes a change in pH proportional to the concentration of the albumin itself. The strip is sensitive to albumin but has a very low sensitivity to other proteins, such as tubular proteins and light-chain immunoglobulins; thus it will not detect tubular proteinuria or overflow proteinuria, which can occur in monoclonal gammopathies. Moreover, the detection limit is 0.25 to 0.3 g/L, so it does not identify microalbuminuria and is influenced by hydration status (false-negative results may occur at low urine SG, and vice versa) and urine pH (false-positive results at strongly alkaline pH). The reagent strip supplies only a semiquantitative measurement of urine albumin, which is expressed on a scale from 0 to +++ or ++++. Some manufacturers also supply numerical results, although these represent only approximate quantitative measurements. Some reagent strips also include a creatinine pad, which supplies an albumin/creatinine ratio (ACR) and reduces the variability caused by changing diuresis and urine dilution.[10] Nevertheless, for accurate quantification, other methods are needed.

Protein

24-Hour Protein Excretion

Although historically the definition of proteinuria has varied, the definitions in the KDIGO guideline are increasingly used.[1] It is accepted

The 24-hour protein excretion averages the variation of proteinuria caused by the circadian rhythm and is still considered the reference

Glucose

method.1 The measurement of proteinuria can be done by chemical assays, turbidimetric techniques, or dye-binding techniques, which quantify total proteins rather than only albumin. However, the 24-hour urine collection can be impractical in some settings (e.g., children, outpatients, elderly patients) and is subject to error from overcollection or undercollection.11

Protein/Creatinine Ratio and Albumin/Creatinine Ratio on Random Urine Sample

The protein/creatinine ratio (PCR) measured on an early morning urine sample represents a practical alternative to the 24-hour urine collection because the sample is easy to supply and is not influenced by variation in water intake or rate of diuresis.1 The PCR is obtained by the ratio between urine protein excretion and creatinine excretion, expressed as milligrams per milligrams or milligrams per millimole.

A close correlation between the PCR in a random urine sample and the 24-hour protein excretion has been demonstrated in a wide range of patients, including those with different types of glomerulonephritis (GN) evaluated longitudinally during treatment.9 However, the results may be influenced by reduced creatinine excretion because of low muscle mass. Thus, in elderly and female patients, PCR values can be higher than in young men. Some investigators consider a normal PCR sufficient to rule out pathologic proteinuria, but an elevated PCR should be confirmed and quantified with a 24-hour collection.12 Others have found poor correlation between PCR and 24-hour proteinuria at high levels of protein excretion13 or that PCR is an unreliable method to monitor some patients with lupus nephritis.14

The KDIGO guideline suggests ACR rather than PCR as the first measurement of proteinuria in adults because albuminuria is a reliable marker of the outcome of CKD, and it provides a specific and sensitive measure of changes in glomerular permeability in several kidney diseases.1 However, false-negative results may occur with ACR, especially in tubulointerstitial diseases and monoclonal gammopathies, in which urine proteins are mostly composed of tubular proteins and monoclonal light chains, respectively. In children, the KDIGO guideline recommends the measurement of PCR rather than ACR because the latter can miss the identification of congenital disorders associated with nonalbumin proteinuria.1 KDIGO also recommends PCR in preference to ACR for patients with glomerulonephritis.

Specific Proteins

Albumin. Albuminuria may be classified as mildly, moderately, or severely increased.1 In persons with diabetes, abnormal albuminuria is correlated with a risk for progressive kidney function loss and is correlated among those with or without diabetes with increased risk for CKD, cardiovascular morbidity, and all-cause mortality.15 Semiquantitative reagent strips are available to screen for urine albumin in this range. Once the reagent strip is positive, a quantitative method must be used for confirmation.1

Tubular proteins. When an isolated tubular lesion is suspected, specific tubular proteins such as α1-microglobulin, retinol-binding protein, or β2-microglobulin should be measured.1 This can be done by qualitative analysis of urine proteins, using electrophoresis.

Bence Jones protein. Bence Jones proteinuria indicates the presence of free monoclonal immunoglobulin (heavy or light chains) as occurs with monoclonal gammopathies. Bence Jones proteinuria is revealed by urine electrophoresis, whereas light-chain identification requires urine immunofixation.16

Leukocyte Esterase

The leukocyte esterase dipstick test evaluates the presence of leukocytes based on the activity of an indoxyl esterase released from lysed neutrophil granulocytes. Leukocyte esterase may be positive but microscopy negative when leukocytes are lysed because of low SG, alkaline pH, or a delay in sample handling and examination. Falsenegative results derive from vitamin C,7 high glucose (≥20 g/L), or high protein (≥5 g/L) concentration or from the presence of antibiotics, such as cephalothin and tetracycline (strong inhibition), cephalexin (moderate inhibition), or tobramycin (mild inhibition). The sensitivity is also reduced by high SG because this prevents leukocyte lysis.

False-positive results may occur when formaldehyde is used as a urine preservative, from the presence in the urine of imipenem, meropenem, or clavulanate,17 and with all discolored urine.

Nitrites

The dipstick nitrites test detects bacteria that reduce nitrates to nitrites by nitrate reductase activity. This includes most gram-negative uropathogenic bacteria, but not Pseudomonas, Staphylococcus albus, or Enterococcus. False-negative results also may occur on a diet with low content of nitrate (vegetables), which form the substrate for nitrite production and short bladder incubation time. Thus, the sensitivity of the dipstick nitrites test is low, whereas specificity is high.18

False-positive results may occur in the presence of abnormally colored urine.

Bile Pigments

Measurement of urinary urobilinogen and bilirubin concentrations has lost its clinical value in the detection of liver disease after the introduction of serum tests of liver enzyme function.

Ketones

The ketone dipstick tests for acetoacetate and acetone (but not β-hydroxybutyrate), which are excreted into urine during diabetic acidosis or during fasting, vomiting, or strenuous exercise. It is based on the reaction of the ketones with nitroprusside.

URINE MICROSCOPY

In current days, urine microscopy is carried out almost exclusively in clinical laboratories. The lack of clinico-laboratory correlation4 may have an impact on the diagnosis and management of kidney patients.

We believe urine microscopy remains a fundamental skill for nephrologists, as we will explore later.

Methods

A shared standardization for urine microscopy sample preparation and examination is lacking. We instruct the patient to deliver the second urine specimen of the morning because it avoids the lysis of particles that can occur in the bladder overnight (Box 4.1). In our laboratory we use the following standardized procedures for urine sample preparation and examination.6 We centrifuge an aliquot of urine within 3 hours from collection and concentrate it by removal of a fixed aliquot of supernatant urine. After this, the sediment is resuspended with a Pasteur pipette, and a fixed aliquot is transferred to the slide and prepared using a coverslip with a fixed surface. Some suggest the use of noncentrifuged urine because centrifugation may cause the damage and/or lysis of particles during the procedure. On the other hand, with this approach, clinically important particles (e.g., erythrocyte casts), when in small numbers, can easily be missed.

We recommend the use of phase-contrast microscopy because it improves the identification of almost all particles, especially cells and casts, whereas polarized light is mandatory for the correct identification of lipids and crystals, especially when they have uncommon morphologies.6

Standardized Procedures for Preparation and Examination of Urine Sediment Used in the Authors' Laboratory

BOX 4.1

- Written instructions for the patient to deliver a correct urine sample (i.e., the second urine of the morning after discarding the first portion of urine [midstream urine] collected in a proper container).
- Sample handling and examination within 3 hours of collection.
- Macroscopic examination of the sample and sediment.
- Testing the urine sample with a reagent strip for specific gravity, pH, albumin, hemoglobin, leukocyte esterase, and nitrites.
- Centrifugation of a 10-mL aliquot of urine at 400 g for 10 minutes.
- Removal of 9.5 mL of supernatant urine.
- Gentle but thorough resuspension with a Pasteur pipette of the sediment in the remaining 0.5 mL of urine.
- Transfer by a precision pipette of 50 µL of resuspended urine to a glass slide.
- Covering of sample with a 24 × 32 mm glass coverslip.
- Examination of the urine sediment with a phase contrast microscope at low (×160) and high magnification (×400).
- Use of polarized light to identify doubtful lipids and crystals.
- Matching of the microscopic findings with reagent strip results.
- Cells expressed as lowest/highest number seen per high-power field, casts as number per low-power field, and all other elements (e.g., bacteria, crystals) on scale from 0 to ++++.

At least 20 microscopic fields, in different areas of the sample, should be examined at both low magnification (e.g., ×100 or ×200) and high magnification (e.g., ×400). More extensive examination may be required in certain clinical settings, such as isolated microhematuria of unknown origin, for which we suggest examination of 50 low-power fields (lpf) to look for erythrocyte casts.[19]

For correct examination, both pH and SG of the sample must be known. Both alkaline pH (≥7.0) and low SG (especially ≤1.010) favor the lysis of erythrocytes and leukocytes, which can cause discrepancies between dipstick readings and the microscopic examination (see earlier discussion). Alkaline pH also impairs the formation of casts and favors the precipitation of amorphous phosphates. On the contrary, high SG (≥1.030) may reduce the sensitivity of reagent strips for hemoglobin and leukocyte esterase.

We quantify the particles seen as number per microscopic field, whereas if counting chambers are used, the elements are quantified as number per volume.

Cells

Erythrocytes

Urinary erythrocytes have a mean diameter of approximately 6 µm.

In the urine, there are two main types of erythrocytes: isomorphic, with regular shapes and contours, derived from the urinary excretory system or from nonglomerular kidney diseases; and dysmorphic, with irregular shapes and contours, which are of glomerular origin (see Fig. 4.1A–B).[20] Erythrocyte dysmorphism is thought to result from deformation of the erythrocytes as they pass through gaps in the glomerular basement membrane, followed by physicochemical insults when the erythrocytes pass through the tubular system.[21]

The distinction between glomerular and nonglomerular hematuria is of special value in the evaluation of patients with isolated microhematuria, in whom it is important to decide whether nephrologic or urologic investigation is needed.

Unfortunately, there is no agreement on the criteria to classify hematuria as glomerular or nonglomerular. Some define glomerular hematuria as more than 80% of erythrocytes being dysmorphic; others define the discriminating cut-off as low as 10% or 15%.[6] Still, others define hematuria as glomerular when at least 5% of erythrocytes examined are acanthocytes,[22] a subtype of dysmorphic erythrocytes with a distinguishing appearance easily identifiable by the presence of one or more blebs of different size and shape protruding from a ring-shaped body (see Fig. 4.1B, inset).

In our laboratory, glomerular hematuria is diagnosed when there are 40% or more dysmorphic erythrocytes and/or 5% or more acanthocytes and/or one or more red blood cell casts/50 lpf (×160). With this approach, a good correlation was found between urinary sediment and kidney biopsy findings in 16 patients with long-standing isolated microhematuria.[19] Rare types of erythrocytes found in the urine include sickle cells, elliptocytes, spherocytes, and dacryocytes.[23]

Leukocytes

Urinary neutrophils have an average diameter of approximately 10 µm and are the most frequently found leukocytes in the urine. Neutrophils are identified by their granular cytoplasm and lobulated nucleus (see Fig. 4.1C). In most patients, neutrophils indicate UTI, but they may also result from urine contamination caused by genital secretions. Variable numbers of neutrophils are often found in acute interstitial nephritis (AIN).[24] Neutrophils can be found in low numbers in chronic interstitial nephritis and in proliferative GN.[25]

Eosinophils, which can be identified only by the use of stains (e.g., Hansel), were once considered a marker of acute allergic interstitial nephritis. This is not specific, however, because eosinophils may be present in various types of GN, prostatitis, chronic pyelonephritis, urinary schistosomiasis, and cholesterol embolism.[26]

Lymphocytes, whose identification also requires staining, may indicate acute cellular rejection in kidney allograft recipients, although this is not sufficiently reliable to preclude the need for kidney biopsy. Lymphocytes are also a typical finding in patients with chyluria.

Macrophages are mononucleated or multinucleated cells of variable size (13–95 µm in diameter) and variable appearance, with some being granular (see Fig. 4.1D). In patients with nephrotic syndrome, macrophages may be engorged with lipid drops, appearing as oval fat bodies (see lipids). Macrophages have been found in the urine of patients with active GN. In our experience, macrophages are frequently seen in the urine of kidney transplant recipients with BK virus infection (see later discussion). However, urinary macrophages are not diagnostic of any specific condition.

Renal Tubular Epithelial Cells

The renal tubular epithelial cells (RTECs) derive from the exfoliation of the tubular epithelium. In the urine, RTECs can differ in size (diameter approximately 9–25 µm, average 14 µm) and shape, from roundish to rectangular or columnar, with a central or peripheral large nucleus (see Fig. 4.1E). RTECs are not found in the normal individual but can be found when there is acute tubular damage, including ATN,[27] AIN,[24] and acute cellular rejection. In smaller numbers, RTECs also can be found in glomerular diseases.[25] In ATN, these cells are frequently damaged and necrotic and may be present in casts (so-called epithelial casts).

Transitional Epithelial Cells

The transitional epithelial cells derive from the exfoliation of the uroepithelium, which lines the urinary tract from the calyces to the bladder in women and to the proximal urethra in men. This multilayered epithelium has small cells in the deep layers and larger cells in the superficial layers. When cells of the deep epithelial layers (average diameter

18 µm; see Fig. 4.1F) are present in large numbers (e.g., ≥1/high-power field [hpf]), this suggests severe uroepithelial damage, such as caused

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Fig. 4.1 Urinary Sediment Cells. (A) Isomorphic nonglomerular erythrocytes (diameter ~6 µm). The arrows indicate the so-called crenated erythrocytes, which are a finding in nonglomerular hematuria. (B) Dysmorphic glomerular erythrocytes (diameter ~6 µm). The dysmorphism consists mainly of irregularities of the cell membrane. Inset, Acanthocytes, with their typical ring-formed cell bodies with one or more blebs of different sizes and shapes. (C) Neutrophils (diameter ~10 µm). Note their typical lobulated nucleus and granular cytoplasm. (D) Granular phagocytic macrophage (diameter ~60 µm). (E) Different types of renal tubular epithelial cells (diameter ~14 µm). (F) Two cells from deep layers of uroepithelium (diameter ~18 µm). (G) Three cells from superficial layers of uroepithelium (diameter ~25 µm). (Note the difference in shape, size, and ratio of nucleus to cytoplasm between the two types of uroepithelial cells. (H) Squamous epithelial cells (diameter ~50 µm). (All images by phase-contrast microscopy; original magnification ×400.)

by neoplasia, stones, obstruction, or long-standing bladder catheters or ureteral stents.6 Transitional cells of the superficial layers (average diameter ~25 µm; see Fig. 4.1G) are a common finding associated with mild uroepithelial damage, as may occur in cystitis.

Squamous Epithelial Cells

Squamous epithelial cells (SECs; average diameter 50 µm; see Fig. 4.1H) derive from the urethra or from the external genitalia. In small numbers, SECs are a normal finding, but in large numbers, they indicate urine contamination from genital secretions and reflect improper urine collection technique.

Lipids

Lipids are found in the urine as drops, which are spherical, translucent, yellowish particles of different sizes that can be isolated or in clusters, free or within cells or casts; as oval fat bodies, which are RTECs or

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Fig. 4.2 Fat Particles. (A) Oval fat body and (B) fat cast–containing lipid drops with very variable diameter which, under polarized light, show a symmetric “Maltese cross” birefringence (insets). (C) Fat particle with an ovoidal shape and multiple blebs as found in the urine of patients with Fabry disease which, under polarized light, shows a truncated and asymmetric Maltese cross appearance (inset) (Phase-contrast microscopy, original magnification ×400.)

macrophages gorged with lipid drops (Fig. 4.2A); as fat casts, cylindrical structures containing variable amounts of fat drops, or even oval fat bodies (see Fig. 4.2B); and cholesterol crystals (see Crystals and Fig. 4.4F). All these particles contain mainly cholesterol esters and free cholesterol. Under polarized light, lipids are birefringent and show “Maltese crosses” with symmetric arms (see Fig. 4.2A and 4.2B inset), whereas cholesterol crystals are nonbirefringent. These lipids are typical of glomerular diseases associated with marked proteinuria.

In Fabry disease, urine sediment may contain fat particles even in the absence of proteinuria. These particles contain glycosphingolipids (especially globotriaosylceramide-3) and differ from the fat particles previously described because they show quite variable shapes, often with external protrusions and/or an internal lamellar structure, and irregular or truncated Maltese crosses under polarized light (see Fig. 4.2C).28

Casts

Casts are cylindrical structures that form in the lumen of distal renal tubules and collecting ducts. Their matrix is made of Tamm-Horsfall glycoprotein, today known as uromodulin, which is secreted by the cells of the thick ascending limb of Henle loop. Trapping of particles within the cast matrix results in casts with different appearances, each of which may have specific clinical significance (Table 4.3). It is important to remember that because casts form in the renal tubules, whatever particle is contained in a cast derives from the kidneys. Specific casts include the following:

✓•✓ Hyaline casts are colorless with a low refractive index (Fig. 4.3A). They are easily seen with phase-contrast microscopy but can be overlooked when bright-field microscopy is used. Hyaline casts can

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be found both in normal and pathologic urine and especially in the setting of dehydration.

Hyaline-granular casts contain variable amounts of granules within the hyaline matrix (see Fig. 4.3B) and are the most common mixed casts (see later discussion). Hyaline-granular casts can occasionally be found in normal subjects. They are common in patients with kidney diseases such as GN and AIN, in which case they are associated with other types of casts.24 25

Granular casts can be finely (see Fig. 4.3C) or coarsely granular. Both types indicate kidney disease. In patients with acute kidney injury (AKI), granular casts, together with RTECs27 or epithelial casts,29 are a sensitive marker of ATN.

Waxy casts derive their name from their appearance, which is similar to that of melted wax (see Fig. 4.3D). They are typically found in patients with kidney disease associated with reduced GFR, whether acute, rapidly progressive, or chronic.30

Fat casts contain variable amounts of lipid drops, isolated, in clumps, or packed or even oval fat bodies or cholesterol crystals (see Fig. 4.2B). Fat casts are typical of glomerular diseases associated with marked proteinuria.

Erythrocyte casts may contain a few erythrocytes (see Fig. 4.3E) or so many that the matrix of the cast cannot be identified. Erythrocyte casts are a marker of renal bleeding, most frequently of glomerular origin, even though they have also been found in patients with AIN.24

Hemoglobin casts generally have a brownish hue and a coarsely granular appearance, which derives from the degradation of erythrocytes entrapped within the cast matrix (see Fig. 4.3F). In such cases, hemoglobin casts have the same clinical significance as

TABLE 4.3 Types of Casts and Their Main Clinical Associations

Cast	Main Clinical Associations
Hyaline	Normal individual; kidney disease
Hyaline-granular	Normal subject; kidney disease
Granular	Kidney disease; AKI associated with ATN
Waxy	Kidney disease with possible functional impairment
Fat	Marked proteinuria, usually but not invariably in the nephrotic range
Erythrocyte	Glomerular hematuria, most frequently because of active proliferative GN; AIN
Leukocyte	AIN; acute pyelonephritis; active proliferative GN
Containing renal tubular epithelial cell (so-called epithelial casts)	AKI associated with ATN; active proliferative GN; nonproliferative GN associated with heavy proteinuria; AIN
Hemoglobin	Glomerular hematuria, most frequently because of active proliferative GN; hemoglobinuria caused by intravascular hemolysis
Myoglobin	AKI because of rhabdomyolysis
Bilirubin	Jaundice caused by increased direct bilirubin

Bacterial, fungal

Bacterial or fungal kidney infections

Crystalline

Crystalline nephropathies

Mixed

According to components present in the cast

AIN, Acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis; GN, glomerulonephritis.

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erythrocyte casts. However, hemoglobin casts also may derive from hemoglobinuria, as may occur in intravascular hemolysis. In these patients, hemoglobin casts usually have a smooth surface.

Leukocyte casts contain variable amounts of polymorphonuclear leukocytes (see Fig. 4.3G). They can be found in patients with acute pyelonephritis and AIN24 and in active proliferative GN.25

Renal tubular epithelial cell containing casts (so-called epithelial casts) contain variable numbers of RTECs, which can be identified by their prominent nucleus (see Fig. 4.3H). Epithelial casts indicate damage of the renal tubular epithelium and can therefore be found in the urine of patients with ATN,27 AIN,24 and glomerular disease.25

Myoglobin casts are cylinders pigmented by myoglobin, akin to hemoglobin casts (see Fig. 4.3F). They can be distinguished from myoglobin casts according only to the clinical setting. Myoglobin casts are observed in the urine of patients with AKI associated with rhabdomyolysis.

Bilirubin casts are cylinders pigmented with bilirubin, which can stain any particle contained in the cast (see Fig. 4.3I). They are observed in the urine of patients with jaundice associated with increased direct (conjugated) bilirubin.

Crystalline casts may contain crystals of different nature. These casts are an important diagnostic element in crystalline-induced nephropathies, which are usually associated with AKI.31

Casts containing microorganisms (bacteria and yeasts) indicate a kidney infection.

Mixed casts contain components of different nature, such as granules, cells, and lipids. Their clinical significance is the same as that of pure casts.

Crystals

Correct identification of urine crystals requires the combined knowledge of their most frequent morphologies, their birefringence features under polarized light, and urine pH range at which each type of crystals precipitates. For unusual crystals, however, additional investigation may be needed, such as infrared or Raman spectroscopy and other techniques that are available in specialized laboratories.[32]

Examination of the urine for crystals is a key test in the assessment of patients with stone disease, with some rare inherited metabolic disorders (e.g., cystinuria, hyperoxaluria, phosphoribosyltransferase deficiency), and with suspected drug nephrotoxicity.[6] The search for crystalluria is best performed on the first voided morning urine samples, which are the most concentrated. We classify crystals into four categories: common crystals, pathologic crystals, rare crystals caused by drugs, and other crystals.

Common Crystals

Uric acid crystals and amorphous urates. These crystals most commonly appear as rhomboidal or barrel-like structures with a typical yellow amber color (Fig. 4.4A). However, uric acid crystals may have a wide spectrum of appearances, such as needle-like or grenade-like morphology.[33,34] Under polarized light, uric acid crystals are strongly birefringent and polychromatic. They are found in acidic urine (pH 5.0–5.8).

Amorphous urates are tiny granules of irregular shape that polarize light and precipitate in acidic urine.

Calcium oxalate crystals. There are two types of calcium oxalate crystals: bihydrated (or weddellite) crystals, which most often have a bipyramidal appearance (see Fig. 4.4B), and monohydrated (or whewellite) crystals, which are ovoid, dumbbell-shaped, or biconcave disks (see Fig. 4.4C). Monohydrated crystals are birefringent under polarized light, whereas bihydrated crystals in most instances are not. Both types precipitate at pH 5.4 to 6.7.

Calcium phosphate crystals (brushite) and amorphous phosphates. Calcium phosphate crystals are pleomorphic, appearing as prisms, star-like particles, or needles of various sizes and shapes (see Fig. 4.4D) that are strongly birefringent under polarized light. Rarely, calcium phosphate can appear as plates with a granular surface that do not polarize light. Both types of crystals precipitate in alkaline urine (pH ≥ 7.0).

Amorphous phosphates are tiny particles identical to amorphous urates, but they do not polarize light and precipitate at a pH of 7.0 or higher.

Triple phosphate (struvite) crystals. These crystals contain magnesium ammonium phosphate and most frequently have the appearance of “coffin lids” (see Fig. 4.4E), although variants such as flower-like and scissors-like structures can be found. These crystals usually polarize light strongly and are found in alkaline urine (pH ≥ 7.0).

Pathologic Crystals

Cholesterol crystals. These are thin, transparent plates, often clumped together, with sharp edges (see Fig. 4.4F), which do not polarize light. They can be found at any urinary pH.

Cystine crystals. These are hexagonal plates with irregular sides that are often heaped on one another (see Fig. 4.4G). They either do not polarize light or show a whitish birefringence. They are insoluble in a urine pH up to 7.4. Their presence is pathognomonic of the autosomal recessive inherited condition cystinuria (see Chapter 50), and their persistence in urine samples indicates a high risk for urinary stone formation.[35]

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Fig. 4.3 Casts. (A) Hyaline cast. (B) Hyaline-granular cast. (C) Finely granular cast. (D) Waxy cast. (E) Erythrocyte cast. (F) Hemoglobin cast with a coarsely granular appearance and typical brownish hue. (G) Leukocyte cast. Note the lobulated nucleus of polymorphonuclear leukocytes (arrows).
(H) Epithelial cell cast. (Note, in its lower extremity, the large nucleus of the renal tubular epithelial cells.) (I) Bilirubin cast with a coarsely granular appearance and typical yellow color. (All images by phase-contrast microscopy; original magnification ×400.)

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Fig. 4.4 Crystals. (A) Uric acid crystals. This rhomboid shape is the most common. (B) Bihydrated calcium oxalate crystals. They appear as bipyramidal colorless structures of variable size. (C) Different types of monohydrated calcium oxalate crystals. (D) Star-like brushite (calcium phosphate) crystal. (E) Struvite (triple phosphate) crystal, with typical “coffin-lid” appearance. (F) Cholesterol crystal.

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Fig. 4.4, cont'd (G) Cystine crystals heaped one on the other. (H) 2,8-Dihydroxyadenine crystal by bright-field microscopy; inset, by polarized light. (I) Amoxicillin crystal resembling a broom or brush. (J) Star-like ciprofloxacin crystals. (K) Large crystal of indinavir. (All images by phase-contrast microscopy; original magnification ×400.) (H, Courtesy Doctor Michel Daudon, Paris.)

2,8-dihydroxyadenine (2,8-DHA) crystals. These are spherical brownish structures with a central umbilicus and a birefringent cross-like appearance under polarized light (see Fig. 4.4H). They are a marker of homozygous deficiency of the enzyme adenine phosphoribosyltransferase.36

Tyrosine and leucine crystals. Both crystals are rare and can be found in the urine of patients with severe liver disease. In addition, tyrosine crystals may be found in patients with tyrosinemia. Leucine crystals appear as yellow-brown spheres with concentric striations, which are birefringent under polarized light. Tyrosine crystals are needle-shaped and often aggregate.

naftidrofuryl oxalate, orlistat, intravenous vitamin C, primidone, felbamate, piridoxylate, sulfasalazine, and methotrexate).3 39

In the presence of crystals with morphologies that differ from those previously described, a drug-related etiology must be sought. Calcium oxalate crystals of drug-related origin (naftidrofuryl oxalate, orlistat, and vitamin C), however, are indistinguishable from other causes.6

Other Crystals

Hippuric acid crystals, calcium carbonate crystals, and ammonium biurate crystals are rare, and it is unclear whether they are clinically significant.

Crystals Caused by Drugs

Clinical Significance of Crystals

Several drugs can cause crystalluria. This happens in the presence of several factors that increase drug supersaturation, such as drug overdose, dehydration, hypoalbuminemia, or reduced kidney function, in the setting of a crystallization favoring pH range (which varies from drug to drug).

Drugs that can cause crystalluria include antimicrobials (sulfadiazine, amoxicillin [see Fig. 4.4I], ciprofloxacin6 [see Fig. 4.4J], ceftriaxone, and sulfamethoxazole37); antivirals (acyclovir, indinavir6 [see Fig. 4.4K], atazanavir, and darunavir38); and other drugs (such as

Uric acid, calcium oxalate, and calcium phosphate crystals may have no clinical significance because they can reflect transient supersaturation of the urine caused by ingestion of some foods (e.g., meat for uric acid, spinach or chocolate for calcium oxalate, milk or cheese for calcium phosphate) or mild dehydration. However, the persistence of calcium oxalate or uric acid crystalluria may reflect hypercalciuria, hyperoxaluria, or hyperuricosuria. In calcium stone formers, the evaluation of crystalluria is an important tool to assess calcium stone disease activity.[40]

from gloves), or the environment (e.g., pollens, plant cells, fungal spores).6

INTERPRETATION OF URINE SEDIMENT FINDINGS

Examination of the urine sediment, coupled with the knowledge of proteinuria and other urine and blood findings, results in urine sediment profiles that aid in diagnosis of urinary tract diseases (Table 4.4).

Acute Kidney Injury

Fig. 4.5 Egg of Schistosoma haematobium (Diameter, ~100 µm). Note the thick shell, which contains the miracidium, and the typical terminal spike (arrow). (Phase-contrast microscopy; original magnification ×400.)

Large numbers of uric acid crystals may be associated with AKI caused by acute urate nephropathy, whereas large numbers of monohydrated calcium oxalate crystals, especially with a spindle shape, may be associated with AKI from ethylene glycol intoxication. Triple phosphate crystals are usually associated with UTI caused by urea-splitting microorganisms such as Proteus spp., Ureaplasma urealyticum, and Corynebacterium urealyticum.

Cholesterol crystals are found in association with other fat particles in patients with marked proteinuria. Cystine crystals are pathognomonic of cystinuria, and 2,8-dihydroxyadenine crystals are pathognomonic of adenine phosphoribosyltransferase enzyme deficiency.

Crystalluria may be isolated and asymptomatic or associated with hematuria, obstructive uropathy, or AKI caused by the precipitation of crystals within the renal tubules.6 31

Organisms

Bacteria: Two types of bacteria are most frequently found in urine—cocci, which have a round to oval shape, and rods, which appear as short sticks. High numbers of bacteria in association with leukocytes are a marker of urinary tract infection. However, the copresence of high numbers of squamous epithelial cells and/or Candida albicans and/or Trichomonas vaginalis suggests urine contamination from genital secretions.

Candida albicans: It is the most frequent yeast found in urine. Its shape is ovoidal, with one or two round to elongated protruding buds of variable size.

Trichomonas vaginalis: It is a protozoon characterized by a pyriform body, the presence of flagella at the two extremities of the body, and quick and whirling movements through the slide.

Schistosoma haematobium: It is an endemic parasite in several geographic regions (see Chapter 56). The search in the urinary sediment of its eggs is the simplest and fastest diagnostic tool. Their distinguishing feature is a terminal spike (Fig. 4.5). The eggs are most frequently found in the urine collected between 10 am and 2 pm, when the parasite female lays the eggs, and after physical exercise such as running, which favors the detachment of the eggs from the bladder mucosa.

Contaminants

A large number of particles can contaminate urine. These particles may come from the patient (e.g., spermatozoa; erythrocytes from menstruation; leukocytes from vaginitis, cloth or synthetic fibers from underclothes), the laboratory (e.g., glass fragments from coverslips, starch

In patients with AKI, the finding in the urine sediment of RTECs, in association with granular casts and/or epithelial casts, is the hallmark of ATN,27 29 whereas these elements are rarely found in prerenal AKI.27

In the latter, hyaline and/or hyaline-granular casts may be seen, along with high SG and low pH. A score based on the number of RTECs and granular casts significantly correlates with the progression and severity of AKI, with new AKI urine biomarkers (NGAL, KIM-1, IL 18), with the need for dialysis, and with death.27 Depending on the cause of the tubular damage, other elements can be seen (e.g., high numbers of dysmorphic erythrocytes and erythrocyte casts in active proliferative glomerular diseases; myoglobin-pigmented casts in AKI because of rhabdomyolysis; and massive amounts of uric acid crystals in acute uric acid nephropathy caused by tumor lysis syndrome).

Acute Interstitial Nephritis

In AIN, the most frequent findings are variable numbers of leukocytes and isomorphic erythrocytes. RTECs may also be present, together with epithelial, leukocyte, and/or erythrocyte casts.24

Active Proliferative Glomerulonephritis

Dysmorphic erythrocytes and erythrocyte and hemoglobin casts are the hallmark of active proliferative glomerulonephritis. Usually, the number of erythrocytes ranges from 30 to 40 cells/hpf to more than 100 cells/hpf, with the higher figure found especially in patients with extracapillary or necrotizing glomerular lesions. Leukocytes are also common in mild numbers (e.g., 3–5/hpf) in most patients, but in those with acute postinfectious GN or active proliferative lupus nephritis, we have seen samples with up to 30 to 40 leukocytes/hpf. Leukocyte casts and waxy casts30 may also be observed. In patients with marked proteinuria, fat particles can be also seen.

Nephrotic Syndrome

The typical nephrotic sediment contains lipids, casts, and RTECs. Fat, epithelial, granular, hyaline, and hyaline-granular casts are frequent, whereas erythrocyte or hemoglobin casts, leukocyte casts, and waxy casts are few or absent. Erythrocytes may be totally absent, especially in minimal change disease or may be in low to moderate numbers (e.g., 3–5/hpf to 20–30/hpf), which is seen especially in membranous nephropathy and focal segmental glomerulosclerosis. Leukocytes are usually not found.

Urinary Tract Infection

Bacteria and leukocytes are the hallmarks of UTI, with or without superficial transitional epithelial cells and/or isomorphic erythrocytes. In patients with pyelonephritis, RTECs and leukocyte casts can also be found. When the infection is caused by urease-producing bacteria such as Proteus spp., Ureaplasma urealyticum, and Corynebacterium urealyticum, triple phosphate (struvite) crystals are often present. The finding of bacteria and leukocytes, together with a high number of squamous epithelial cells, suggests the presence of urine contamination from genital secretion rather than UTI.

TABLE 4.4

Main Urinary Profiles

Kidney Disease	Hallmark	Associated Findings
AKI with ATN (proteinuria: absent to +)	RTECs Epithelial casts Granular casts	Variable according to cause of ATN (e.g., high number of dysmorphic erythrocytes in active proliferative GN; myoglobin casts in rhabdomyolysis; uric acid crystals in acute urate nephropathy)
Acute interstitial nephritis (proteinuria: absent to +)	Leukocytes Isomorphic erythrocytes	RTECs Leukocyte casts Erythrocyte casts
Active proliferative glomerulonephritis (proteinuria: + to ++++)	Dysmorphic erythrocytes (moderate to high number) Erythrocyte/hemoglobin casts	Leukocytes (low to moderate number) RTECs Epithelial, hyaline, hyaline-granular, granular, waxy, leukocytic casts
Nephrotic syndrome (proteinuria: ++++)	Fat particles High number of casts (fat, hyaline, hyaline-granular, granular epithelial)	Renal tubular epithelial cells Dysmorphic erythrocytes (absent or low-to-moderate number)
Urinary tract infection (proteinuria: absent)	Bacteria Leukocytes	Isomorphic erythrocytes Transitional epithelial cells

Triple phosphate crystals (for infections caused by
urease-producing bacteria)
Epithelial ± leukocyte casts (in pyelonephritis)

Polyomavirus BK infection (proteinuria: absent)

Decoy cells

Decoy cell casts (in BK virus nephropathy)
Macrophages

Urologic diseases (proteinuria: absent)

Isomorphic erythrocytes (low to high number)
Leukocytes
Transitional cells (deep, superficial, atypical)

Crystals (urolithiasis)
Atypical/malignant transitional cell (neoplasia of
excretory urinary system)

AKI, Acute kidney injury; ATN, acute tubular necrosis; GN, glomerulonephritis; RTEC, renal tubular epithelial cell.

A

B

C

D

Fig. 4.6 Decoy Cells. (A) Cell with nuclear ground-glass or gelatinous appearance (phenotype 1). (B) Cytomegalovirus-like cell with a large intranuclear inclusion surrounded by a clear halo (phenotype 2). (C) A binucleated cell (bottom, phenotype 3) and a cell with an enlarged ground glass nucleus (phenotype 1). (D) Cell with clumped chromatin (phenotype 4). (Phase-contrast microscopy; original magnification ×400.)

BK Virus Infection

The KDIGO clinical practice guideline for kidney transplant recipients recommends monitoring for BK polyomavirus (BKV) reactivation (which may lead to BKV nephropathy [BKVN] and graft loss) by measuring viral nucleic acid in the blood (i.e., viremia).41 This approach is expensive and not always available.42 As an alternative, searching for “decoy cells” on either smeared or cytocentrifuged alcohol-fixed and Papanicolaou-stained urine specimens provides satisfactory diagnostic accuracy.42 43

However, decoy cells can also be easily identified by phase-contrast microscopy in routine unstained samples44 (Fig. 4.6). Four decoy cell phenotypes are recognized45: (1) nuclear ground-glass or gelatinous appearance (see Fig. 4.6A); (2) intranuclear inclusion surrounded by a clear halo (cytomegalovirus-like; see Fig. 4.6B); (3) multinucleated cells (see Fig. 4.6C); and (4) vesicular nuclei with clumped chromatin and nucleoli (see Fig. 4.6D). In addition, hybrid forms are frequently seen, as are cells with eccentric nucleus and comet-like appearance. The presence of decoy cells may indicate solely the reactivation of BKV infection; however, when they persist over time, are in high numbers, or are found in urinary casts, they are a reliable marker of likely BKVN, which should be confirmed by measurement of BK viremia.42 43 45

Urologic Diseases

Urinary tract disorders such as cancer, urolithiasis, and hydronephrosis are associated with variable numbers of isomorphic urinary erythrocytes, which are often associated with leukocytes or transitional epithelial cells (from deep or superficial layers of uroepithelium). In addition, in uroepithelial cancer, malignant transitional cells can be found, which show abnormal size and shape, increased number and size of nuclei, and enlarged nucleoli.46

Nonspecific Urinary Abnormalities

Some urine sediment findings are nonspecific. This occurs when variable numbers of hyaline or hyaline-granular casts are found with or without low numbers of isomorphic erythrocytes, leukocytes, common crystals, or superficial transitional epithelial cells. In such cases, the correct interpretation of the urinary findings requires adequate clinical information and the knowledge of other laboratory tests.

AUTOMATED ANALYSIS OF URINE SEDIMENT

In high-income countries, automated urinary sediment analyzers are increasingly used in clinical laboratories where several hundreds of urine samples are analyzed every day. Three main types of automated instruments using different technology are available: flow cytometry, automated intelligent microscopy, and cuvette-based microscopy.

Flow cytometry supplies quantitative results and graphics (“scattergrams”) of the identified particles.47

Intelligent microscopy supplies quantitative results and images of the particles present in the sample, which are pooled and shown on the screen by particle categories (e.g., all erythrocytes, leukocytes).48

Cuvette-based microscopy supplies high-quality grayscale images of elements within whole microscopic fields, obtained with both bright-field and phase-contrast microscopy.49

Compared with manual microscopy, automated urine sediment analyzers offer several advantages: small volumes of urine are required (1–3 mL); high numbers of samples can be examined in a short time (up to 130/h); elimination of the drawbacks caused by sample centrifugation (e.g., time consumption, loss/lysis of particles); and quantitative results with small variation coefficients. However, they also have limitations: their findings correlate well with manual microscopy for elements such as erythrocytes, leukocytes, and SECs, but not for others such as casts and nonsquamous epithelial cells (i.e., RTECs and deep and superficial transitional cells). Finally, they cannot identify the subtypes of pathologic casts, lipids, decoy cells, and malignant atypical epithelial cells.

For these reasons, in spite of their continuous diagnostic improvement, automated instruments cannot yet replace manual microscopy for samples from renal patients.50

SELF-ASSESSMENT QUESTIONS

1. The reagent strip for protein:
A. detects exclusively urinary albumin.
B. detects Bence Jones proteinuria.
C. is not influenced by the pH of the urine.
D. is not influenced by the specific gravity of the urine.
2. Regarding the preparation of the urine sample and its microscopic

examination, which of the following is false?
A. The sample should be examined within 3 hours of collection.
B. All crystals are birefringent under polarized light.

C. When collecting the urine sample, only the midstream urine should be collected.
D. Phase-contrast microscopy is helpful for particle identification.
3. The automated urine sediment analyzers available today:
A. are adequate for the evaluation of the kidney patient.
B. require high volumes of urine.
C. adequately identify renal tubular epithelial cells.
D. allow the examination of a high number of samples in a short period of time.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
2. Perazella MA. The urine sediment as a biomarker of kidney disease. Am J Kidney Dis. 2015;66:748–755.
3. Becker GJ, Garigali G, Fogazzi GB. Advances in urine microscopy. Am J Kidney Dis. 2016;67:954–964.
4. Tsai JJ, Yeun JY, Kumar VA, Don BR. Comparison and interpretation of urinalysis performed by a nephrologist versus a hospital-based clinical laboratory. Am J Kidney Dis. 2005;46:820–829.
5. Clinical and Laboratory Standard Institute. GP-16 A3. Urinalysis and Collection, Transportation, and Preservation of Urine Specimens: Approved Guideline. 3rd ed. Wayne, PA: Clinical and Laboratory Standard Institute; 2009.
6. Fogazzi GB. The Urinary Sediment: An Integrated View. 3rd ed. Milan: Elsevier; 2010.
7. Lee W, Kim Y, Chang S, et al. The influence of vitamin C on the urine dipstick tests in the clinical specimens: a multicenter study. J Clin Lab Anal. 2017;32(5).
8. Lam MO. False hematuria due to bacteriuria. Arch Pathol. 1995;119:717–721.
9. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? Ann Clin Biochem. 2009;46:205–217.
10. Hermida FJ, Soto S, Benitez AJ. Evaluation of the urine/protein/creatinine ratio measured with the dipstick Clinitek Atlas PRO 12. Clin Lab. 2016;62:735–738.
11. John KA, Cogswell ME, Campbell NR, et al. Accuracy and usefulness of select methods for assessing complete collection of 24-hour urine: a systematic review. J Clin Hypertens. 2016;18(5):456–467.
12. Price CP, Newall R, Boyd JC. Use of protein/creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. Clin Chem. 2005;51:1577–1586.
13. Hogan MC, Reich HN, Nelson PJ, et al. The relatively poor correlation between random and 24-hour urine protein excretion in patients with biopsy-proven glomerular diseases. Kidney Int. 2016;90(5):1080–1089.
14. Shidham G, Ayoub I, Birmingham D, et al. Limited reliability of the spot urine protein/creatinine ratio in the longitudinal evaluation of patients with lupus nephritis. Kidney Int Rep. 2018;3(5):1057–1063.
15. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514–525.
16. Dimopoulos MA, Kastritis E, Terpos E, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34(13):1544–1557.
17. Beer JH, Vogt A, Neftel K, et al. False positive results for leucocytes in urine dipstick test with common antibiotics. BMJ. 1996;313:25.
18. Ramlakhan SL, Burke DP, Goldman RS. Dipstick urinalysis for the emergency department evaluation of urinary tract infections in infants aged less than 2 years. Eur J Emerg Med. 2011;18:221–224.
19. Fogazzi GB, Edefonti A, Garigali G, et al. Urine erythrocyte morphology in patients with microscopic haematuria caused by a glomerulopathy. Pediatr Nephrol. 2008;23:1093–1110.
20. Fairley K, Birch DF. Hematuria: a simple method for identifying glomerular bleeding. Kidney Int. 1982;21:105–108.
21. Rath B, Turner C, Hartley B, Chantler C. What makes red cells dysmorphic in glomerular hematuria? Pediatr Nephrol. 1992;6:424–427.
22. Köhler H, Wandel E, Brunck B. Acanthocyturia: a characteristic marker for glomerular bleeding. Kidney Int. 1991;40:115–120.
23. Tesser Poloni JA, Bosan IB, Garigali G, Fogazzi GB. Urinary red blood cells: not only glomerular and nonglomerular. Nephron Clin Pract. 2012;120:c36–c41.

24. Fogazzi GB, Ferrari B, Garigali G, et al. Urinary sediment in acute interstitial nephritis. Am J Kidney Dis. 2012;60:330–332.
25. Fogazzi GB, Saglimbeni L, Banfi G, et al. Urinary sediment features in proliferative and nonproliferative glomerular diseases. J Nephrol. 2005;18:703–710.
26. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. Clin J Am Soc Nephrol. 2013;8:1857–1862.
27. Hall IE, Coca SG, Perazella MA, et al. Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. Clin J Am Soc Nephrol. 2011;6:167–174.
28. Fogazzi GB, Garigali G, Pieruzzi F, et al. A morphological classification of the fat particles found in the urinary sediment of patients with Fabry disease. Clin Chem Lab Med. 2021;59:1832–1843.
29. Chawla LS, Dommu A, Berger A, et al. Urinary sediment cast scoring index for acute kidney injury: a pilot study. Nephron Clin Pract. 2008;110:c145–c150.
30. Spinelli D, Consonni D, Garigali G, Fogazzi GB. Waxy casts in the urinary sediment of patients with different types of glomerulonephritis: results of a prospective study. Clin Chim Acta. 2013;424:47–52.
31. Luciano RL, Perazella MA. Crystalline-induced kidney disease: a case for urine microscopy. Clin Kidney J. 2015;8:131–136.
32. Frochot V, Castiglione V, Lucas IT, et al. Advances in the identification of calcium carbonate urinary crystals. Clin Chim Acta. 2021;515:1–4.
33. Baroni S, Garigali G, Primiano A, Gervasoni J, Fogazzi GB. Very unusual “needle-and pencil-like” uric acid crystals in the urine unmasked by infrared spectroscopy investigation. Clin Chim Acta. 2018;479:72–73.
34. Covarelli C, Primiano A, Garigali G, et al. Other very rare and poorly known uric acid crystals for the first time also shown by polarized light and definitively identified by infrared spectroscopy. Clin Chim Acta; Int J Clin Chem. 2018;484:148–149.
35. Wong KA, Pardy C, Pillay S, et al. Can the presence of crystalluria predict stone formation in patients with cystinuria? J Endourol. 2016;30:609–614.
36. Garigali G, Marra G, Rizzo V, et al. A virtuous diagnostic and therapeutic roadmap triggered by a motivated and skilful urinary sediment examination. Clin Chim Acta. 2019;492:23–25.
37. De Liso F, Garigali G, Ferraris Fusarini C, et al. How to identify sulfamethoxazole crystalluria. Clin Chim Acta. 2016;452:106–108.
38. de Lastours V, Ferrari Rafael De Silva E, Daudon M, et al. High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients. J Antimicrob Chemother. 2013;68:1850–1856.
39. Daudon M, Frochot V, Bazin D, Jungers P. Drug-induced kidney stones and crystalline nephropathy: pathophysiology, prevention and treatment. Drugs. 2018;78(2):163–201.
40. Daudon M, Hennequin C, Boujelben G, et al. Serial crystalluria determination and the risk of recurrence in calcium stone formers. Kidney Int. 2005;67:1934–1943.
41. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;(suppl 31):S1–S157.
42. Chakera A, Dyar OJ, Hughes E, et al. Detection of polyomavirus BK reactivation after renal transplantation using an intensive decoy cell surveillance program is cost-effective. Transplantation. 2011;93:1018–1023.
43. Nickeleit V, True K, Detwiler T, et al. Risk assessment for polyomavirus nephropathy using urine cytology and the detection of decoy cells: cheap and efficient. Transplantation. 2012;94:e42–e44.
44. Fogazzi GB, Cantù M, Saglimbeni L. Decoy cells” in the urine due to polyomavirus BK infection: easily seen by phase-contrast microscopy. Nephrol Dial Transplant. 2001;16:1496–1498.
45. Singh HK, Bubendorf L, Mihatsch MJ, et al. Urine cytology of polyomavirus infection. Adv Exp Med Biol. 2006;577:201–212.
46. Fogazzi GB, Pallotti F, Garigali G. Atypical/malignant urothelial cells in

routine urinary sediment: worth knowing and reporting. Clin Chim Acta. 2015;439:107–111.

References

47. Previtali G, Ravasio R, Seghezzi M, Buoro S, Alessio MG. Performance evaluation of the new fully automated urine particle analyser UF-5000 compared to the reference method of the Fuchs-Rosenthal chamber. Clin Chim Acta. 2017;472:123–130.
48. İnce FD, Ellidağ HY, Koseoğlu M, et al. The comparison of automated urine analyzers with manual microscopic examination for urinalysis automated urine analyzers and manual urinalysis. Practical laboratory medicine. 2016;5:14–20.

49. Falbo R, Sala MR, Bussetti M, et al. Performance evaluation of a new and improved cuvette-based automated urinalysis analyzer with phase contrast microscopy. Clin Chim Acta. 2019;491:126–131.
50. Oyaert M, Speeckaert M, Boelens J, Delanghe JR. Renal tubular epithelial cells add value in the diagnosis of upper urinary tract pathology. Clin Chem Lab Med (CCLM). 2020;58(4):597–604.

5

Point of Care Ultrasound in Nephrology

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DEFINITION AND SCOPE

Point-of-care ultrasonography (POCUS) is a limited ultrasound examination performed by the clinician at the patient’s bedside to answer focused questions. Most of these questions are binary in nature; for example, “Does the patient have hydronephrosis?” “Is there a pericardial effusion?” In conjunction with history and physical examination findings, POCUS helps to arrive at a diagnosis or narrow the differential diagnosis. Although it may expedite care and eliminate the need for further imaging, POCUS is not a replacement for comprehensive ultrasound studies. The latter usually involves detailed assessment of an anatomic region and a report that includes a set of standard parameters, whereas POCUS answers focused clinical questions to guide the diagnostic process and management.

The scope of nephrologist-performed POCUS has recently expanded. Kidney ultrasound; volume status assessment using focused cardiac, lung, and abdominal vein Doppler ultrasound; and vascular access ultrasound are all within the scope of contemporary nephrology practice.[1,2] Fig. 5.1 illustrates the common nephrology-relevant POCUS applications. POCUS has evolved as one of the pillars of bedside clinical examination.[3,4]

the diameter of the inferior vena cava [Fig. 5.2B], excursion of cardiac valves, pleural sliding).

Color Doppler

In color flow mode, the velocity of mobile acoustic interfaces (red blood cells [RBCs]) is measured as a shift in frequency and represented as a range of colors. This mode is used to detect the presence of flow and identify its direction. When the RBCs move away from the transducer, the reflected frequency is lower than the transmitted frequency, and the difference or shift is represented as blue. On the other hand, if the RBCs move toward the transducer, reflected frequency is higher than the transmitted frequency and the shift is represented as red. The detection of frequency shift is optimal when the angle of insonation (direction of the ultrasound beam) is parallel to the flow, whereas a perpendicular angle (90 degrees) results in minimal color display with ambiguous directionality. Fig. 5.2C illustrates the arterial and venous flow in a renal allograft using color Doppler.

Spectral Doppler

Various modes of ultrasound display allow evaluation of different aspects of a tissue. The key modes pertinent to POCUS are described below.

This mode enables quantitative assessment of the blood flow by graphically representing velocity over time. The spectral waveform is displayed above the baseline if the flow is toward the transducer (analogous to red in color mode) and below the baseline if the flow is away from the transducer (blue in color mode). Spectral Doppler is of two main types: pulsed wave (PW) and continuous wave (CW) Doppler. PW Doppler involves emission of ultrasound waves in pulses and is used to quantify blood flow at a particular location (e.g., to measure the velocity in the renal artery, to assess the flow pattern in portal vein). Figure 5.2D illustrates PW Doppler tracing of a renal artery.

CW Doppler involves continuous emission of ultrasound waves and can measure higher velocities than PW Doppler. However, it does not sample a specific area and displays the signals received from all the vessels along the path of the Doppler line. This mode is useful in echocardiography when accurate measurement of peak velocity across a region is needed, such as the assessment of valvular stenosis.

B-Mode

Transducer Selection

B, or the brightness mode, denotes the regular two-dimensional (2D) grayscale display composed of several dots of varying brightness. It is the universal imaging mode, where structures appear in different shades of gray from black to white (Fig. 5.2A).

The transducer or probe is a component of the ultrasound machine that contains piezoelectric crystals and is used to acquire images. There are various types of transducers that differ by frequency, crystal arrangement, and shape. High-frequency waves produce high-resolution images but penetrate shallower depths. Conversely, low-frequency waves penetrate deeper at the expense of resolution. Therefore highfrequency transducers are typically used to image superficial structures such as an arteriovenous fistula, and low-frequency transducers are used for deeper structures such as the kidney and the heart. For

BASIC PHYSICS AND INSTRUMENTATION

The piezoelectric crystals in the ultrasound transducer produce highfrequency sound waves and convert the returning echoes (from the organs) into electrical signals, which are then displayed as a twodimensional grayscale image on the monitor. Although some newer handheld ultrasound devices use chip technology instead of piezoelectric crystals, the wave characteristics, modes, and principles of image acquisition essentially remain the same.

Ultrasound Imaging Modes

M-Mode

M, or the motion mode, is a unidimensional imaging mode that displays the movement of a structure over time. It is used to detect and/or quantify the movement of structures (e.g., respiratory variations in

Cardiac
Pericardial effusion?
Pump function OK?
Chamber enlargement?
Valves grossly OK?

Lung
Pulmonary congestion?
Pleural effusion?
Pneumonia?

Vascular access
Site of cannulation?
Fistula mature?
Pseudoaneurysm?
Thrombosis?

Kidney
Size?
Urinary obstruction?
Cyst? Stone? Mass?

Inferior vena cava
Size?
Respiratory variability?

Urinary bladder
Bladder outlet obstruction?
Obstructed Foley catheter?

Lower limb vessels
Deep vein thrombosis?

Fig. 5.1 Common sonographic applications and focused questions encountered in nephrology practice. (Created with Biorender.com.)

IVC

A

B

C

D

Fig. 5.2 (A) Grayscale image of a normal kidney. (B) M-mode image of the inferior vena cava. Tracing represents movement of the structure over time along the cursor (dotted line). (C) Color Doppler image of a normal transplanted kidney. (D) Pulsed wave Doppler image of renal artery. Note the Doppler line, which is like the M-mode cursor but with a small opening called sample volume, which should be placed in the region of interest to measure the flow. (Created with Biorender.com.)

A

C

B

Fig. 5.3 Curvilinear (A), phased array (B), and linear (C) transducers illustrating their respective fields of view.
(Created with Biorender.com.)

nephrology-related applications, the three most common types of transducers are curvilinear, phased array, and linear. A curvilinear transducer is a low-frequency probe that consists of curvilinear or convex arrangement of crystals and produces a broad field of view (Fig. 5.3A). This allows scanning wider areas and deeper structures; hence it is best suited for abdominal applications. A phased array transducer is also a low-frequency transducer but with a small footprint and central arrangement of crystals producing a pie-shaped image (Fig. 5.3B). Because this enables scanning through narrow spaces such as rib interspaces, it is well suited for cardiac applications. Moreover, phased, or differential, excitation of piezoelectric elements produces sequential pulses of ultrasound waves, which allows optimal imaging of mobile structures (e.g., heart). A linear transducer is a high-frequency probe with crystals arranged in a straight line and produces a rectangular image (Fig. 5.3C). It is best suited for vascular applications, which require higher resolution. Some newer handheld ultrasound devices combine these different properties into one transducer, allowing multisystem scanning by changing the presets (e.g., abdomen, vascular, cardiac) without actually switching the probe.

Image Orientation and Interpretation

Understanding the image orientation is key to accurate interpretation. A structure that is closer to the transducer is displayed at the top of the image, whereas a structure that is farther from the transducer is displayed at the bottom. What is displayed on the right and left of the image depends on the direction of transducer orientation marker (probe marker) while obtaining the image. This marker can be a dot, a light, or a ridge on the transducer and corresponds to the orientation marker on the screen (screen indicator), which is toward the left in the abdomen preset. During a standard abdominal exam, the probe marker is pointed toward the patient’s head when obtaining longitudinal images. Therefore the superior pole of the kidney is on the left and the lower pole is on the right of the image in the long axis view. Fig. 5.4 illustrates image orientation.

The displayed echogenicity or brightness of a tissue or structure depends on the strength of the reflected signals. Structures that efficiently transmit sound waves without reflection appear black and

are described as anechoic (i.e., not making echoes). Examples include urine, blood, bile, and serous fluid in cysts. On the other hand, hyperechoic structures reflect more sound waves (make more echoes) and appear bright/white. Examples include calcified and fibrous structures such as stones, diaphragm, and pericardium. Some hyperechoic structures (e.g., stones, bones) create shadows due to near-total reflection of ultrasound waves precluding visualization of the underlying structures. Air is also a poor ultrasound transmitter, and its presence will preclude imaging of deeper structures. Most soft tissues appear in different shades of gray and are described in terms of relative echogenicity, that is, in comparison with the brightness of surrounding structures. Structures that reflect fewer sound waves compared to surrounding structures are described as being hypoechoic (e.g., renal cortex vs. liver). The term isoechoic is used to describe structures that make echoes of similar intensity to that of the surrounding structures. For example, cortex of the kidney can be isoechoic to that of the medulla in some cases of chronic kidney disease, where corticomedullary differentiation is lost.

KIDNEY AND BLADDER ULTRASOUND

Technique

Kidney ultrasound is performed using a curvilinear transducer. If the latter is not available, a phased array transducer can be used to rule out gross abnormalities such as hydronephrosis; however, parenchymal characteristics and small lesions may not be well visualized. Liver and spleen act as acoustic windows to image the right and left kidneys, respectively—meaning that the right kidney is visualized through the liver and the left kidney is visualized through the spleen; otherwise, bowel gas will impede the view. Examination is performed with the patient in the supine position, though lateral decubitus, oblique, or even prone positions may sometimes be required for visualization of the left kidney due to overlying bowel gas. To acquire longitudinal views of the kidney, the transducer is positioned in the mid or anterior axillary line at the tenth rib interspace, with the orientation marker pointing toward the patient’s head and aiming slightly posterior. The transducer may have to be moved superiorly or inferiorly depending

Probe orientation marker

Screen indicator
Close to the probe

Away from the probe

Fig. 5.4 Orientation to an Ultrasound Image. The green arrow denotes direction of the probe orientation marker. The right kidney is shown here, but the principles remain the same for any organ being imaged.
(Created with Biorender.com.)

on the patient’s body habitus. Once the entire long axis of the kidney is in view, the transducer must be fanned (tilted) anteriorly and posteriorly to image it completely. The transducer is then rotated 90 degrees counterclockwise to obtain a short axis or transverse view of the kidney. With the transverse view obtained, the transducer is fanned superiorly and inferiorly to visualize the kidney from pole to pole.

Although comprehensive Doppler evaluation to detect renal artery stenosis is beyond the scope of POCUS, color Doppler images of the kidney should be obtained. They provide a global assessment of kidney perfusion and allow detection of gross vascular abnormalities such as an arteriovenous malformation that can sometimes mimic a dilated collecting system.5

Image acquisition of the transplanted kidney is relatively easy because of its superficial location in the pelvis. Longitudinal and transverse views should be obtained, paying attention to the surgical anatomy and perinephric space to evaluate for collections such as hematoma or lymphocele. In children and thin individuals, a linear transducer may be used to obtain images with higher resolution.

The urinary bladder is also imaged using a curvilinear transducer with the patient supine. Usually, the transverse view is obtained first by placing the transducer just above the pubic symphysis with the orientation marker to the patient’s right and aiming the beam inferiorly. A fanning movement should be performed to visualize the bladder superoinferiorly. The transducer is then rotated 90 degrees clockwise with the orientation marker facing the patient’s head to obtain the longitudinal view and fanned to visualize the right and left walls of the bladder.

Interpretation

On sonographic images, the kidney appears as a well-defined, beanshaped structure surrounded by an echogenic capsule. The kidney is about 9 to 12 cm long in the longitudinal plane and varies with patient height. Kidney parenchyma is composed of the outer cortex and inner medulla, which in turn is organized into multiple pyramids. Cortex is usually hypoechoic (or isoechoic) compared to the adjacent normal liver and spleen. Cortical tissue normally extends into the medulla, separating pyramids in the form of columns called columns of Bertin. These columns can sometimes hypertrophy and mimic a neoplasm. The medullary pyramids appear anechoic or hypoechoic compared to the cortex. These are prominent in young children but not always well visualized in adults. The echogenic sinus fat, which encases the renal collecting system, occupies the majority of the inner kidney. The undilated collecting system is not typically visible as a distinct structure; therefore the appearance of an anechoic area amid sinus fat should raise the suspicion for hydronephrosis. On the other hand, the collecting system of a well-functioning transplanted kidney is often slightly dilated, likely because of a combination of an increased volume of urine produced (solitary functioning kidney) and loss of the ureter’s tonicity from denervation.[6] In the transverse or short axis view, the midportion of the kidney is C-shaped, with the vessels entering and leaving through the hilum, and the poles appear circular (Fig. 5.5).

The urinary bladder appears as an anechoic, fluid-filled structure (urine is black on ultrasound). It is ovoid to rectangular when full, but the shape varies with the amount of urine present. Note should be made of the uterus in females and the prostate in males where applicable.

When evaluating a patient with acute kidney injury (AKI), excluding urinary obstruction is the main indication for POCUS. In addition, evaluating kidney size and echogenicity gives information about chronicity of the kidney dysfunction (see Chapter 97).

Hydronephrosis

Hydronephrosis is essentially anechoic backlogged urine that appears as branching, interconnected areas in the renal collecting system. The severity of hydronephrosis is qualitatively graded as mild, moderate, or severe (Fig. 5.6). In mild hydronephrosis, there is dilation of the renal pelvis and calyces, but the overall parenchymal architecture is retained. In moderate hydronephrosis, the medullary pyramids start to flatten due to back pressure in addition to increasing dilation of the pelvicalyceal system. In severe cases, the renal pelvis and calyces appear ballooned (occupying most of the kidney), and corticomedullary differentiation is lost (making the parenchyma thin). If the hydronephrotic area demonstrates internal echoes, pyonephrosis (pus in

L

C
F

*

A

B

Fig. 5.5 Longitudinal (A) and Transverse (B) Views of a Normal Kidney. The green arrow denotes direction of the probe orientation marker during image acquisition. The asterisk denotes the medullary pyramid. In the transverse image, the arrowhead indicates renal vein (use color Doppler to differentiate from a hydroureter). C, Cortex; F, sinus fat; L, liver. (Created with Biorender.com.)

A

C

B

Fig. 5.6 Mild (A), moderate (B), and severe (C) hydronephrosis.

the collecting system) should be considered in the appropriate clinical context, such as when the patient presents with fever and flank pain. False negatives for hydronephrosis can occur in the setting of acute or partial obstruction, volume depletion, and retroperitoneal fibrosis.[7,8] It is prudent to perform repeat POCUS examination and/or excretory urography when the suspicion for obstruction is high. Prominent renal vasculature and vascular malformations can mimic hydronephrosis, as both blood and urine appear anechoic. However, demonstrating the presence of flow using color Doppler confirms vasculature (Fig. 5.7A–B). Similarly, cysts are also anechoic and may be confused with hydronephrosis, particularly when close to the renal pelvis (parapelvic cysts) (Fig. 5.7C–D). However, cysts tend to be round and well circumscribed as opposed to hydronephrosis, which is an irregular branching structure. In addition, continuity can be demonstrated between dilated renal pelvis and hydroureter while the cyst is not connected to the ureter. Comparison with prior imaging helps when available.

Stones

Kidney stones may be encountered in patients with urinary obstruction. On grayscale images, they appear as hyperechoic structures with a posterior acoustic shadow. Acoustic shadowing is the black area or signal void seen beyond structures that do not transmit ultrasound waves. In the color Doppler mode, stones exhibit the “twinkling sign,” which refers to a rapidly alternating focus of color Doppler signals mimicking turbulent flow, which is more pronounced with rougher stones.

Urinary Bladder

Sonographic evaluation of urinary obstruction should always include images of the urinary bladder. It helps in assessing urinary retention,

A

B

C

D

Fig. 5.7 (A) Grayscale image of the kidney demonstrating an anechoic area mimicking mild hydronephrosis.
(B) Color Doppler image of the same kidney demonstrating blood flow suggestive of vasculature (arteriovenous malformation in this case). (C–D) Longitudinal and transverse images of kidney demonstrating a large parapelvic cyst mimicking hydronephrosis.

and pathologies such as enlarged prostate, bladder stones, and masses may be found that guide management. Furthermore, a misplaced or obstructed Foley catheter can be easily identified (Fig. 5.8).

FOCUSED CARDIAC ULTRASOUND

Accurate assessment of volume status allows effective management of patients with complex fluid and electrolyte disorders commonly encountered in nephrology practice. Goal-directed ultrasonography of the pump, pipes, and leaks provides helpful insights into a patient's hemodynamics. Pump represents focused cardiac ultrasound (FoCUS), pipes represent inferior vena cava (IVC) ultrasound and venous Doppler, and the leaks indicate assessment of the extravascular lung water and ascites. Though separately mentioned here, IVC ultrasound is often considered a component of FoCUS.

Technique

There are five standard views of FoCUS, namely, parasternal long axis, parasternal short axis, apical four-chamber, subcostal four-chamber, and subcostal IVC. It is important to be familiar with all these views, as some of them may not be well visualized depending on the patient's body habitus, surgical dressings, and so forth, necessitating an alternative approach. The following is a brief description of the image acquisition technique as well as key cardiac structures visualized in each of these views. Also, note that by convention the screen indicator is displayed to the right in the cardiac preset (as opposed to left in the abdominal and vascular presets) but still corresponds to the probe marker. Therefore failure to select the appropriate preset results in flipped images.

Parasternal Long Axis (PLAX) View

This view images the heart in its long axis, which is oblique with respect to the body's long axis. The transducer is placed just to the left of the sternum (parasternal) in the third or fourth intercostal space with the probe marker toward patient's right shoulder.

In the PLAX image (Fig. 5.9A), the right ventricular outflow tract (RVOT) is seen on the top of the screen as it is closer to the transducer. The long axis view of the left ventricle (LV) is seen posterior to it with its inflow (i.e., the left atrium [LA] and mitral valve) and the outflow (i.e., the aortic valve and ascending aorta [Ao]). Slight rotation and tilting of the transducer may be needed to fully open the LV cavity. The depth of the image should be appropriately adjusted to visualize the descending aorta, which appears as an anechoic circular structure posterior to the LA/LV. This is an important landmark to differentiate pericardial from pleural effusion in this view (see below).

Parasternal Short Axis (PSAX) View

This view images the heart in its transverse plane. It is obtained by rotating the transducer 90 degrees clockwise from the PLAX position

F

A

F

B

C

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F

E

Fig. 5.8 (A) Normal urinary bladder ultrasound, transverse plane. (B) Decompressed bladder with Foley catheter. (C) Bladder filled with anechoic urine despite having a Foley catheter indicative of obstructed catheter. (D) Misplaced Foley catheter balloon in prostatic urethra; asterisk indicates prostate gland. (E) Enlarged prostate gland (arrow) compressing the bladder. (F) Bladder stone (arrow). Note the acoustic shadowing (asterisk) and surrounding debris (arrowhead). F, Fluid-filled balloon of the catheter.

RVOT
LV

RV
Ao

AV

LV

MV LA

A

DAo

B

Liver
RV

RV

LV
RA

TV RA

C

LA MV

LV

LA

D

Fig. 5.9 Standard Views of Focused Cardiac Ultrasound. Left, Transducer position to acquire these views. Green arrows denote direction of the transducer orientation marker. Right, Sonographic images of parasternal long axis (A), parasternal short axis (B; arrow indicates papillary muscle), and apical (C) and subcostal (D) four-chamber views. Ao, Aorta; AV, aortic valve; DAo, descending thoracic aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve. (Created with Biorender.com.)

such that the orientation marker is facing the patient’s left shoulder. There are three main levels of visualization in PSAX that can be obtained by tilting the probe superiorly and inferiorly. The aortic valve can be seen by tilting up the transducer toward the patient’s right shoulder. The mitral valve level is obtained when the probe is

almost perpendicular to the chest wall. The papillary muscle level comes into view when the face of the probe is slightly tilted down toward the patient’s left flank. Of these, the papillary muscle or the midventricular view is considered a standard FoCUS view and consists of the semilunar right ventricle (RV) on the top followed by the round LV with papillary muscles appearing as inward projections (Fig. 5.9B). This view allows evaluation of the radial function of the LV and detection of the RV enlargement.

Apical Four-Chamber View

This view images the heart in its coronal plane from the apex. It is obtained by placing the transducer in the fourth or fifth intercostal space (where the apical impulse is felt) with the orientation marker facing the patient’s left shoulder (somewhere between 2 o’clock and 3 o’clock positions). Another approach is to slide the transducer inferolaterally from the PSAX position toward the apex. Whenever possible, positioning the patient in the left lateral position improves the image quality; this also applies to parasternal views.

The apical four-chamber view demonstrates all four chambers of the heart and the tricuspid and mitral valves. The right atrium (RA) and RV are on the left of the screen and the LA/LV on the right (Fig. 5.9C). This is a good view to assess atrioventricular valve regurgitation using color Doppler and vegetations, if they are large enough to be seen on transthoracic echo. The apical five-chamber view is obtained by tilting the transducer slightly anterior from the four-chamber view, which brings the LV outflow tract and the aortic valve into view (fifth chamber).

Subcostal Four-Chamber View

This view images the heart through the liver from the subxiphoid area. The transducer is placed just below the xiphoid process in the midline with the orientation marker toward the patient’s left side. The transducer should be pressed firmly and tilted such that it is almost parallel to the skin surface. Having the patient bend their knees when possible helps to relax the abdominal wall musculature. This view is particularly useful in patients with difficult or inaccessible chest windows, such as those with hyperinflated lungs (obstructive airway disease, mechanical ventilation), surgical dressings, and so forth.

The subcostal four-chamber view shows the same structures as an apical four-chamber view but appears tilted because a different scan plane is used (Fig. 5.9D). RV size can be underestimated in this view; hence caution should be exercised when commenting on the relative chamber size. In general, it is a good practice to corroborate abnormal findings in at least two different cardiac views.

Subcostal Inferior Vena Cava View

This view is obtained by rotating the transducer approximately 90 degrees counterclockwise from the subcostal four-chamber view. The IVC is seen as a longitudinal anechoic structure joining the heart (RA) (Fig. 5.2B). The hepatic vein is often seen entering the IVC close to the IVC-RA junction. Care must be taken to visualize the widest diameter of the IVC by tiling the transducer from left to right (the ultrasound beam should pass through the center of the vessel). When assessing the RA pressure, maximal diameter and respiratory variation of the IVC are measured just distal to the hepatic vein–IVC confluence, or approximately 2 cm from the IVC-RA junction. IVC size should not be measured at the IVC-RA junction because the diaphragmatic pull can mimic collapse and lead to misinterpretation. A transverse view of the IVC can be obtained by rotating the transducer 90 degrees counterclockwise from this position; this helps to clarify the measurements when in doubt. Care must be taken to avoid mistaking the aorta for the IVC. Contrary to the IVC, the aorta is not in direct contact with the liver, and no IVC-RA junction will be seen.

Interpretation

FoCUS quickly provides the answers to the five Es, that is, the qualitative estimation of left ventricular ejection; the presence or absence of

pericardial effusion; equality (relative ventricular size); entrance (IVC size and collapsibility); and the exit (stroke volume measurement at the left ventricular outflow tract [LVOT]).9,10 In addition, attention should be paid to any gross abnormalities such as intracardiac thrombi and valvular vegetations. Also, a quick color Doppler assessment of atrioventricular valves in the apical four-chamber view is helpful to exclude significant regurgitant lesions leading to pulmonary or systemic vascular congestion.

Ejection

Assessment of LV systolic function, or the ejection, is a key component of volume status assessment. Qualitative estimation of or “eyeballing” the ejection fraction is done by observing wall motion and comparison of the chamber size between systole and diastole. Wall motion constitutes both thickening and inward motion of the endocardium during systole. In general, the walls should approximate by one-third or more. In patients with depressed LV function, both wall thickening and inward motion are decreased. On the other hand, a hyperdynamic ventricle, that is, where ventricular walls/papillary muscles in the parasternal short axis view almost touch at end systole, may indicate volume depletion if the overall clinical picture is suggestive. In addition, the movement of the mitral valve should be observed. Normally, the anterior leaflet almost touches the interventricular septum with each heartbeat. If the ejection fraction is low, reduced stroke volume results in decreased blood flow across the mitral valve, and it does not open maximally, increasing the distance between the septum and anterior leaflet (Video 5.1). When visual estimation is ambiguous or the physician does not have enough experience in eyeballing, M-mode measurement of this motion can be helpful. The distance between the peak of mitral valve tracing during early passive diastolic filling (E-point) and interventricular septum of greater than 7 mm is generally considered as a marker of significant LV systolic dysfunction (LVEF <30%).11 This is called E-point septal separation (EPSS).

Effusion

Pericardial effusion is an important cause of hypotension and hemodynamic compromise. On ultrasound, it appears as an anechoic space between the two pericardial layers. PLAX and subcostal views allow better visualization of the effusion, though it is generally identifiable on all the standard FoCUS views (Fig. 5.10A–B). In the PLAX view, a left pleural effusion may be mistaken for pericardial effusion because the pleural space is immediately posterior to the pericardium. The descending thoracic aorta is an anatomic landmark that helps to differentiate pericardial and pleural effusions in this view. Pericardial effusion is seen anterior to the descending aorta, whereas the pleural effusion is seen posteriorly or starts at the same level (Fig. 5.10C–D). Moreover, a collapsed lung is often seen as a mobile echogenic structure within the pleural effusion.

With respect to severity, a separation between the pericardial layers in diastole of less than 1 cm is considered mild effusion, whereas 1 to 2 cm is considered moderate and greater than 2 cm severe.12 Whenever a pericardial effusion is detected, note should be made of right atrial collapse at the onset of systole, or diastolic right ventricular collapse. These suggest cardiac tamponade, as does a dilated IVC with minimal or absent respiratory variation.

Equality

Equality refers to relative chamber size, particularly of the RV compared to LV. A normal RV is less than two-thirds the size of the LV and can quickly dilate with pressure or volume overload. When the RV is mildly enlarged, it is slightly more than two-thirds the size of the LV and is of the same size as the LV when moderately enlarged.

A

B

*

D

C

Fig. 5.10 Subcostal (A) and parasternal short axis (B) views demonstrating pericardial effusion (arrowhead).
(C) Schematic of normal parasternal long axis view. (D) Parasternal long axis view demonstrating a small
pericardial effusion (arrowhead) anterior to the descending aorta (arrow) and a left pleural effusion (asterisk)
posterior to it. (C, Created with Biorender.com.)

Severe RV dilation is characterized by it being bigger than the LV (Fig. 5.11A). The apical four-chamber and PSAX are good views to assess this. With volume overload, the RV becomes dilated and the interventricular septum is flattened predominantly in diastole, giving a D-shaped appearance to the LV in the PSAX view. This is called the D-sign (Fig. 5.11B). This occurs in both systole and diastole if there is pressure overload (e.g., pulmonary embolism or severe pulmonary hypertension). Although these patients are often hypotensive, indiscriminate administration of intravenous fluids results in further compromise of the LV cavity from excess preload-induced RV dilation leading to drop in cardiac output.

Entrance

Entrance (to the heart) refers to evaluation of IVC size and collapsibility to estimate RA pressure, which is a driver of systemic venous congestion and congestive nephropathy.13 In spontaneously breathing patients, the IVC collapses during inspiration due to negative intrathoracic pressure. An IVC diameter of 2.1 cm or less and collapsibility greater than 50% with a sudden inspiration (a sniff) indicates normal RA pressure of 3 mm Hg (0–5 mm Hg); an IVC diameter greater than 2.1 cm with less than 50% inspiratory collapse indicates high RA pressure of 15 mm Hg (10–20 mm Hg); scenarios in between are ascribed to an intermediate value of 8 mm Hg (5–10 mm Hg). These cutoffs cannot be used in mechanically ventilated patients because the IVC is dilated at baseline due to positive pressure ventilation and may not collapse at all during the respiratory cycle. Moreover, not all patients are able to sniff on request and IVC collapsibility can significantly vary with magnitude of the inspiratory effort. In general, IVC ultrasound can be used as an indicator of fluid tolerance, that is, as a stop point for administering fluids when the IVC is plethoric. However, assessment of fluid responsiveness (increase in cardiac output in response to fluids) should not be based on IVC alone. Bedside stroke volume should be measured when possible as described below. Video 5.2 illustrates a small collapsible IVC and a plethoric IVC.

Exit

Exit (from the heart) refers to measurement of the stroke volume at the LVOT. In the emergency medicine literature, exit was originally used to denote assessment of the aortic root for thoracic aortic aneurysm and thoracic aortic dissection.10 In patients with tenuous fluid status but no gross volume overload, assessing fluid responsiveness using FoCUS is helpful when intravenous fluid therapy is contemplated. The passive

A

B

C

Fig. 5.11 Apical four-chamber (A) and parasternal short axis (B) views obtained from a patient with severe pulmonary hypertension. Note severe enlargement of the right ventricle (larger than left ventricle in apical view) and interventricular septal flattening with D-sign on short axis. Arrowhead points to hypertrophied moderator band in the right ventricle. (C) Components of stroke volume assessment. Velocity time integral (VTI) is obtained by tracing the pulsed wave Doppler envelope of the left ventriuclar outflow tract (LVOT) in apical five-chamber view. Cross sectional area of the LVOT is obtained by measuring its diameter (d) at the base of the aortic valve in midsystole and using the formula for area of a circle, πr^2 (where r = radius, or diameter divided by 2). (Created with Biorender.com.)

leg raise is a simple bedside method of predicting fluid responsiveness. It is performed by tilting the patient from a 45-degree semirecumbent head-up position to a 45-degree leg-up position, which transfers up to 300 to 400 mL of blood into the central circulation and acting as an autogenous fluid bolus. Stroke volume is measured at the LVOT before and 1 minute after the leg raise; an increase by 10% suggests fluid responsiveness.14 Stroke volume is the product of the crosssectional area (CSA) of the LVOT and the velocity time integral (VTI). LVOT CSA is derived from the LVOT diameter in PLAX view using the formula πr^2, and LVOT VTI is obtained by tracing the envelope of the Doppler spectrum of systolic flow in the apical five-chamber view (Fig. 5.11C). As the LVOT diameter is constant for a given person, VTI (normal: approximately 18–22 cm) is generally used as a surrogate for cardiac output changes, assuming the heart rate is relatively constant. This parameter is also used to differentiate between true hypovolemia (VTI will be low) and high cardiac output states (VTI will be high); both conditions are often associated with a hyperdynamic left ventricle and small IVC.

ULTRASOUND OF THE LUNG AND PLEURA

Because air transmits ultrasound poorly, the normally aerated lung parenchyma prevents the visualization of anatomic structures beyond the interface between the parietal and the visceral pleura. Nonetheless, ultrasound can provide important information related to the pleural and subpleural space. A key feature of lung ultrasound is that it relies on the interpretation of artifacts, which are nonanatomic images generated by the interaction between ultrasound and tissues.

Technique

Lung and pleural ultrasound can be performed using most entry-level POCUS devices. Linear (vascular probe), phased array (cardiac), and curvilinear (abdominal) transducers may be used. However, the preferred transducer will depend on the type of pathology, and multiple types of transducers may be required. The linear transducer has improved resolution of superficial structures, which makes it better for assessing the chest wall, pleura, and superficial subpleural space. Phased array and curvilinear transducers can image structures at a higher depth, which make them superior for imaging lung consolidation and pleural effusion. All transducers are able to visualize artifacts arising from below the pleural line. However, phased array and curvilinear transducers may be superior to linear transducers for this indication.15 Ultrasound manufacturers usually include a preconfigured setting for lung ultrasound.

To adequately visualize the structures and to reduce artifacts, it is important to position the probe at a perpendicular (90-degree) angle to the chest. This usually produces normal A-line artifacts, as shown in Fig. 5.12A–B. Using a cephalocaudal orientation, the rib shadows help with the identification of intercostal spaces. Because lung ultrasound only provides information at the site where the transducer is located, multiple sites of assessment on the thorax are always required: protocols include assessment of 28 zones (16 right zones and 12 left zones),16 eight zones (four on each side),17 or six zones (three on each side).18 Multiple factors related to the clinical context must be considered when deciding the number of zones to assess. For example, a six-zone protocol might be sufficient for the rapid assessment of an acutely dyspneic patient (Fig. 5.13).18 On the other hand, evaluation of lung congestion in asymptomatic or minimally symptomatic patients may require more than six zones.16 Although the evidence is limited, the use of simpler protocols (eight zones) may be comparable to the more time-consuming 28-zone approach.17

Interpretation

After adequate visualization of an intercostal space (the area between two rib shadows), the first step is to examine the hyperechoic pleural line just deep to intercostal muscles. This line oscillates or shimmers with respiration, which represents pleural sliding. The presence of sliding confirms that air is not present between the parietal and visceral pleurae (Video 5.3). Movement transmitted from the heart, commonly referred to as a lung pulse, also serves the same purpose. This can rule out the presence of a pneumothorax or subcutaneous emphysema at the site of assessment. It is important to first exclude these diagnoses because air will preclude the assessment of deeper structures and produce a pseudonormal A-line pattern that could mislead. Lung sliding and lung pulse can be better visualized by decreasing the depth of the image and by using a linear transducer.

After confirmation of the pleural sliding, depth should be increased up to 10 to 12 cm below the pleural line to examine the subpleural space and optimize the visualization of artifacts, which are illustrated in Fig. 5.12A–D. The normal A-line pattern represents linear artifacts that are parallel and equidistant from the pleural line. These are created by ultrasound reverberation from the pleural interface. B-lines represent linear artifacts that arise from the pleural line, extend to the end of the image without fading, and move synchronously with lung sliding. They tend to completely or partially erase A-line in their path (Video 5.4). B-lines can become confluent or coalescent, completely erasing the A-lines and giving a white lung appearance in cases where there is severe loss of lung aeration. B-lines are the hallmark of increased density of lung parenchyma in the first millimeters below the pleural interface with partial aeration and generally represent increased extravascular lung water. However, they can be seen in multiple pathologies as summarized in Table 5.1. One or two isolated B-line artifacts per rib interspace may not indicate pathology, particularly in the dependent lung zones. The visualization of three or more B-lines in a rib interspace (a B-line region) is often significant, and more than two positive B-line regions bilaterally constitute interstitial syndrome. The distribution of B-lines, associated ultrasound findings, and clinical context may help differentiate between possible etiologies.

Consolidated or atelectatic lung parenchyma will transmit ultrasound because it is devoid of air and will produce variable appearance on ultrasound, from a hypoechoic region to a tissue or liver-like appearance (hepatization) (Fig. 5.12E–F). It is important to note that central consolidations that do not reach the pleura are not detected by ultrasound because air is present between the pathology and the transducer. Because of this, lung ultrasound has variable sensitivity for the diagnosis of pneumonia.

Pleural effusion appears as an anechoic space above the diaphragm, usually surrounding the atelectatic lung. Effusions can be identified, characterized, and quantified using POCUS (Fig. 5.12G–H). Detection of small pleural effusions require the phased array or curvilinear transducer to be positioned in the midaxillary line to obtain a coronal view of the interface between the lung, the diaphragm, and the liver/spleen. Seeing the dorsal vertebral column in this position usually implies the presence of fluid permitting the transmission of sound. This is called the spine sign and is the most sensitive sign to detect a small pleural effusion. Unlike uniformly anechoic simple effusions, complex effusions often contain swirling internal echoes (plankton sign) and may demonstrate fibrin stranding or distinct septations. Although most complex effusions tend to be of infectious etiology, a hemothorax with partially clotted blood can have a similar appearance and should be interpreted in the appropriate clinical context.

Clinical Applications

Lung and pleural ultrasound is a valuable adjunct to physical examination in the management of patients with undifferentiated dyspnea and those with difficult-to-determine fluid status. Both of these clinical scenarios are frequently encountered in the care of patients with kidney disease, including those on kidney replacement therapy.

In patients with dyspnea, POCUS is highly sensitive to detect pneumothorax,19 pleural effusions,20 and diffuse interstitial syndromes such as acute pulmonary edema,21 acute respiratory distress syndrome (ARDS), and diffuse viral pneumonia22 (see Table 5.1). Subpleural consolidations, an irregular pleural line, or a patchy involvement with spared areas all suggest diffuse pneumonia or ARDS, whereas a homogenous distribution of B-lines without pleural anomalies is more compatible with pulmonary edema. B-lines observed in a single location on the thorax may indicate localized pneumonia, partial atelectasis, or pulmonary embolism. However, the sensitivity of lung ultrasound is moderate for bacterial pneumonia23 and low for pulmonary embolism.24 These pathologies may present with dyspnea in the presence of primarily an A-line pattern with lung sliding. An A-line pattern will also be seen in acute exacerbations of asthma or chronic obstructive pulmonary disease. A diagnostic algorithm based on the bedside lung ultrasound in emergency (BLUE) protocol18 used in the intensive care and emergency medicine settings is presented in Fig. 5.13.

Even in the absence of dyspnea, pulmonary congestion may be present, and its detection provides important information to guide fluid management decisions. For example, B-lines are detected in a significant

Ribs

Ribs

Pleural interface
Pleural interface

A-line

A-line

B

A

Subpleural
consolidation

C

B-line

D

B-line

Air
bronchogram

Consolidation

Consolidation

F

E

LEFT
Liver
Pleural
effusion

Spleen
Pleural
effusion

Lung

G

Spine

(Atelectasis)
96
BPM

H

Spine

Fig. 5.12 Examples of Lung and Pleural Ultrasound. Normal ultrasound (A-line pattern) using a linear transducer (A) and a curvilinear transducer (B). B-lines shown using a linear transducer (C) and a curvilinear transducer (D). Note that B-lines move with respiration (see Video 5.4). Examples of lung consolidation (also referred often as the C-pattern) showing a heterogeneous tissue-like appearance (E–F). Pleural effusion of the right lower thorax region (G) and to the left lower thorax region (H).

1
3

2

2

Yes

A-line pattern
Without lung sliding

Pneumothorax
Subcutaneous emphysema

No

B-line pattern
Diffuse

A-line pattern
With lung sliding

Asthma/COPD
exacerbation
Pneumonia
Pulmonary
embolism

Consolidation

Loc

al

Pulmonary edema
Diffuse
pneumonia

Pneumonia
Partial
atelectasis

ARDS
Interstitial lung
disease

Pulmonary
embolism

Pneumonia
Atelectasis

Partial atelectasis

Fig. 5.13 Proposed Approach to Acute Dyspnea Using Lung Ultrasound Based on the Bedside Lung Ultrasound in Emergency (BLUE) Protocol. 4 Three zones on each side are assessed: the upper point (1), the lower point (2), and the posterolateral point (3). The original BLUE protocol also includes assessment of

lower extremity veins to detect deep venous thrombosis suggestive of pulmonary embolism. ARDS, Acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

proportion of asymptomatic patients with end-stage kidney disease[25] and chronic heart failure, and B-lines appear to be more sensitive than chest auscultation to identify pulmonary congestion.[26] In hemodialysis patients, the B-line count is reduced in proportion to the amount of intradialytic ultrafiltration[27] and seems to correlate with mortality,[16,17,28] although it is unclear whether modifying fluid removal prescription to target resolution of B-lines improves outcomes.[29] A recent small trial showed that target weight prescription guided by lung ultrasound improved blood pressure without increasing the risk of intradialytic hypotension[30] and improved LV filling pressures by echocardiography.[31] Interestingly, two single-center trials performed in ambulatory chronic heart failure patients showed that the addition of lung ultrasound to the physical examination may reduce the risk of hospitalization.[32,33]

ARTERIAL AND VENOUS DOPPLER OF THE KIDNEY AND OTHER ORGANS

Doppler ultrasonography enables assessment of blood flow velocity and patterns during the cardiac cycle at various locations in the circulatory system. Arterial Doppler waveforms are influenced by upstream and downstream factors including pulse pressure, the presence of stenosis, blood flow, and vascular resistance of the downstream vascular bed. Venous Doppler waveforms are primarily influenced by the pattern of venous return during the cardiac cycle and systemic venous compliance. The next sections provide a brief overview of this topic; a more detailed account can be found elsewhere.[34,35]

Arterial Doppler

A comprehensive ultrasound examination to evaluate suspected renal artery stenosis involves visualizing the renal arteries throughout their course from the aorta to the level of the segmental and interlobar arteries. In addition, accurate flow velocities need to be measured at multiple sites, which depends on an appropriate angle of insonation and requires a higher operator skill level. Therefore it is better performed by a trained sonographer, rather than a physician, using POCUS to answer focused questions at the bedside.

On the other hand, renal resistive index (RI), which is an indirect indicator of renal artery stenosis, is a ratio and therefore is less

TABLE 5.1 Differential Diagnosis of B-Line Artifacts on Lung Ultrasound

Etiology of B-Lines	Associated Findings/Comments
Diffuse Pattern	
Pulmonary edema	Higher severity in dependent lung regions
Viral pneumonia	Nonhomogeneous distribution (some areas are “spared”) with irregular pleural line and subpleural consolidations[a]
ARDS	Nonhomogeneous distribution with irregular pleural line and subpleural consolidations
Interstitial lung disease	Nonhomogeneous distribution irregular pleural line and subpleural consolidations
Local Pattern	
Localized pneumonia	Sensitivity is imperfect because the pneumonia must extend to the pleural interface before ultrasound can detect it Pleural sliding often decreased/absent
Partial atelectasis	Pleural sliding often decreased/absent
Pulmonary embolism	Low sensitivity

Lung ultrasound findings must be interpreted in the appropriate clinical context and in conjunction with physical examination/other sonographic findings. For example, history might indicate preexisting interstitial lung disease or suggest an infectious etiology in a patient presenting with fever, etc.

[a] Pleural line irregularities and subpleural consolidations are better appreciated using a linear transducer.

dependent on the angle of insonation. RI is calculated from intrarenal arterial (typically interlobar) Doppler tracing using the following formula:

(Peak systolic velocity − End diastolic velocity)/Peak systolic velocity

The normal range is approximately 0.50 to 0.70. Despite its name, the renal vascular resistance is only one factor affecting the RI, and the interpretation must take into consideration the influence of systemic hemodynamics. Hemodynamically significant renal artery stenosis is often associated with a lower RI in the affected kidney. A side to side difference of greater than 0.05 is highly suggestive of unilateral renal artery stenosis and should prompt further investigations to confirm the diagnosis. RI may also provide prognostic information in this context; the presence of a high RI (>0.80) is associated with a lower chance of response to revascularization.36 Similarly, in kidney transplant

recipients, an RI of 0.80 or greater has been shown to be associated with increased incidence of mortality.37 Elevated renal RI is also found in advanced chronic kidney disease and acute kidney injury and does not inform on the cause of kidney injury. Moreover, it is uncertain whether an elevated RI can help to predict the likelihood of recovery from acute kidney injury.38-40

Venous Doppler

The normal Doppler tracing of portal and intrarenal veins (usually interlobar) is relatively continuous, whereas hepatic vein Doppler is triphasic with a dominant systolic component. Portal waveform is above the baseline, as the flow is toward the transducer, whereas in renal veins it is below the baseline, as the flow is away from the transducer while acquiring the images. Similarly, the systolic and diastolic waves of the hepatic vein are below the baseline. Intrarenal Doppler can be technically challenging because the vessels are small, and the pulsed wave Doppler sample volume gets displaced with respiratory movement of the kidney.

When the RA pressure increases, venous return during systole is reduced (because the RA is already distended), and the venous circulation become distended and thus less compliant. This results in the alteration of the associated venous waveforms. First, the usually dominant systolic wave on hepatic vein Doppler is progressively reduced and even reversed in severe cases. Next, portal and intrarenal vein waveforms become increasingly pulsatile, ultimately resulting in flow reversal during systole when RA pressure is severely elevated. In other words, in cases of severe congestion, venous return occurs only during diastole (Fig. 5.14). Interestingly, these changes can be reversed with measures aimed at reducing RA pressure, such as diuretic or ultrafiltration therapy, and can be monitored in real time.

These venous Doppler flow alterations have been associated with adverse outcomes in congestive heart failure,41 42 after cardiac surgery,43 44 and in general critically ill patients.45 A venous excess ultrasound (VExUS) grading system combining the presence of these abnormal venous Doppler signals may have some advantages in certain clinical settings (e.g., significant tricuspid regurgitation, ventricular pacing, portal hypertension) and correlates with the risk of acute kidney injury in a cohort of cardiac surgery patients.46 However, it is unknown whether using these sonographic markers to guide management will improve outcomes.

Not all dyspnea is due to extravascular lung water, nor is all hypotension due to hypovolemia. Therefore the use of multiorgan POCUS in conjunction with conventional clinical assessment aids in diagnosis. Table 5.2 summarizes typical POCUS findings in major types of shock (hypovolemic, cardiogenic, obstructive, and distributive). The same applies to undifferentiated hypotension without overt shock. However, it is not uncommon to encounter overlapping etiologies in clinical practice; therefore these findings should not be considered absolute.

A

C

B

D

F

E

G

H

I

Fig. 5.14 Examples of Normal and Abnormal Venous Doppler Waveforms. (A) Color Doppler image showing the site of intrarenal Doppler assessment. (B) Normal intrarenal Doppler showing a normal arterial resistive index (above the baseline) and a continuous venous signal during the cardiac cycle (below the baseline). (C) Abnormal intrarenal Doppler showing both a high resistive index and discontinued venous signal only present in diastole (indicated by letter D). (D) Color Doppler image showing the right hepatic vein. (E) Normal hepatic vein Doppler with dominant systolic component. (F) Abnormal hepatic vein flow with reverse systolic component and only D-wave below the baseline. (G) Color Doppler image showing the main portal vein. (H) Normal portal vein Doppler showing minimal (<30%) variation in velocities during the cardiac cycle. (I) Abnormal portal vein Doppler with pulsatility (≥50% variation) during the cardiac cycle.

TABLE 5.2

Characteristic Point-of-Care Ultrasound Findings in Major Types of Shock

Type of Shock	Hypovolemic	Cardiogenic	Obstructive	Distributive
Hemodynamic mechanism	Volume depletion	Pump failure	Obstruction of pump function (e.g., pulmonary embolism, pericardial effusion)	Vasodilation leading to improper distribution of cardiac output resulting in impaired organ perfusion

Lung ultrasound

A-lines

Diffuse B-lines
Pleural effusions

A-lines
Focal B-lines may be seen in
lung infarction

A-lines
Pleural line irregularities with diffuse
B-lines in ARDS
Consolidation in pneumonia

FoCUS including
IVC

Hyperdynamic LV
(increased ejection)
Decreased stroke volume
(exit)
Small, collapsible IVC (entry)

Decreased LV ejection
Decreased cardiac output (exit)
Plethoric IVC (entry)
Chamber enlargement in some
cases (altered equality)

Pericardial effusion
Dilated RV in pulmonary
embolism (altered equality)
Decreased cardiac output (exit)
Plethoric IVC (entry)

Hyperdynamic LV (increased ejection)
with increased cardiac output (exit)
Decreased LV function in septic
cardiomyopathy
IVC variable (entry)

Venous Doppler

Hepatic: S > D
Portal: continuous
Intrarenal: continuous

Hepatic: S < D, possible S reversal
Portal: pulsatile, possible
systolic flow reversal
Intrarenal: Pulsatile, possible
systolic flow reversal

Variable depending on the
etiology

Similar to hypovolemic if volume
depleted
Similar to cardiogenic if excessively
volume resuscitated or
cardiomyopathy

Others

Intraperitoneal free fluid
in case of hemorrhage

Ascites
Bowel wall edema

Deep vein thrombosis in case
of pulmonary embolism

Source of sepsis (e.g., cholecystitis,
pyonephrosis)

ARDS, Acute respiratory stress syndrome; FoCUS, focused cardiac ultrasound; IVC, inferior vena cava; LV, left ventricle; RV, right ventricle; S, systolic wave; D, diastolic wave.

SELF-ASSESSMENT QUESTIONS

1. Which ultrasound mode is used to obtain the following image?

A.
B.
C.
D.

Color Doppler
M-mode
Pulsed wave Doppler
Continuous wave Doppler

[cm]
2
4
6
8
10
-3

-2

-1

0

12

2. Below are the grayscale and color Doppler images of the left kidney obtained from a patient with AKI. What is the sonographic finding?
A. Hydronephrosis
B. Parapelvic cyst
C. Prominent blood vessels
D. Hematoma

3. You are evaluating a renal transplant recipient in early postoperative period. The allograft demonstrates an abnormal appearing area at the upper pole (arrow). What is the likely diagnosis?

A. Hematoma
B. Urinoma
C. Hydronephrosis
D. Pelvic ascites
4. B-lines on lung ultrasound can be seen in which of the following conditions?

Right lower
quadrant
allograft

A.
B.
C.
D.

Pulmonary edema
Pulmonary fibrosis
Pneumonia
All the above

5. Which of the following images represents normal portal vein Doppler waveform?
A.
B.
C.
D.

A
B
C
D

A

B

MPV

C

67

D

REFERENCES

1. Koratala A, Teodorescu V, Niyyar VD. The nephrologist as an ultrasonographer. Adv Chronic Kidney Dis. 2020;27(3):243–252.
2. Koratala A, Kazory A. Point of care ultrasonography for objective assessment of heart failure: integration of cardiac, vascular, and extravascular determinants of volume status. Cardiorenal Med. 2021:1–13.
3. Narula J, Chandrashekhar Y, Braunwald E. Time to add a fifth pillar to bedside physical examination: inspection, palpation, percussion, auscultation, and insonation. JAMA Cardiol. 2018;3(4):346–350.
4. Solomon SD, Saldana F. Point-of-care ultrasound in medical educationstop listening and look. N Engl J Med. 2014;370(12):1083–1085.
5. Koratala A, Bhattacharya D, Kazory A. Point of care renal ultrasonography for the busy nephrologist: a pictorial review. World J Nephrol. 2019;8(3):44–58.
6. Kolofousi C, Stefanidis K, Cokkinos DD, et al. Ultrasonographic features of kidney transplants and their complications: an imaging review. ISRN Radiol. 2012;2013:480862.
7. Koratala A, Chamarthi G, Loy JL, Olaoye OA. Illusion, suspicion, and obstruction: an intriguing case of acute kidney injury. Am J Med. 2018;131(12):e489–e491.
8. Esprit DH, Koratala A, Chornyy V, Wingo CS. Obstructive nephropathy without hydronephrosis: suspicion is the key. Urology. 2017. 101e9-e10.
9. Koratala A, Kazory A. Point of care ultrasonography for objective assessment of heart failure: integration of cardiac, vascular, and extravascular determinants of volume status. Cardiorenal Med. 2021;11(1):5–17.
10. Kennedy Hall M, Coffey EC, Herbst M, et al. The “5Es” of emergency physician-performed focused cardiac ultrasound: a protocol for rapid identification of effusion, ejection, equality, exit, and entrance. Acad Emerg Med. 2015;22(5):583–593.
11. McKaigney CJ, Krantz MJ, La Rocque CL, et al. E-point septal separation: a bedside tool for emergency physician assessment of left ventricular ejection fraction. Am J Emerg Med. 2014;32(6):493–497.
12. Pérez-Casares A, Cesar S, Brunet-Garcia L, Sanchez-de-Toledo J. Echocardiographic evaluation of pericardial effusion and cardiac tamponade. Front Pediatr. 2017;5:79.
13. Damman K, van Deursen VM, Navis G, et al. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–588.
14. Miller A, Mandeville J. Predicting and measuring fluid responsiveness with echocardiography. Echo Res Pract. 2016;3(2):G1–G12.
15. Tasci O, Hatipoglu ON, Cagli B, Ermis V. Sonography of the chest using linear-array versus sector transducers: correlation with auscultation, chest radiography, and computed tomography. J Clin Ultrasound. 2016;44(6):383–389.
16. Zoccali C, Torino C, Tripepi R, et al. Pulmonary congestion predicts cardiac events and mortality in ESRD. J Am Soc Nephrol. 2013;24(4):639–646.
17. Torino C, Tripepi R, Loutradis C, et al. Can the assessment of ultrasound lung water in haemodialysis patients be simplified? Nephrol Dial Transplant. 2020.
18. Lichtenstein DA, Meziere GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;134(1):117–125.
19. Alrajhi K, Woo MY, Vaillancourt C. Test characteristics of ultrasonography for the detection of pneumothorax: a systematic review and meta-analysis. Chest. 2012;141(3):703–708.
20. Yousefifard M, Baikpour M, Ghelichkhani P, et al. Screening performance characteristic of ultrasonography and radiography in detection of pleural effusion; a meta-analysis. Emerg (Tehran). 2016;4(1):1–10.
21. Al Deeb M, Barbic S, Featherstone R, Dankoff J, Barbic D. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema

in patients presenting with acute dyspnea: a systematic review and metaanalysis. Acad Emerg Med. 2014;21(8):843–852.

22. Testa A, Soldati G, Copetti R, Giannuzzi R, Portale G, Gentiloni-Silveri N. Early recognition of the 2009 pandemic influenza A (H1N1) pneumonia by chest ultrasound. Crit Care. 2012;16(1):R30.
23. Alzahrani SA, Al-Salamah MA, Al-Madani WH, Elbarbary MA. Systematic review and meta-analysis for the use of ultrasound versus radiology in diagnosing of pneumonia. Crit Ultrasound J. 2017;9(1):6.
24. Reissig A, Heyne JP, Kroegel C. Sonography of lung and pleura in pulmonary embolism: sonomorphologic characterization and comparison with spiral CT scanning. Chest. 2001;120(6):1977–1983.
25. Giannese D, Puntoni A, Cupisti A, et al. Lung ultrasound and BNP to detect hidden pulmonary congestion in euvolemic hemodialysis patients: a single centre experience. BMC Nephrology. 2021;22(1):36.
26. Torino C, Gargani L, Sicari R, et al. The agreement between auscultation and lung ultrasound in hemodialysis patients: the LUST study. CJASN. 2016;11(11):2005–2011.
27. Noble VE, Murray AF, Capp R, Sylvia-Reardon MH, Steele DJR, Liteplo A. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. Chest. 2009;135(6):1433–1439.
28. Beaubien-Souligny W, Rheaume M, Blondin MC, et al. A simplified approach to extravascular lung water assessment using point-of-care ultrasound in patients with end-stage chronic renal failure undergoing hemodialysis. Blood Purif. 2018;45(1–3):79–87.
29. Siriopol D, Onofriescu M, Voroneanu L, et al. Dry weight assessment by combined ultrasound and bioimpedance monitoring in low cardiovascular risk hemodialysis patients: a randomized controlled trial. Int Urol Nephrol. 2017;49(1):143–153.
30. Loutradis C, Papadopoulos CE, Sachpekidis V, et al. Lung ultrasoundguided dry weight Assessment and echocardiographic measures in hypertensive hemodialysis patients: a randomized controlled study. Am J Kidney Dis. 2020;75(1):11–20.
31. Loutradis C, Sarafidis PA, Theodorakopoulou M, et al. Lung ultrasoundguided dry-weight reduction in hemodialysis patients does not affect short-term blood pressure variability. Am J Hypertens. 2019;32(8):786–795.
32. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, et al. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). Eur J Heart Fail. 2019;21(12):1605–1613.
33. Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, et al. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). Am Heart J. 2020;227:31–39.
34. McNaughton DA, Abu-Yousef MM. Doppler US of the liver made simple. Radiographics. 2011;31(1):161–188.
35. Al-Katib S, Shetty M, Jafri SM, Jafri SZ. Radiologic assessment of native renal vasculature: a multimodality review. Radiographics. 2017;37(1):136–156.
36. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med. 2001;344(6):410–417.
37. Naesens M, Heylen L, Lerut E, et al. Intrarenal resistive index after renal transplantation. N Engl J Med. 2013;369(19). 1797-806.
38. Ninet S, Schnell D, Dewitte A, Zeni F, Meziani F, Darmon M. Dopplerbased renal resistive index for prediction of renal dysfunction reversibility: a systematic review and meta-analysis. J Crit Care. 2015;30(3):629–635.
39. Darmon M, Bourmaud A, Reynaud M, et al. Performance of Dopplerbased resistive index and semi-quantitative renal perfusion in predicting persistent AKI: results of a prospective multicenter study. Intens Care Med. 2018;44(11):1904–1913.
40. Wiersema R, Kaufmann T, van der Veen HN, et al. Diagnostic accuracy of arterial and venous renal Doppler assessment for acute kidney injury in

critically ill patients: a prospective study. J Crit Care. 2020;59:57–62.
41. Iida N, Seo Y, Sai S, et al. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. JACC Heart Fail. 2016;4(8):674–682.
42. Ikeda Y, Ishii S, Yazaki M, et al. Portal congestion and intestinal edema in hospitalized patients with heart failure. Heart Ves. 2018;33(7):740–751.

References

43. Eljaiek R, Cavayas YA, Rodrigue E, et al. High postoperative portal venous flow pulsatility indicates right ventricular dysfunction and predicts complications in cardiac surgery patients. Br J Anaesth. 2019;122(2):206–214.
44. Beaubien-Souligny W, Benkreira A, Robillard P, et al. Alterations in portal vein flow and intrarenal venous flow are associated with acute kidney injury after cardiac surgery: a prospective observational cohort study. J Am Heart Assoc. 2018;7(19). e009961-e.

45. Spiegel R, Teeter W, Sullivan S, et al. The use of venous Doppler to predict adverse kidney events in a general ICU cohort. Crit Care. 2020;24(1):615.
46. Beaubien-Souligny W, Rola P, Haycock K, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J. 2020;12(1):16.

6

Radiologic and Nuclear Imaging in Nephrology

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Options for imaging of patients with kidney disease have changed significantly in recent years. Intravenous urography (IVU) is infrequently used and has mostly been replaced by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scanning. Rapidly changing computer-based data manipulation has resulted in major technologic advances in each of these modalities. Three-dimensional (3D) or even 4D (time-sensitive) image analysis is now available. Molecular imaging, which visualizes cellular function using biomarkers, is providing both functional and anatomic information.

The American College of Radiology (ACR) has published Appropriateness Criteria[1] that suggest the best choice of imaging modality to answer the clinical questions while minimizing cost and potential adverse effects, such as contrast-induced adverse events and radiation exposure. Tables 6.1 through 6.3 list relative radiation exposures, first-choice imaging modalities in kidney disease, and risk estimates, respectively. Risks of imaging and cost need to be balanced against benefits.

ULTRASOUND

Ultrasound is relatively inexpensive and provides a rapid way to assess renal location, contour, and size without radiation exposure. Nephrologists are increasingly undertaking bedside ultrasound examination; the practical techniques as well as the appropriate interpretative skills are discussed in Chapters 5 and 97. Portable ultrasound is available and is essential in the pediatric or emergency setting. Obstructing renal calculi can be readily detected, and renal masses can be identified as cystic or solid. In cases of suspected obstruction, the progression or regression of hydronephrosis is readily evaluated. Color Doppler imaging permits assessment of renal vascularity and perfusion. Unlike the other imaging modalities, ultrasound is highly dependent on operator skills. Limitations of ultrasound include lack of an acoustic window, body habitus, and poor patient cooperation.

Kidney Size

The kidney is imaged in the transverse and sagittal planes and is normally 9 to 12 cm in length in adults. Differences in kidney size can be detected with all imaging modalities. Figure. 6.1 shows the common causes of enlarged and shrunken kidneys.

Renal Echo Pattern

The normal kidney cortex is hypoechoic compared with the fatcontaining echogenic renal sinus (Fig. 6.2A). The cortical echotexture is defined as isoechoic or hypoechoic compared with the liver or spleen. In children, the renal pyramids are hypoechoic (Fig. 6.2B) and the cortex is characteristically hyperechoic compared with the liver and

the spleen. In adults, an increase in cortical echogenicity is a sensitive marker for parenchymal renal disease but is nonspecific (Fig. 6.3). Decreased cortical echogenicity can be found in acute pyelonephritis and acute renal vein thrombosis.

The normal renal contour is smooth, and the cortical mantle should be uniform and slightly thicker toward the poles. Two common benign pseudomasses that can be seen with ultrasound are the dromedary hump and the column of Bertin. The column of Bertin results from bulging of cortical tissue into the medulla; it is seen as a mass with an echotexture similar to that of the cortex, but it is found within the central renal sinus (Fig. 6.4). The renal pelvis and proximal ureter are anechoic. An extrarenal pelvis refers to the renal pelvis location outside the renal hilum. The ureter is not identified beyond the pelvis in nonobstructed patients.

Obstruction can be identified by the presence of hydronephrosis (Fig. 6.5). Parenchymal and pelvicalyceal nonobstructing renal calculi as well as ureteral obstructing calculi can be readily detected (Fig. 6.6). The upper ureter also will be dilated if obstruction is distal to the pelviureteral junction (see Fig. 6.5C). False-negative ultrasound examination findings with no hydronephrosis occasionally occur in early obstruction. Obstruction without ureteral dilation also may occur in retroperitoneal fibrosis and in transplanted kidneys as a result of periureteral fibrosis.

Renal Cysts

Cysts can be identified as anechoic lesions and are a frequent coincidental finding during renal imaging. Ultrasound usually readily identifies renal masses as cystic or solid (Figs. 6.7 and 6.8). However, hemorrhagic cysts may be mistakenly called solid because of increased echogenicity. Differentiation of cysts as simple or complex is required to plan intervention.

Simple Cysts

A simple cyst on ultrasound is anechoic, has a thin or imperceptible wall, and demonstrates through-transmission because of the relatively rapid progression of the sound wave through fluid compared with adjacent soft tissue.

Complex Cysts

Complex cysts contain calcifications, septations, and mural nodules. Instead of being anechoic, these masses may contain internal echoes representing hemorrhage, pus, or protein. Complex cysts may be benign or malignant; cyst wall nodularity, septations, and vascularity strongly suggest malignancy. Complex cysts identified by ultrasound require further evaluation by contrast-enhanced CT (or MRI) to identify abnormal contrast enhancement of the cyst wall, mural nodule, or septum, which may indicate malignancy.

Relative Radiation Doses of
Imaging Examinations

TABLE 6.3

Examination

Imaging Risk

Estimated Risk

Cancer from 10 mSv of radiation
(1 body CT)2

1 in 1000

Contrast-induced nephropathy in
patient with reduced GFR4

Uncertain but higher with diabetes or
hyperuricemia

Nephrogenic systemic fibrosis4,6

1 in 25,000 to 1 in 30,000 (depends on
gadolinium agent)
Higher risk if GFR >30 mL/min

Death from iodine contrast
anaphylaxis5

1 in 130,000

Death from gadolinium contrast
anaphylaxis6

1 in 280,000

TABLE 6.1

Effective Dose (mSv)

Chest: PA radiograph

0.02

Lumbar spine

1.8

KUB abdomen

0.53

CT abdomen

10

CT chest

20–40

PET-CT

25

Ultrasound or MRI

0

CT, Computed tomography; KUB, kidney, ureter, bladder (plain film);
MRI, magnetic resonance imaging; mSv, millisieverts; PA, posteroanterior; PET, positron emission tomography.

TABLE 6.2

Disease

Suggested Imaging in Renal

Pathology

First-Choice Imaging

Acute kidney injury, chronic kidney disease

Ultrasound

Hematuria

Ultrasound or CT

Proteinuria, nephrotic syndrome

Ultrasound
Multiphase CT urography

Hypertension with normal kidney function

Ultrasound
Consider CTA or MRA

Hypertension with impaired kidney function

Ultrasound with Doppler

Kidney infection

Contrast-enhanced CT

Hydronephrosis identified on ultrasound

Nuclear renogram

Retroperitoneal fibrosis

Contrast-enhanced CT

Papillary or cortical necrosis

Contrast-enhanced CT

Renal vein thrombosis

Contrast-enhanced CT

Kidney infarction

Contrast-enhanced CT

Nephrocalcinosis and nephrolithiasis

CT

These recommendations assume availability of all common imaging modalities.
CT, Computed tomography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography.
Modified from American College of Radiology. Appropriateness criteria: http://www.acr.org/ac

Bladder

Real-time imaging can be used to evaluate for bladder wall tumors and bladder stones. Color flow Doppler evaluation of the bladder in wellhydrated patients can be used to identify a ureteral jet, produced when peristalsis propels urine into the bladder. The incoming urine has a higher specific gravity relative to the urine already in the bladder (Fig. 6.9). Absence of the ureteral jet can indicate total ureteral obstruction.

Renal Vasculature

Color Doppler investigation of the kidneys provides a detailed evaluation of the renal vascular anatomy. The main renal arteries can be identified in most patients (Fig. 6.10). Power Doppler imaging is a more sensitive indicator of flow, but unlike color Doppler imaging, power Doppler provides no information about flow direction and

Risk Estimates in Diagnostic

CT, Computed tomography; GFR, glomerular filtration rate; mSv, millisieverts.

cannot be used to assess vascular waveforms. However, power Doppler imaging is exquisitely sensitive for detection of renal parenchymal flow and has been used to identify cortical infarction.

RENAL ARTERY DUPLEX SCANNING

The role of gray-scale and color Doppler sonography in evaluating for renal artery stenosis is controversial. The principle is that a narrowing in the artery will cause a velocity change commensurate with the degree of stenosis, as well as a change in the normal renal artery waveform downstream from the lesion. The normal renal artery waveform demonstrates a rapid systolic upstroke and an early systolic peak (Fig. 6.11A). The waveform becomes damped downstream from a stenosis. This consists of a slow systolic acceleration (tardus) and a decreased and rounded systolic peak (parvus) (see Fig. 6.11B). It also results in a decrease in the resistive index, defined as the end-diastolic velocity (EDV) subtracted from the peak systolic velocity (PSV) divided by PSV: (PSV − EDV)/PSV. The normal resistive index is 0.70 to 0.72. The entire length of the renal artery should be examined for the highest velocity signal. The origins of the renal arteries are important to identify because this area is often affected by atherosclerosis, but the arteries are often difficult to visualize because of overlying bowel gas. Within the kidney, medullary branches and cortical branches in the upper, middle, and lower thirds should be included to attempt detection of stenosis in accessory or branch renal arteries.

Proximal and distal criteria exist for diagnosis of significant renal artery stenosis, usually defined as stenosis greater than 60%. The proximal criteria detect changes in the Doppler signal at the site of stenosis and provide sensitivities and specificities ranging from, respectively, 0% to 98% and 37% to 98%.2,3 Technical failure rates are typically 10% to 20%.4 Renal artery stenosis also may be missed if PSV is low because of poor cardiac output or aortic stenosis. False-positive results can occur when renal artery velocity is increased because of high-flow states, such as hyperthyroidism or vessel tortuosity. The distal criteria are related to detection of a tardus-parvus waveform distal to a stenosis; sensitivities and specificities of 66% to 100% and 67% to 94%, respectively, have been reported.5,6 Technical failure with distal criteria is much lower than with proximal evaluation (<5%). False-negative results can occur from stiff poststenotic vessels, which will decrease the tardus-parvus effect. The tardus-parvus effect also may be a result of aortic stenosis, low cardiac output, or collateral vessels in complete occlusion, giving a false-positive result.

Common Causes of Abnormal Renal Size
Smooth
Compensatory hypertrophy
Renal vein thrombosis
Hydronephrosis

Unilateral

Irregular
Tumor
Cyst

Large kidneys
>12 cm
Smooth
Infiltration (e.g., edema, lymphoma)
Diabetic nephropathy
HIV-associated nephropathy
Renal vein thrombosis

Smooth
Congenital hypoplasia
Renal artery stenosis
Chronic renal vein thrombosis
Radiation nephritis

Smooth
Congenital hypoplasia
Renal artery stenosis
Chronic renal vein thrombosis
Radiation nephritis
Chronic glomerulonephritis
Chronic interstitial nephritis
Hypertensive nephrosclerosis

Bilateral

Irregular
Polycystic kidney disease
Other multicystic disease
Angiomyolipoma

Unilateral

Irregular
Reflux nephropathy
Congenital dysplasia
Papillary necrosis
Renal tuberculosis
Segmental renal infarction

Small kidneys
<9 cm

Bilateral

Irregular
Reflux nephropathy
Congenital dysplasia
Papillary necrosis

Renal tuberculosis

Fig. 6.1 Common causes of abnormal kidney size.

A

Fig. 6.3 Nephropathy Associated With Human Immunodeficiency Virus. Enlarged echogenic kidney with lack of corticomedullary distinction. Bipolar length of kidney is 14.2 cm.

B

Fig. 6.2 Ultrasound Images of Kidney. (A) Normal sagittal renal ultrasound image. The cortex is hypoechoic compared with the echogenic fat containing the renal sinus. (B) Normal renal ultrasound image in an infant. Note the hypoechoic pyramids.

Fig. 6.4 Sagittal Kidney Ultrasound. The column of Berlin (arrows) is easily identified because of echotexture similar to that of kidney cortex.

A
A

B

B
Fig. 6.7 Evaluation of Kidney Mass. (A) Sagittal ultrasound image shows large hyperechoic mass arising from the lower pole (arrows). (B) Corresponding contrast-enhanced computed tomography scan shows kidney cell carcinoma (arrow)

C
Fig. 6.5 Kidney Ultrasound Study Demonstrating Hydronephrosis. (A) Sagittal ultrasound image. (B) Transverse image. (C) Transverse three-dimensional surface-rendered image. Arrows indicate the dilated proximal ureter.
Fig. 6.8 Sagittal ultrasound image of a complex kidney cyst (arrows)

Fig. 6.6 Renal Calculus (Arrow) of Upper Pole. Note the acoustic shadowing (arrowhead) on sagittal ultrasound image.

Fig. 6.9 Bilateral Ureteral Jets in Bladder. Color Doppler ultrasound study detects this normal appearance.

Fig. 6.10 Transverse color Doppler ultrasound evaluation of the kidney shows the artery as red and the vein as blue.

A

A

B

B

Fig. 6.11 Renal Artery Color Doppler Image and Spectral Imaging. (A) Normal renal artery tracing shows rapid systolic upstroke and early systolic peak velocity (~100 cm/s). (B) Tardus-parvus waveform demonstrates slow systolic upstroke (acceleration) and decreased peak systolic velocity (~20 cm/s) associated with renal artery stenosis. Note different scales on vertical axis.

Fig. 6.12 Contrast Ultrasonography. (A) Sagittal kidney ultrasound image with a large, central kidney cell carcinoma (arrows). (B) Central carcinoma better seen after injection of contrast material. (Courtesy Dr. Christoph F. Dietrich.)

Combining the proximal and distal criteria improves detection of stenoses. Sensitivity of 97% and specificity of 98% can be achieved when both the extrarenal and the intrarenal arteries are examined.7 When it is technically successful, Doppler ultrasound has a negative predictive value of more than 90%.7 However, reliable results require a skilled and experienced sonographer and a long examination time. Despite these limitations, Doppler studies also have several advantages. Noninvasive, inexpensive, and widely available, Doppler studies also allow structural and functional assessment of the renal arteries and imaging without exposure to radiation or contrast material.

Some physicians prefer computed tomography angiography (CTA) or magnetic resonance angiography (MRA) as a faster and more reliable test than ultrasound, but at present the choice should depend on local expertise and preference. For further discussion of the diagnosis and management of renovascular disease, see Chapter 41

such as the kidney. These intravenous agents are microbubbles 1 to 4 µm in diameter (smaller than erythrocytes) that consist of a shell surrounding the echo-producing gas core. The microbubbles oscillate in response to the ultrasound beam frequency and give a characteristic increased echo signal on the image. Preliminary studies evaluating renal perfusion in dysfunctional kidneys show reduced flow compared with normal kidneys, as well as improved lesion detection (Fig. 6.12). However, the clinical adoption of microbubble imaging in the kidney remains uncertain, particularly with the general availability and robustness of CT and MRI.

Two-dimensional ultrasound images can be reconstructed into 3D volume images by a process similar to 3D reconstructions for MRI and CT. Potential applications include vascular imaging and fusion with MRI or positron emission tomography (PET).

CONTRAST-ENHANCED AND THREE-DIMENSIONAL ULTRASOUND

Ultrasound contrast agents, initially introduced to assess cardiac perfusion, are now being used to evaluate perfusion to other organs,

PLAIN RADIOGRAPHY AND FLUOROSCOPY

Although infrequently used today in high-income countries, contrast urography may still be a key investigation in parts of the world where cross-sectional imaging is not readily available. Plain radiography, often called KUB (kidneys, ureter, bladder), still has an important role in the identification of soft tissue masses, bowel gas patterns, calcifications, and renal location.

A

B

C

Fig. 6.13 Nephrocalcinosis. (A) Plain radiograph shows bilateral medullary nephrocalcinosis in a patient with distal renal tubular acidosis. (B) Noncontrast computed tomography (CT) scan in a patient with hereditary oxalosis and dense bilateral renal calcification (arrows). The left kidney is atrophic. (C) Noncontrast CT scan shows cortical nephrocalcinosis in the right kidney (arrows) after cortical necrosis.

Renal Calcification

Most renal calculi are radiodense, although only about 60% of urinary stones detected on CT are visible on plain films.[8] CT demonstrates nonopaque stones, which include uric acid, xanthine, and struvite stones. However, neither CT nor plain radiography may detect calculi associated with protease inhibitor therapy.[9] Oblique films are sometimes obtained to confirm whether a suspicious upper quadrant calcification is renal in origin. CT is the imaging modality of choice for detection of urinary calculi.[10]

Nephrocalcinosis may be medullary (Fig. 6.13A–B) or cortical (Fig. 6.13C) and is localized or diffuse. The causes of nephrocalcinosis are discussed in Chapter 57 (see Box 57.7).

RETROGRADE PYELOGRAPHY

Retrograde pyelography is performed when the ureters are poorly visualized on other imaging studies or when samples of urine must be obtained from the kidney for cytology or culture. Patients who have severe allergies to contrast agents or impaired kidney function can be evaluated with retrograde pyelography. The examination is performed by placing a catheter through the ureteral orifice under cystoscopic guidance and advancing it into the renal pelvis. The catheter is slowly withdrawn under fluoroscopy while radiocontrast is injected (see Figs. 58.2 and 58.11). This provides excellent visualization of the renal pelvis and ureter and can be used for cytologic sampling from suspect areas.

ANTEGRADE PYELOGRAPHY

Antegrade pyelography is performed through a percutaneous renal puncture and is used when retrograde pyelography is not possible. Ureteral pressures can be measured, hydronephrosis evaluated, and ureteral lesions identified (Fig. 58.14). The examination is often performed as a prelude to nephrostomy placement. Both antegrade and retrograde pyelography are invasive and should be performed only when other studies are inadequate.

Fig. 6.15 Bilateral pelvic kidneys (arrows) on computed tomography.

A

Fig. 6.16 Normal kidney transplant (arrows) on computed tomography.

B

Fig. 6.14 Imaging of an Ileal Conduit. (A) Loop-o-gram. A recurrent transitional carcinoma is present in the reimplanted left ureter (arrow). (B) Computed tomography scan clearly shows the tumor as a filling defect in anterior aspect of the opacified ureter (arrow).

IMAGING ILEAL CONDUITS

After cystectomy or bladder failure, numerous types of continent or incontinent urinary diversions can be surgically created. One of the most common diversions is the ileal conduit: an ileal loop is isolated from the small bowel, and the ureters are implanted into the loop. This end of the loop is closed, and the other end exits through the anterior abdominal wall. This type of conduit can be evaluated by an excretory or a retrograde study. The excretory or antegrade study is performed and monitored in the same way as an IVU. A retrograde examination, also referred to as a “loop-o-gram,” is obtained when the ureters and conduit are suboptimally evaluated on the excretory study. A Foley catheter is placed into the stoma and contrast slowly instilled. The ureters should fill by reflux because the ureteral anastomoses are not of the antireflux variety (see Fig. 6.14).

CYSTOGRAPHY

A cystogram is obtained when more detailed radiographic evaluation of the bladder is required. Voiding cystography is performed to identify ureteral reflux and assess bladder function and urethral anatomy. A urethral catheter is placed into the bladder, the urine drained, contrast infused, and the bladder filled under fluoroscopic guidance. Early frontal and oblique films with the patient supine are obtained while the bladder is filling. Ureteroceles are best identified on early films. When the bladder is full, multiple films are obtained with varying degrees of obliquity. Reflux may be seen on these films. To obtain a voiding cystogram, the catheter is removed, the patient voids, and the contrast is followed into the urethra. Occasionally, bladder diverticula are seen only on the voiding films. When the patient has completely voided, a final film is used to assess the amount of residual urine and the mucosal pattern.

Radionuclide cystography is an alternative often used in children. It is useful in the diagnosis of reflux, but it does not provide the detailed anatomy seen with contrast cystography.

COMPUTED TOMOGRAPHY

Computed tomography of the kidneys is performed to evaluate renal masses, locate ectopic kidneys (Figs. 6.15 and 6.16), investigate calculi, assess retroperitoneal masses, and evaluate the extent of parenchymal involvement in patients with acute pyelonephritis (Figs. 6.17 and 6.18). Helical CT scanners allow the abdomen and pelvis to be scanned at submillimeter intervals with single breath–held acquisitions, which eliminates motion artifact. Newer multidetector row CT results in multiple slices of information (64-slice and even 320slice machines) being acquired simultaneously, allowing the entire abdomen and pelvis to be covered in very fast acquisition times of less than 30 seconds. Although the improved CT imaging usually comes at a price of increased radiation exposure to the patient, new reconstruction software with iterative reconstruction significantly reduces radiation exposure by as much as 30%. The CT data can be reconstructed in multiple planes and even 3D for improved anatomic visualization and localization.

Tissue Density

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Distilled water at standard pressure and temperature is defined as 0 HU; the radiodensity of air is defined as −1000 HU. All other tissue densities are derived from this measurement (Table 6.4). Tissues can vary in their exact HU measurements and will

Computed Tomography

TABLE 6.4 Determination of Density of Common Substances

Substance	Hounsfield Units[a]
Air	−1000
Fat	−120
Water	0
Muscle	+40
Bone	+400 or more

[a]The Hounsfield unit (HU) scale is a measurement of relative densities compared with distilled water.

G

P

Fig. 6.17 Emphysematous Pyelonephritis. Contrast-enhanced computed tomography scan shows gas (arrowheads) within an enlarged left kidney and marked enhancement of the Gerota fascia (G) and posterior perirenal space (P), indicative of inflammatory involvement.

Noncontrast CT is the examination of choice in patients with suspected nephrolithiasis and has replaced the KUB and IVU in most situations. The study consists of unenhanced images from the kidneys through the bladder for detection of calculi. CT is highly sensitive (97%–100%) and specific (94%–96%) for diagnosis of urinary calculi.[10] Noncontrast CT can identify a possible obstructing calculus and the extent of parenchymal and perinephric involvement.

In cases other than stone evaluation, the kidneys are imaged after contrast administration. The kidneys are imaged in the corticomedullary phase for evaluation of the renal vasculature and in the nephrographic phase for evaluation of the kidney parenchyma. The degree of enhancement can be assessed in both solid masses and complex cysts.

Computed Tomography Urography

A

B

Fig. 6.18 Acute Pyelonephritis. (A) Ultrasound image demonstrates an enlarged echogenic kidney. Bipolar length of kidney is 12.9 cm. (B) Computed tomography scan with contrast enhancement obtained 24 hours later demonstrates multiple nonenhancing abscesses (arrows).

also change with contrast enhancement. Water, fat, and soft tissue often can look identical on the scan, depending on the window and level settings of the image, so actual HU measurement is essential to characterize the tissues accurately.

Contrast-Enhanced and Noncontrast Computed Tomography

CT examination of the kidneys can be performed with or without intravenous administration of contrast material. Noncontrast imaging allows the kidneys to be evaluated for the presence of calcium deposition and hemorrhage, which are obscured after contrast administration.

Delayed images through the kidneys and bladder are performed for evaluation of the opacified and distended collecting system, ureters, and bladder.11 12 After acquisition, the axial images can be reformatted into coronal or sagittal planes to optimize visualization of the entire collecting system (Fig. 6.19). The CT study can be tailored to the individual clinical scenario. For example, the corticomedullary phase can be eliminated to decrease the radiation dose if there is no concern about a vascular abnormality or no need for presurgical planning. A diuretic or saline bolus can be administered after contrast to better distend the collecting system and ureters during the excretory phase.

The kidneys should be similar in size and show equivalent enhancement and excretion. During the corticomedullary phase, there is brisk enhancement of the cortex. The cortical mantle should be intact. Any disruption of the cortical enhancement requires further evaluation; it may be caused by acute pyelonephritis (see Fig. 6.18), scarring, mass lesions, or infarction (Fig. 6.20). During the excretory phase, the entire kidney and renal pelvis enhance. Delayed excretion and delay in pelvicalyceal appearance of contrast material may be found in obstruction (Fig. 6.21) but also in parenchymal disease such as acute tubular necrosis (ATN).

The ureters are often seen segmentally because of active peristalsis. The ureters should be free of filling defects and smooth. In the abdomen, the ureters lie in the retroperitoneum, passing anterior to the transverse processes of the vertebral bodies. In the pelvis, the ureters course laterally and posteriorly, eventually draining into the posteriorly located vesicoureteral junction. At the vesicoureteral junction, the ureters gently taper.

Medial bowing or displacement of the ureter is often abnormal and can be seen secondary to ureter displacement from retroperitoneal masses, lymphadenopathy, and retroperitoneal fibrosis.

The bladder should be rounded and smooth walled. Benign indentations on the bladder include the uterus, prostate gland, and bowel. In chronic bladder outlet obstruction and neurogenic bladder, numerous trabeculations and diverticula may be seen around the bladder outline.

Other incidental bladder diverticula, such as the Hutch diverticulum,

A

Fig. 6.19 Noncontrast Computed Tomography (CT) of Bladder and Kidney. Computer-reformatted, volume-rendered CT urogram obtained from axial CT acquisition.

can be seen and are usually of no significance unless they are large and do not empty completely on voiding.

Computed Tomographic Angiography

Helical scanning facilitates CT angiography (CTA), which can produce images similar to conventional angiograms but is less invasive. A bolus of contrast material is administered, and the images are reconstructed at 0.5- to 3-mm consecutive intervals. The contrast bolus is timed for optimal enhancement of the aorta. The tightly focused and narrow CT beam allows higher resolution and better subsequent multiplanar reconstructions. The aorta and branch vessels are well demonstrated (Fig. 6.22). This technique is widely used in living transplant donor evaluation (see Fig. 104.2), providing information not only on arterial and venous anatomy but also on size, number, and location of the kidneys and any ureteral anomalies of number or position.

In addition, CTA can be used to evaluate for atheromatous renal artery stenosis, with sensitivity of 96% and specificity of 99% for the detection of hemodynamically significant stenosis compared with digital subtraction angiography (DSA).[2] Furthermore, CTA allows visualization of both the arterial wall and lumen, which helps in planning renal artery revascularization procedures. Another advantage of CTA is the depiction of accessory renal arteries and nonrenal causes of hypertension, such as adrenal masses. CTA can be used to diagnose fibromuscular dysplasia but has a lower sensitivity (87%) than DSA.[3]

Dual-Energy Computed Tomography

In dual-energy CT (DECT), two or more CT data sets are acquired using different tube potentials, usually 140 and 80 kilovolts (kV), resulting in different x-ray spectra. The density values at the acquired spectra differentiate materials on the basis of the photoelectric effect. The most common application of DECT is to allow the acquisition of “virtual noncontrast” images. A single acquisition after the administration of contrast can, using the photoelectric characteristics of iodine, be used to create a full set of images that appear as though no contrast was administered (Fig. 6.23A). These can be used to better identify kidney stones, differentiate stones and calcification from early excreted contrast in the urinary system, and can be compared against the postcontrast images to verify whether or not something is demonstrating enhancement. Among the more specialized uses of DECT include allowing kidney stone differentiation (i.e., differentiation of uric acid from magnesium or calcium), which may permit tailored treatment

B

Fig. 6.20 Renal Infarction. (A) Computed tomography (CT) scan showing a chronic calcified infarct (open arrows) involving half of the right kidney after aortic bypass surgery. The native aorta has a densely calcified wall (arrow). The aortic graft is anterior to the native aorta (arrowhead). (B) CT scan showing acute infarct in the right kidney with decreased parenchymal enhancement (arrows).

Fig. 6.21 Delayed Excretion in Left Kidney Secondary to Distal Calculus. Contrast-enhanced computed tomography scan shows dilated left renal pelvis (arrows).

strategies.4 5 Radiation dose in DECT has been shown to be the same as traditional CT, and optimized protocols can even reduce overall dose.6

Limitations of Computed Tomography

CT does have some limitations. The cradle that the patient lies on usually has an upper weight limit of 100 to 200 kg (300–400 lb), but newer scanners can now accommodate up to 270 kg (600 lb). Obese patients often have suboptimal scans because of weight artifact and need higher radiation exposures to adjust for x-ray attenuation. Contrast-enhanced CT studies may be contraindicated in patients with an allergy to radiographic contrast. For further discussion on contrast use in patients with impaired kidney function, see Radiologic Contrast Agents.

CT is very sensitive to metal artifact and patient motion. Retroperitoneal clips and intramedullary rods will cause extensive streak artifact, which severely degrades the images. However, recent advances in image reconstruction can be used to significantly decrease the streak artifact from metal implants, although this is still not perfect (see Fig. 6.23B). Patients who are unable to remain motionless will also have suboptimal or even nondiagnostic studies, and sedation or general anesthesia may be needed to obtain diagnostic scans, particularly in children. Critically ill patients may not be stable enough for transport to the CT suite, and ultrasound can be considered as an alternative to CT in that setting.

Fig. 6.22 Normal Renal Arteries. Three-dimensional reformatted computed tomography angiogram.

MAGNETIC RESONANCE IMAGING

Although it rarely should be the first examination used to evaluate the kidneys, MRI is typically an adjunct to other imaging. The major advantage of MRI over other modalities is direct multiplanar imaging. CT is limited to slice acquisition in the axial plane of the abdomen, and coronal and sagittal planes are acquired only by reconstruction, which can lead to loss of information.

Images on MR are typically described as T1 or T2 based on their acquisition. Fat is bright on T1 and not as bright on rapid acquisition T2 sequences (Fig. 6.24). The sequences and imaging planes selected must be tailored to the individual MR study. Diffusion-weighted imaging (DWI) evaluates the freedom of water molecules to diffuse in tissues; restriction of diffusion is imaged as bright areas on the DWI image set. Using the DWI data, regional apparent diffusion coefficients of the tissue can be calculated and an image of the distribution of the coefficients of the tissue can be produced. Dark areas on what is known as an apparent diffusion coefficient map are seen in infection, neoplasia, inflammation, and ischemia (Fig. 6.25). Because diffusion occurs in three dimensions, more advanced acquisitions can be obtained that show the direction of diffusion. This process is called diffusion tensor imaging (DTI). This is mostly seen in brain and neurologic imaging for imaging axonal tracts, but visualization of the orientation of renal tubules can be done with this method as well (Fig. 6.26).

On T1-weighted sequences, the normal kidney cortex is higher in signal than the medulla, producing a distinct corticomedullary differentiation, which becomes indistinct in parenchymal kidney disease.

It is analogous to the echogenic kidney seen on ultrasound. On rapid acquisition T2 sequences, the corticomedullary distinction is not as

A

B

Fig. 6.23 (A) Following only one postcontrast computed tomography (CT) acquisition with dual energy, mathematical algorithms are used to obtain two sets of images. On the left is the standard postcontrast image, and on the right is the virtual noncontrast calculated image. (B) New CT software postprocessing permits much more diagnostic image quality with metal artifact reduction. The usual image obtained is at right, and the image using metal artifact reduction is at left.

A

B

Fig. 6.24 Tuberous Sclerosis on Magnetic Resonance (MR) Imaging. Multiple renal angiomyolipomas are seen. (A) T1-weighted MR image. The tumors are high in signal on T1 because of their fat; arrow shows the largest tumor. (B) T1-weighted MR image with fat suppression. The fat within the tumors is now low in signal (arrow).

Fig. 6.25 Magnetic Resonance Image of Kidney Tumor. T1-weighted, contrast-enhanced image shows enhancing left renal tumor.

sharp but should still be present. Usually, at least one sequence is performed in the axial plane. Sagittal and coronal images cover the entire length of the kidney and can make some subtle renal parenchymal abnormalities more conspicuous (Fig. 6.27).

Contrast-Enhanced Magnetic Resonance Imaging

As with CT, intravenous contrast material can be administered to allow further characterization of kidney lesions. Gadolinium is a paramagnetic contrast agent frequently used in MRI. Nephrotoxicity to gadolinium agents is rare and insignificant.7 A scleroderma-like condition could be seen with early contrast agents in subjects with chronic kidney disease (CKD), but this is not observed with agents used today (see Magnetic Resonance Contrast Agents). Paramagnetic contrast agents are being evaluated for measurement of glomerular function.

After injection of gadolinium, the vessels appear high in signal, or white, on T1-weighted sequences. Multiple images can be obtained in a single breath–held acquisition. This technique is useful for lesion characterization in patients who cannot receive iodinated contrast material. As with contrast-enhanced CT, the kidneys initially show symmetric cortical enhancement, which progresses to excretion. A delay in enhancement can be seen with renal artery stenosis.

Magnetic Resonance Urography

Two techniques are used to perform magnetic resonance urography (MRU).13 The first technique is sometimes called static MRU. Because

Fig. 6.26 Diffusion Tensor Imaging (DTI) Permits Imaging of Eigenvectors of Relative Diffusion Through Tissues. This image shows a kidney DTI with visualization of the diffusion through the medullary tubules.

B

A

D

C

Fig. 6.27 Normal Magnetic Resonance (MR) Images Through Kidneys. (A) T1-weighted MR image. Note the distinct corticomedullary differentiation. (B) Fast spin echo MR image. Urine in the collecting tubules causes the high signal within the renal pelvis on this sequence. (C) Coronal T1-weighted, fat-suppressed MR image after contrast administration. (D) Axial T1-weighted, fat-suppressed image after contrast administration.

urine contains abundant water, it will demonstrate high signal on a T2-weighted image. Therefore, a heavily T2-weighted sequence accentuates the static fluid in the collecting system and ureters, which stands out against the darker background soft tissues. Static MRU can be performed rapidly, which is a benefit in imaging of children. A disadvantage is that any fluid in the abdomen or pelvis, such as fluid collections or fluid in the small bowel, will demonstrate a similar bright signal that can obscure superimposed structures. Also, the collecting system and ureters need to be distended for acquisition of good MR images.

The second technique, often referred to as excretory MRU, is similar to CT urography (CTU). Intravenous administration of gadolinium is followed by T1-weighted imaging. This technique allows some assessment of kidney function because the contrast is filtered by the kidney and excreted into the urine (see Fig. 58.10). The opacified collecting system and ureters are well seen, and a diuretic can be administered to further dilate the renal pelvis and ureters if necessary. MRU has limited capacity to detect calculi because calcification is poorly visualized by MRI.

Because CTU and MRU are comparable for identifying the cause and anatomic location of urinary obstruction, the choice of modality is a matter of local preference. CTU is the better choice in the evaluation of urinary tract calculi. In patients with reduced glomerular filtration rate (GFR) caused by obstruction, MRU is superior to CTU in identifying noncalculous causes of obstruction, whereas CTU is superior in identifying calculi as a cause of obstruction.14 CTU is also more widely available, faster, and less expensive than MRU. MRU is better suited in patients with allergy to iodinated contrast agents and sometimes in children when radiation is an issue. MRU is also useful in depicting the anatomy in patients with urinary diversion to bowel conduits.

Magnetic Resonance Angiography

Although magnetic resonance angiography (MRA) can be performed with or without intravenous contrast, contrast provides better images. The aorta and branch vessels are beautifully demonstrated (Fig. 6.28). By adjustment of timing and type of sequences, the abdominal venous structures can be visualized (Fig. 6.29). MRA is performed to evaluate the renal arteries for stenosis and is less invasive than catheter angiography

Fig. 6.28 Magnetic Resonance Angiography. Coronal threedimensional magnetic resonance angiogram after contrast administration shows normal renal arteries.

Fig. 6.30 Dysplasia on Magnetic Resonance (MR) Angiography. Posterior view of coronal three-dimensional MR angiogram shows typical beaded appearance of fibromuscular dysplasia of the right renal artery and focal high grade stenosis of the origin of the left renal artery.

(Fig. 6.30). Technical advances, including faster sequences, now give sensitivity of 97% and specificity of 93% compared with DSA for contrastenhanced MRA in the detection of renal artery stenosis.15 MRA without gadolinium has a lower sensitivity (53%–100%) and specificity (65%–97%) for detection of renal artery stenosis.16 MRA has limited ability to assess accessory renal arteries and therefore is not an ideal study to evaluate fibromuscular dysplasia. It has become the most commonly used modality in patients with hypertension, declining kidney function, or allergy to iodinated contrast agents.17 Where MRA is unavailable, Doppler ultrasound can be used.

Disadvantages of Magnetic Resonance Imaging

Fig. 6.29 Magnetic resonance venography.

Like CT, MRI has some disadvantages. The table and gantry are confining, so claustrophobic patients may be unable to cooperate. Patients with some types of internal metallic hardware cannot undergo MRI. MRI safety guidelines have been developed with an extensive list of devices that are or are not MRI approved, and any devices in the patient need to be checked against this list. Examples of contraindications include neural stimulator devices and cerebral aneurysm clips. Many cardiac pacemakers are now compatible with MRI, but if the patient is pacemaker dependent, they cannot be scanned. Determination of in-stent stenosis is impossible, as metallic artifacts from renal artery stents completely obscure the lumen. Even with the new, fast imaging techniques, patients need to be able to cooperate with breath-holding instructions to minimize motion-related artifacts. The safety of the use of MRI contrast agents in patients with impaired kidney function is discussed later (see Magnetic Resonance Contrast Agents). MRI can be used in the intensive care unit and in critically ill patients only if they are stable enough to be transported to the MRI suite and have no implanted metallic devices. Ventilated patients can undergo MRI; however, specific MRI-compatible, nonferromagnetic ventilators and other life support devices must be used. Because of the confined nature of the MRI gantry, visualization and monitoring of the patient during the scan are compromised.

Incidental Findings

Incidental kidney lesions are being found with increasing frequency. Almost 70% of renal cell carcinomas are discovered incidentally on imaging studies performed for other reasons. There is an agedependent incidence of renal cysts, from about 5% in patients younger than 30 years to almost one-third of those older than 60 years.18 The differentiation of solid and cystic lesions is the first mandate because as many as two-thirds of solid lesions are found to be malignant.19 MRI is ideally suited for lesion evaluation and is often better than ultrasound, particularly for complex cystic lesions. Parameters being characterized include solid versus cystic appearance, overall lesion complexity, lesion enhancement, involvement of renal vasculature and collecting system, and extension into perirenal tissues and organs. Diffusion-weighted MRI sequences are often useful as a means of further differentiating benign and malignant solid lesions.

A

MEASUREMENT OF GLOMERULAR FILTRATION RATE

Renal blood flow and split kidney function can be evaluated by CT and MRI.20-22 The attenuation of the accumulated contrast material within the kidney is directly proportional to the GFR. Taking into account the renal volume, the function of each kidney can be determined. Although both modalities yield similar information, MRI is used more in children and in patients with allergy to contrast agents. However, scintigraphy is still widely used for assessing kidney function, as discussed later.

ANGIOGRAPHY

Angiography is now most often performed for therapeutic intervention, such as embolotherapy or angioplasty and stenting, preceded by diagnostic angiography to evaluate the renal arteries for possible stenosis (Fig. 6.31). With improved resolution and scanning techniques, CTA and MRA have replaced conventional angiography, even for detection of accessory renal arteries, which are often small and bilateral but a possible cause of hypertension. However, angiography remains the gold standard reference test for the diagnosis of renal artery stenosis and fibromuscular dysplasia. There also remains a role for diagnostic angiography in the evaluation of medium- and large-vessel vasculitis and detection of renal infarction.

The conventional angiogram is performed through arterial puncture, followed by catheter placement in the aorta and subsequent selective renal artery catheterization as necessary. Contrast is administered intraarterially, and the images are obtained with DSA. DSA uses computer reconstruction and manipulation to generate the images, with the advantage that previously administered and excreted contrast material and bones can be digitally removed to better visualize the renal vasculature. Angiography can cause contrast-induced nephropathy and cholesterol embolization (see Chapter 41). Pathologic evidence of cholesterol embolization is common, but clinically significant symptoms occur infrequently (1%–2%).23

RENAL VENOGRAPHY

Catheter venography was once used for evaluation of renal vein and gonadal vein thrombosis and for renal vein sampling to measure renin,

B

Fig. 6.31 Left Renal Artery Stenosis and Angioplasty. (A) Aortogram demonstrating a tight left renal artery stenosis (arrow). (B) Postangioplasty image with marked improvement of the stenosis (arrow). (Courtesy Dr. Harold Mitty.)

but it has largely been replaced with Doppler ultrasound, followed by contrast-enhanced CT or MRI (see Fig. 6.17).

NUCLEAR SCINTIGRAPHY

Nuclear scintigraphy evaluates function and anatomy seen with other diagnostic imaging modalities. Radiotracers are designed to accumulate in tissues or organs on the basis of underlying functions unique to that organ. The gamma camera captures the photons from a radiotracer within the patient and generates an image. Single-photon emission computed tomography (SPECT) is a specialized type of imaging in which the emitted photons are measured at multiple angles, similar to CT, and multiplanar or even 3D images can be created. Three categories of radiotracers that differ in mode of renal clearance are used in kidney imaging: glomerular filtration, tubular secretion, and tubular retention agents (Table 6.5).

TABLE 6.5 Choice of Radionuclide in Kidney Imaging

Imaging Target	Radiotracer
Glomerular filtration rate	99mTc-DTPA
Glomerular filtration rate with renal impairment	99mTc-MAG3, 131I-OIH
Effective renal plasma flow	99mTc-MAG3, 131I-OIH
Kidney scarring	99mTc-DMSA, 99Tc-GH
Renal pseudotumor	99mTc-DMSA
Upper renal tract obstruction	99mTc-DTPA
Upper renal tract obstruction with reduced GFR	99mTc-MAG3

Normal Renal Scintigraphy at 0–1 min

1500
1350

Total counts

1200

Tubular Secretion Agents

99mTc-labeled MAG3 is handled primarily by tubular secretion and can be used to estimate effective renal plasma flow. The clearance rate for 99mTc-MAG3 is 340 mL/min.26

Tubular Retention Agents

Tubular retention agents include 99mTc-labeled dimercaptosuccinate (DMSA) and less often 99mTc-labeled glucoheptonate (GH). These agents provide excellent cortical imaging and can be used in suspected renal scarring or infarction, in pyelonephritis, and for clarification of renal pseudotumors. These agents bind with high affinity to sulfhydryl groups on the surface of proximal tubular cells.

Renogram

A renogram (or renal scintigram) is generated by scintigraphy and provides information about blood flow, renal uptake, and excretion. Time-activity graphs are produced that plot blood flow of the radiotracer into each kidney relative to the aorta. Peak cortical enhancement and pelvicalyceal clearance of the tracer are also plotted. DTPA or MAG3 can be used to generate the renogram. The relative radiotracer uptake can be measured and can provide split or differential information about kidney function (Fig. 6.32).

600

150
0
0

6

12

18

A

24

30

36

42

48

54

60

Time (seconds)

Normal Renal Scintigraphy at 1–30 min
45000
Left
Right

40000
35000
30000
25000
20000
15000
10000
5000
0

Glomerular Filtration Agents

Glomerular filtration agents can be used to measure GFR. Technetium 99m–labeled diethylenetriaminepentaacetic acid (99mTc-DTPA) is the most common glomerular agent used for imaging and also can be used for GFR calculation. In patients with poor kidney function, renal imaging with tubular secretion agents such as mercaptoacetyltriglycine (99mTc-MAG3) is superior to DTPA.24 25

750

300

99mTc-DMSA,

Scintigraphy remains superior to the other imaging modalities in the evaluation of renal flow. It is the study of choice in the evaluation of renal transplants and functional obstruction, especially when ultrasound evidence is equivocal. Scintigraphy is also widely used to measure GFR, although CT or MRI is preferred in some centers.

Although CT, MRI, and contrast-enhanced ultrasound can be used to evaluate kidney function (e.g., after nephron-sparing surgery), scintigraphy remains the preferred modality. Both CTA and MRA have replaced nuclear scintigraphy in the evaluation of renal artery stenosis and benign renal masses, such as a column of Bertin. Nuclear medicine is still used to assess the functional significance of renal artery stenosis independent of anatomy.

1050

900

450

Total counts

Technetium 99m–labeled dimercaptosuccinate; 99mTcDTPA, technetium 99m–labeled diethylenetriaminepentaacetic acid; 99mTc-MAG3, mercaptoacetyltriglycine; 99mTc-GH, technetium 99m glucoheptonate; 131I-OIH, 131I orthoiodohippurate.

Aorta

Left kidney

Right kidney

0

4

8

12

16

20

24

28

32

B

Time (minutes)

Fig. 6.32 Normal 99mTc-Labeled DTPA Study: Time-Activity Curves. (A) Early (0–1 minute), showing renal blood flow. (B) Later (1–30 minutes), showing renal uptake and excretion of tracer. (Courtesy Dr. Chun Kim.)

The blood pool or flow images are obtained after bolus injection of the radiotracers. Images are obtained with the gamma camera every few seconds for the first minute. The second component of the renogram evaluates kidney function by measuring radiotracer uptake and excretion by the kidney. In health, the peak renal cortical concentration occurs between 3 and 5 minutes after injection of tracer.

Delayed transit of the isotope secondary to kidney dysfunction (e.g., ATN or rejection) or obstructive uropathy will alter the curve of the renogram.

In cases of suspected obstructive uropathy, a diuresis renogram can be obtained. A loop diuretic is injected intravenously when radiotracer activity is present in the renal pelvis; a computer-generated washout curve is obtained. In patients with true obstruction, activity will remain in the renal pelvis, whereas it will quickly wash out in patients without an obstruction (Fig. 6.33; see also Fig. 58.12).

Cortical Imaging

Imaging of the kidney cortex is performed with tubular retention agents, usually 99mTc-DMSA. Information about renal size, location, and contour can be obtained (Fig. 6.34). The cortical study is used most frequently for evaluation of renal scarring, particularly in children with reflux or chronic infections (see Chapter 61). Cortical imaging

Diuresis Renogram Showing
Obstructed Right Kidney

Total counts

60,000

Furosemide

Left
Right

40,000

20,000

0

10

20

30

40

50

Minutes

Fig. 6.33 Diuresis Renogram Showing Obstructed Right Kidney. Isotope continues to accumulate in the right kidney despite intravenous furosemide (given at 30 minutes). Isotope excretion in the left kidney is normal.

L

R

Fig. 6.35 Normal Positron Emission Tomography Scan. Note normal radiotracer uptake in brain, heart, intestines, and liver, with normal excretion in kidneys.

Fig. 6.34 Renal Infarct. 99mTc-DMSA scan in a newborn with an infarct of the right lower pole (R) secondary to embolus from umbilical catheter. (Courtesy Dr. Chun Kim.)

may be better than ultrasound in the evaluation of the young patient with urinary tract infection.27 An infection, scar, or space-occupying lesion (tumor or cyst) will create a cortical defect, and correlation of the cortical defect site with other cross-sectional imaging should be performed to differentiate these entities.

Vesicoureteral Reflux

In children with suspected vesicoureteral reflux, a standard cystogram is obtained. If reflux is shown, follow-up is subsequently performed with radioisotope cystography, which exposes the child to a lower radiation dose and can be used to quantitate the bladder capacity when reflux occurs. The study is performed after instillation of technetium pertechnetate through a catheter into the bladder. Images are obtained during voiding.

Kidney Transplant

Kidney transplants are easily evaluated with scintigraphy. 99mTcMAG3 is cleared through tubular secretion, which is maintained in most kidneys to a better degree than glomerular filtration in kidney failure. Because many transplant recipients have declining kidney function, 99mTc-MAG3 is the first-choice nuclide.

As with the normal kidneys, information about blood flow and function can be determined. Postoperative complications involving the artery, vein, or ureter are also well delineated. Nuclear imaging can help define ATN versus rejection in transplant patients with declining kidney function. Ultrasound with Doppler evaluation of resistive index is often a complementary investigation, and choice of imaging modality in part depends on local expertise and preference.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) scanning uses radioactive positron emitters, most often fluorine-18–labeled fluorodeoxyglucose (FDG). The FDG is intravenously injected and distributes in the body according to metabolic activity. Any process, such as a tumor or infection, that causes increased metabolic activity will result in an area of increased uptake on the scan. These areas of abnormality need to be differentiated from normally hypermetabolic tissues, such as brain, liver, bone marrow, and to some extent heart and bowel (Fig. 6.35).

Because FDG is cleared through the kidneys and excreted in the urine, which can obscure renal masses or infection, PET scanning has a limited role in renal imaging but is useful in the staging and follow-up of metastatic renal cancer.28 29 Other ligands exist with lower levels of urinary excretion, but the application of this in renal imaging is still being investigated.

MOLECULAR IMAGING

With molecular imaging, radiology is moving from the identification of generic anatomy and nonspecific enhancement patterns to assessment of specific molecular differences in tissues and disease processes.

Nuclear imaging presently is molecular based but still nonspecific (e.g., FDG-PET, renal DTPA). The newer focus of molecular imaging studies is dynamic processes such as metabolic activity, cell proliferation, apoptosis, receptor status, fibrosis, and antigen modulation.

Typically, this involves imaging of biochemical and physiologic processes. Techniques are being developed with optical scanning, MRI, and ultrasound as well as with radionuclides.

Applications are established in clinical practice, particularly in oncology (e.g., CD20 imaging in lymphoma), and work is under way for renal-specific molecular imaging. For example, MR renal cell imaging may be available soon to help differentiate ATN from renal rejection and renal cell cancer from benign tumors.

RADIOLOGIC CONTRAST AGENTS

X-Ray Contrast Agents

Contrast agents continue to have a role in many imaging techniques.

A triiodinated benzene ring forms the chemical basis for CT intravascular contrast agents. Conventional contrast agents have high osmolality, about five times greater than plasma osmolality. Modifications to the benzene ring have led to newer contrast agents, including low-osmolar (which is still hyperosmolar compared with normal plasma) and more recently iso-osmolar nonionic agents, which are less nephrotoxic.

In patients with normal GFR, the kidneys eliminate almost all the contrast agent. Extrarenal routes of excretion include the liver and bowel wall and account for less than 1% of elimination, but this can increase when kidney function is compromised. The half-time in patients with normal GFR is 1 to 2 hours, compared with 2 to 4 hours in dialysis patients.[30]

Contrast reactions for iodinated agents occur in 3.1% to 4.7% of patients.[31-33] Of those patients who have a contrast reaction, 20% will experience a reaction on reexposure that may be similar or worse. Contrast reactions can be anaphylactoid or chemotoxic reactions. The anaphylactoid reactions mimic an allergic response, whereas the chemotoxic reactions are believed to be mediated by direct toxic effects of the contrast material. The exact mechanism of contrast reaction is not known but is likely to be multifactorial. Formation of antigen-antibody complexes, complement activation, protein binding, and histamine release have been cited as possible mechanisms.

Reactions may be minor, intermediate, or severe. Minor reactions include heat sensation, nausea, and mild urticaria. Intermediate reactions include vasovagal reaction, bronchospasm, and generalized urticaria. Severe reactions include profound hypotension, pulmonary edema, and cardiac arrest. The use of low-osmolar or iso-osmolar contrast agents reduces the incidence of minor and intermediate contrast reactions. The reported incidence of death related to high-osmolar contrast agents is 1 in 40,000. Immediate treatment of reactions should be directed toward the symptoms. In patients with a history of contrast allergy, pretreatment is recommended with antihistamines and corticosteroids on reexposure.

Contrast-Induced Nephropathy

Although acute kidney injury (AKI) associated with the administration of contrast material has been reported as the third most common cause of in-hospital AKI, recent data indicate this risk has been markedly overestimated.[33] The original studies and reports often occurred using high-osmolarity contrast agents in subjects who were not well hydrated. Biopsies from those patients often showed osmotic nephrosis or acute tubular necrosis.[34] Today, contrast-induced AKI is rare, even in patients with GFR less than 45 mL/min/1.73m2, and thus the risk of AKI does not preclude the use of intravenous contrast if clinically necessary. Despite the concern for long-term complications, there is evidence suggesting that intravenous contrast carries little risk for dialysis dependence or mortality.35

Studies of the pathogenesis of contrast-induced nephropathy have suggested that the injury is due to the high osmolality of the agent, which can induce renal vasoconstriction, activation of the polyol-fructokinase pathway in the proximal tubule associated with oxidative stress,36 and possibly the effects of the acute osmotic-induced uricosuria. Most underlying cellular events were thought to occur within the first 60 minutes after administration of the contrast agent, with the greatest risk in the first 10 minutes. Tubular injury produces oxygen free radicals, possibly from the vasoconstriction. In animal studies, reduction in antioxidant enzymes associated with hypovolemia contributes to the injury.37

An important differential diagnosis for contrast-induced nephropathy in patients with vascular disease undergoing catheter angiography is cholesterol embolization (see Chapter 41).

Possible risk factors include preexisting chronic kidney disease, diabetes, cardiovascular disease, use of diuretics, advanced age (>75 years), multiple myeloma in dehydrated patients, hypertension, uricosuria, and high-dose contrast. In patients with kidney failure, contrast administration may result in fluid overload because of thirst induced by the osmotic load. Hydration with normal saline is the mainstay of prevention; there is no substantial evidence that sodium bicarbonate offers any advantage over saline.38 Oral N-acetylcysteine, a thiol-containing antioxidant, is often given in conjunction with hydration but has not proved consistently to be protective.39 Note that even the use of hydration is controversial, with excessive hydration putting these patients at risk of fluid overload.40

In patients with estimated GFR less than 60 mL/min/1.73m2, low-osmolar or iso-osmolar contrast agents can be used and the doses reduced. Repetitive, closely performed contrast studies should be avoided. In high-risk patients, alternative imaging studies (ultrasound, MRI, or noncontrast CT) always should be considered. Issues related to contrast-induced nephropathy are further discussed in Chapter 72.

Magnetic Resonance Contrast Agents

The two classes of MRI contrast agents are diffusion and nondiffusion agents. Diffusion agents, with appropriate timing of imaging sequences, can delineate vessels and parenchymal tissues. Nondiffusion agents remain in the bloodstream and are primarily useful for MRA. All the contrast agents are based on the paramagnetic properties of gadolinium. Gadolinium itself is highly toxic and is given only when it is tightly chelated (e.g., Gd-tetraazacyclododecane-1,4,7,10-tetraacetic acid [Gd-DOTA], Gd-diethylenetriamine penta-acetic acid [Gd-DTPA]).

Minor reactions such as headache and nausea occur in 3% to 5% of patients, but life-threatening reactions and nephrotoxic reactions are rare. In patients with reduced GFR, a rare severe reaction (nephrogenic systemic fibrosis [NSF]), has been described (see Chapter 91).

Guidelines confirm that MRI using high-risk gadolinium-containing contrast agents is contraindicated in patients with AKI and in those with chronic kidney disease stages 4 and 5 (i.e., GFR <30 mL/min/1.73 m2),16 because some agents have been linked to NSF. Cases of NSF are particularly associated with the linear structure chelates (such as gadodiamide, gadopentetate, and gadoversetamide). However, some linear chelates have a higher dissociation constant and to date have not been associated with NSF (such as gadobenate).41 The newer macrocyclic gadolinium-containing contrast agents (e.g., gadoterate and gadoteridol) also have not been associated with NSF, even in patients with GFR less than 30 mL/min/1.73 m2. Recently, studies have shown gadolinium deposition and retention in tissues, especially the brain, and especially after multiple injections of the contrast material. To date, there are no documented adverse events associated with this retention.

The choice of gadolinium agent in each case should be determined by discussion between the nephrologist and radiologist.

Radiomics and Artificial Intelligence

Radiomics and artificial intelligence are areas of ongoing research. Radiomics deals with the conversion of images into data formats that allow assessment and quantification of pixel or voxel gray levels (spatial heterogenicity). This allows texture analysis that can be used as is or with further machine learning and adaption of artificial intelligence algorithms.

These tools are being studied for differentiating benign and malignant lesions as well as characterizing renal cell cancer types. Additionally, these tools may be useful in following response of renal cell cancer to chemotherapeutic agents.42-44

Although these techniques show promise, there are still many limitations and challenges before these tools can be adapted to routine clinical use.

SELF-ASSESSMENT QUESTIONS

1. On ultrasound, compared with the liver, the normal adult kidney cortex is:
A. isoechoic.
B. hyperechoic.
C. hypoechoic.
D. anechoic.
2. Which of the following imaging modalities has the least chance of inducing contrast nephropathy?
A. CO2 angiography.
B. Contrast-enhanced CT.
C. Contrast-enhanced MRI.
D. Intravenous urography.
3. The imaging modality that exposes the patient to the least radiation risk is:
A. CT urography.
B. dual-energy CT with virtual noncontrast imaging.

C. intravenous urography.
D. diffusion-weighted MRI.
4. Which of the following is a mandatory reason that an MRI of the kidneys cannot be performed?
A. Cardiac pacemaker in a patient who is not pacemaker dependent.
B. Titanium total hip replacement less than 6 weeks old.
C. When eGFR is 35 mL/min.
D. History of cerebral aneurysm clip.
5. Which of the following is usually the recommended best modality to evaluate for kidney stones?
A. Noncontrast CT scan.
B. MRI.
C. Ultrasound.
D. Nuclear medicine renogram.

REFERENCES

1. American College of Radiology. Appropriateness criteria. Available at: http://www.acr.org/ac.
2. Wittenberg G, Kenn W, Tschammler A, et al. Spiral CT angiography of renal arteries: comparison with angiography. Eur Radiol. 1999;9:546–551.
3. Beregi JP, Louvegny S, Gautier C, et al. Fibromuscular dysplasia of the renal arteries: comparison of helical CT angiography and arteriography. AJR Am J Roentgenol. 1999;172:27–34.
4. Yeh BM, Shepherd JA, Wang ZJ, et al. Dual-energy and low-kVp CT in the abdomen. AJR. 2009;193:47–54.
5. Thorsten RC, Johnson Dual-Energy CT. General principles. AJR. 2013;199(suppl 5):S3–S8.
6. Henzler T, Fink C, Schoenberg SO, Schoepf UJ. Dual-energy CT: radiation dose aspects. AJR. 2012;199:S16–S25.
7. Prince MR, Arnoldus C, Frisoli JK. Nephrotoxicity of high dose gadolinium compared with iodinated contrast. J Magn Reson Imaging. 1996;6:162–166.
8. Mutgi A, Williams JW, Nettleman M. Renal colic: utility of the plain abdominal roentgenogram. Arch Intern Med. 1991;151:1589–1592.
9. Blake SP, McNicholas MM, Raptopoulos V. Nonopaque crystal deposition causing ureteric obstruction in patients with HIV undergoing indinavir therapy. Am J Radiol. 1998;171:717–720.
10. Niall O, Russell J, MacGregor R, et al. A comparison of noncontrast computerized tomography with excretory urography in the assessment of acute flank pain. J Urol. 1999;161:534–537.
11. Joffe SA, Servaes S, Okon S, Horowitz M. Multi-detector row CT urography in the evaluation of hematuria. Radiographics. 2003;23:1441–1455.
12. Caoili EM, Cohan RH, Korobkin M, et al. Urinary tract abnormalities: initial experience with CT urography. Radiology. 2002;222:353–360.
13. Nolte-Ernsting CC, Staatz G, Tacke J, Gunther RW. MR urography today. Abdom Imaging. 2003;28:191–209.
14. Shokeir AA, El-Diasty T, Eassa W, et al. Diagnosis of ureteral obstruction in patients with compromised renal function: the role of noninvasive imaging modalities. J Urol. 2004;171:2303–2306.
15. Tan KT, van Beek EJR, Brown PWG, et al. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. Clin Radiol. 2002;51:617–624.
16. Grenier N, Trillaud H. Comparison of imaging methods for renal artery stenosis. BJU Int. 2000;86(suppl 1):84–94.
17. Marcos HB, Choyke PL. Magnetic resonance angiography of the kidney. Semin Nephrol. 2000;20:450–455.
18. Marumo K, Horiguchi Y, Nakagawa K, et al. Incidence and growth pattern of simple cysts of the kidney in patients with asymptomatic microscopic hematuria. Int J Urol. 2003;10:63–67.
19. Vasudevan A, Davies RJ, Shannon BA, Cohen RJ. Incidental renal tumours: the frequency of benign lesions and the role of preoperative core biopsy. BJU Int. 2006;97:946–949. [comment]. BJU Int. 2006;98:465-466.
20. Krier JD, Ritman EL, Bajzer Z, et al. Noninvasive measurement of concurrent single-kidney perfusion, glomerular filtration and tubular function. Am J Physiol Renal Physiol. 2001;281:F630–F638.
21. Nilsson H, Wadstrom J, Andersson LG, et al. Measuring split renal function in renal donors: can computed tomography replace renography? Acta Radiol. 2004;45:474–480.
22. Lee VS, Rusinek H, Noz ME, et al. Dynamic three-dimensional MR renography for the measurement of single kidney function: initial experience. Radiology. 2003;227:289–294.

23. Fukumoto Y, Tsutsui H, Tsuchihashi M, et al. The incidence and risk factors of cholesterol embolization syndrome. J Am Coll Cardiol. 2003;42:211–216.
24. Taylor A, Nally JV. Clinical applications of renal scintigraphy. Am J Radiol. 1995;64:31–41.

25. Taylor Jr A, Ziffer JA, Echima D. Comparison of Tc-99m MAG3 and Tc99m DTPA in renal transplant patients with impaired renal function. Clin Nucl Med. 1990;15:371–378.
26. Taylor A, Eshima D, Christian PE, et al. A technetium-99m MAG3 kit formulation: preliminary results in normal volunteers and patients with renal failure. J Nucl Med. 1988;29:616–662.
27. Mastin ST, Drane WE, Iravani A. Tc 99m DMSA SPECT imaging in patients with acute symptoms or history of UTI: comparison with ultrasonography. Clin Nucl Med. 1995;20:407–412.
28. Kayani I, Groves AM. 18F-Fluorodeoxyglucose PET/CT in cancer imaging. Clin Med. 2006;6:240–244.
29. Majhail NS, Urbain JL, Albani JM, et al. F-18 fluorodeoxyglucose positron emission tomography in the evaluation of distant metastases from renal cell carcinoma. J Clin Oncol. 2003;21:3995–4000.
30. Bahlmann J, Kruskemper HL. Elimination of iodine-containing contrast media by hemodialysis. Nephron. 1973;19:25–55.
31. Shehadi WH. Adverse reactions to intravascularly administered contrast media. Am J Radiol. 1975;124:145–152.
32. Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese committee on the safety of contrast media. Radiology. 1990;175:616–618.
33. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol. 2016. Pii: ASN.2016010021.
34. Moreau JF, Droz D, Sabto J, et al. Osmotic nephrosis induced by watersoluble triiodinated contrast media in man. A retrospective study of 47 cases. JR Radiology. 1975;115(2):329–336.
35. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media–induced renal injury in volume depletion. Kidney Int. 1992;41:1008.
36. Andres-Hernando A, Li N, Cicerchi C, et al. Protective role of fructokinase blockade in the pathogenesis of acute kidney injury in mice. Nat Commun. 2017;8:14181.
37. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate. JAMA. 2004;291:2328–2334.
38. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. N Engl J Med. 2006;354:379–386.
39. McDonald RJ, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology. 2014;273(3):714–725.
40. Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomized, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017;389(10076):1312–1322.
41. Nandwana SB, Moreno CC, Osipow MT, et al. Gadobenate dimeglumine administration and nephrogenic systemic fibrosis: is there a real risk in patients with impaired renal function? Radiology. 2015;276(3):741–747.
42. Meghan G, Lubner MD. Radiomics and artificial intelligence for renal mass characterization. Radiol Clin N Am. 2020;58:995–1008.
43. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278(2):563–577.
44. Kocak B, Durmaz ES, Ates E, et al. Radiomics with artificial intelligence: a practical guide for beginners. Diagn Interv Radiol. 2019;25(6):485–495.

7

Kidney Biopsy

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Percutaneous kidney biopsy was first described in the early 1950s by Iversen and Brun1 and Alwall.2 These early biopsies were performed with the patient in the sitting position by use of a suction needle and intravenous urography for guidance. An adequate tissue diagnosis was achieved in less than 40% of these early cases. In 1954 Kark and Muehrcke3 described a modified technique using the Franklin-modified Vim-Silverman needle, with the patient in a prone position and an exploring needle used to localize the kidney before insertion of the biopsy needle. These modifications yielded a tissue diagnosis in 96% of cases, and no major complications were reported. Since then, the kidney biopsy procedure has remained largely unchanged, although the use of real-time ultrasound and refinement of biopsy needle design have offered significant improvements. Kidney biopsy now provides a tissue diagnosis in more than 95% of patients, with a life-threatening complication rate of less than 0.1%.

INDICATIONS FOR KIDNEY BIOPSY

Ideally, analysis of a kidney biopsy sample should identify a specific diagnosis, reflect the level of disease activity, and provide information to allow informed decisions about treatment. Although not always able to fulfill these criteria, the kidney biopsy remains a valuable clinical tool and is particularly beneficial in the clinical situations discussed in Box 7.1.

Nephrotic Syndrome

Routine clinical and serologic examination of patients with nephrotic syndrome usually allows the clinician to determine whether a systemic disorder is present. In adults and in adolescents beyond puberty without systemic disease, the glomerular pathologic process cannot be predicted with confidence by noninvasive criteria alone; therefore a renal biopsy should be performed. In children age 1 year up to puberty, a presumptive diagnosis of minimal change disease (MCD) usually can be made. Kidney biopsy is reserved for nephrotic children with atypical features, including microhematuria, hypocomplementemia, reduced glomerular filtration rate (GFR), and failure to respond to corticosteroids. Antibodies against phospholipase A2 receptor 1 (PLA2R1) are found in 80% of patients with membranous nephropathy and are a noninvasive aid to diagnosis,4 response to treatment,5 and prediction of remission.6 Unfortunately, the test only identifies 70% of cases of primary membranous nephropathy. In addition, biopsy still provides information on disease chronicity and the extent of irreversible fibrosis.

Acute Kidney Injury

In most patients with acute kidney injury (AKI) on a background of chronic kidney disease (CKD), the cause can be determined without a renal biopsy. In a minority of patients, however, a confident diagnosis

cannot be made, and a renal biopsy should be performed urgently so appropriate treatment can be started before irreversible renal injury develops. This is particularly true in patients with AKI accompanied by an active urine sediment or with suspected drug- or infection-induced acute interstitial nephritis.

Systemic Disease Associated With Kidney Dysfunction

Patients with diabetes mellitus and kidney dysfunction do not usually require biopsy if they have clinical features that suggest diabetic nephropathy (e.g., isolated proteinuria, diabetes of long duration, other microvascular complications). However, kidney biopsy should be performed if the presentation is atypical, such as proteinuria associated with glomerular hematuria, absence of retinopathy or neuropathy (in patients with type 1 diabetes), onset of proteinuria less than 5 years from the documented onset of diabetes, uncharacteristically rapid change in kidney function or kidney disease of acute onset, or immunologic abnormalities.

Serologic testing for antineutrophil cytoplasmic antibody (ANCA) and for anti–glomerular basement membrane (anti-GBM) antibodies usually allows a confident diagnosis of kidney small-vessel vasculitis or Goodpasture disease without invasive measures. Nonetheless, a kidney biopsy still should be performed to confirm the diagnosis and clarify the extent of chronic fibrosis and thus the potential for recovery. This information may be important in helping decide whether to initiate or continue immunosuppressive therapy, particularly when complications of immunosuppression are observed or expected.

Lupus nephritis usually can be diagnosed by noninvasive criteria such as autoantibodies, urine protein excretion, kidney function, and urine sediment abnormalities, which can also be used to inform decisions about initial immunosuppressive treatment. However, a kidney biopsy will clarify the underlying pathologic lesion, level of active inflammation, and extent of chronic fibrosis, thereby providing robust guidance for therapy.

The diagnosis of viral infection–related nephropathy (e.g., hepatitis B virus–associated membranous nephropathy) is suggested by characteristic histologic lesions together with evidence of active viral infection. However, the identification of virus-specific protein or DNA or RNA in the kidney biopsy tissue by immunopathologic and molecular pathologic techniques (e.g., in situ hybridization) can confirm the diagnosis.

Other systemic diseases, such as amyloidosis, sarcoidosis, and myeloma can be diagnosed with kidney biopsy. However, a kidney biopsy is indicated only if the diagnosis remains uncertain or if knowledge of kidney involvement would change management.

Kidney Transplant Dysfunction

Kidney levels of calcineurin inhibitors require a kidney biopsy to determine the cause. In the early posttransplantation period, this is most

BOX 7.1

Indications for Kidney Biopsy

Nephrotic Syndrome
- Routinely indicated in adults
- In prepubertal children, indicated only if clinical features atypical of minimal change disease are present

Acute Kidney Injury
- Indicated if obstruction, reduced kidney perfusion, and acute tubular necrosis have been ruled out

Systemic Disease With Kidney Dysfunction
- Indicated in patients with small-vessel vasculitis, anti–glomerular basement membrane disease, and systemic lupus
- Indicated in patients with diabetes only if atypical features present

Nonnephrotic Proteinuria
- May be indicated if proteinuria is >1 g/24 h

Isolated Microscopic Hematuria
- Indicated only in unusual circumstances

Unexplained Chronic Kidney Disease
- May be diagnostic (e.g., identify immunoglobulin A nephropathy even in “end-stage kidney”)

Familial Kidney Disease
- Biopsy of one affected member may give diagnosis and minimize further investigation of family members

Kidney Transplant Dysfunction
- Indicated if ureteral obstruction, urinary sepsis, renal artery stenosis, and toxic calcineurin inhibitor levels are not present

useful in differentiating acute rejection from acute tubular necrosis (ATN) and the BK virus nephropathy. Later, kidney biopsy can differentiate acute rejection from chronic allograft nephropathy, recurrent or de novo glomerulonephritis (GN), and calcineurin inhibitor toxicity. The location of the kidney transplant in the iliac fossa facilitates biopsy of the allograft and allows repeated biopsies when indicated. This has encouraged many units to adopt a policy of protocol (surveillance) biopsies to detect subclinical acute rejection and kidney scarring and to guide the choice of immunosuppressive therapy (see Chapter 109).

Nonnephrotic Proteinuria

The value of kidney biopsy in patients with nonnephrotic proteinuria is debatable. All conditions that result in nephrotic syndrome can cause nonnephrotic proteinuria, except for MCD. However, the benefit of specific treatment with corticosteroids and other immunosuppressive agents in these patients probably does not justify the risk for significant drug-related side effects. In patients with proteinuria of more than 1 g/day, generic treatment with strict blood pressure control and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria and reduces the risk for development of progressive kidney dysfunction (see Chapter 82). Nonetheless, although the kidney biopsy may not lead to an immediate change in management, it can be justified in these circumstances if it will provide prognostic information, identify a disease for which a different therapeutic approach is indicated, or provide clinically important information about the future risk for disease recurrence after kidney transplantation.

Isolated Microhematuria

Patients with microhematuria should be evaluated to identify structural lesions such as kidney stones or kidney and urothelial malignant neoplasms. The absence of a structural lesion suggests that the hematuria may have a glomerular source. Biopsy studies have identified glomerular lesions in up to 75% of biopsies.7 In all series, immunoglobulin A (IgA) nephropathy is the most common lesion, followed by thin basement membrane nephropathy and normal kidney morphology. In the absence of nephrotic proteinuria, kidney impairment, or hypertension, the prognosis for patients with these conditions is excellent, and because specific therapies are not available, kidney biopsy is not necessary and patients require only follow-up. Biopsy should be performed only if the result would reassure the patient, avoid repeated urologic investigations, or provide specific information, as in the evaluation of potential living kidney donors, in familial hematuria, or for life insurance and employment purposes.

Unexplained Chronic Kidney Disease

Kidney biopsy can be informative in the patient with unexplained chronic kidney impairment and normal-sized kidneys, because in contrast to AKI, it is often difficult to determine the underlying cause with clinical criteria alone. In almost half of such patients, the biopsy will demonstrate an unexpected cause of CKD.8 However, if both kidneys are small (<9 cm on ultrasound), the risks of biopsy are increased, and the diagnostic information may be limited by extensive glomerulosclerosis and tubulointerstitial fibrosis. In this setting, however, immunofluorescence studies still may be informative. For example, glomerular IgA deposition may be identified despite advanced structural damage.

Familial Kidney Disease

A kidney biopsy can be helpful in the investigation of patients with a family history of kidney disease. A biopsy performed in one affected family member may secure the diagnosis for the whole family and avoid the need for repeat investigation. Conversely, a kidney biopsy may unexpectedly identify inherited disease, thereby prompting evaluation of other family members.

Role of Repeat Kidney Biopsy

In some patients, a repeat biopsy may be indicated. For example, the pathologic changes in lupus nephritis may evolve, necessitating treatment adjustment. In addition, corticosteroid-resistant, corticosteroiddependent, or frequently relapsing MCD may represent a missed diagnosis of focal segmental glomerulosclerosis (FSGS), which may be detected on repeat biopsy. Some nephrologists think repeat biopsy in patients who have had aggressive immunosuppressive therapy of crescentic GN can help determine the most appropriate next line of therapy.

VALUE OF KIDNEY BIOPSY

Biopsy Adequacy

In the assessment of a kidney biopsy, the number of glomeruli in the sample is the major determinant of whether the biopsy will be diagnostically informative.

For a focal entity such as FSGS, the diagnosis could be made on a biopsy specimen containing a single glomerulus that contains a typical sclerosing lesion. However, the probability that FSGS is not present in a patient with nephrotic syndrome and minimal changes on the biopsy specimen depends on the actual proportion of abnormal glomeruli in the kidney and the number of glomeruli obtained in the biopsy specimen. For example, if 20% of glomeruli in the kidney have sclerosing

Effect of Sampling on Kidney Biopsy Interpretation

B

A

to proceed before the tissue is placed in fixative, so the material can be processed in a way that will provide maximum information for the specific clinical scenario. For example, if the patient has heavy proteinuria, most information will be gained from EM because it can demonstrate podocyte foot process effacement, focal sclerosis, electron-dense deposits of immune complexes, and the organized deposits of amyloid.

If a sample is supplied for immunofluorescence microscopy but contains no glomeruli, it may be possible to reprocess the paraffinembedded part of the sample to identify immune deposits by immunoperoxidase or immunofluorescence techniques.

Is Kidney Biopsy Always Necessary?

Early studies suggested that kidney biopsy provided diagnostic clarity in most patients, but that this information did not alter management, except for those with heavy proteinuria or systemic disease. More recent prospective studies have suggested that the kidney biopsy identifies a diagnosis different from that predicted on clinical grounds in 50% to 60% of patients and leads to a treatment change in 20% to 50%.[9] This is particularly apparent in patients with heavy proteinuria or AKI, more than 80% of whom have biopsy findings that alter their management.[10]

PREBIOPSY EVALUATION

Unaffected glomeruli

Diseased glomeruli

Fig. 7.1 Effect of Sampling on Kidney Biopsy Interpretation. Red dots represent unaffected glomeruli. Blue dots represent diseased glomeruli. The size of the biopsy core affects the probability that the observed glomerular involvement is a true reflection of involvement in the whole kidney. In a biopsy specimen containing 10 glomeruli (core A), of which three are abnormal (30%), there is a 95% probability that the actual glomerular involvement is between 7% and 65%. In the same kidney, if the biopsy specimen contained 30 glomeruli with 30% being abnormal (core B), the 95% confidence intervals are narrowed to 15% and 50%.

lesions and five glomeruli are sampled, there is a 35% chance that all the glomeruli in the biopsy specimen will be normal and the biopsy will miss the diagnosis. By contrast, in the same kidney, if 10 or 20 glomeruli are sampled, the chance of obtaining all normal glomeruli is reduced to 10% and less than 1%, respectively, and the biopsy is therefore more discriminating. This argument assumes that any segmental lesions present in the biopsy specimen are actually identified; this requires the biopsy specimen to be sectioned at multiple levels.

Unless all glomeruli are affected equally, the probability that the observed involvement in the biopsy specimen accurately reflects true involvement in the kidney depends not only on the number of glomeruli sampled but also on the proportion of affected glomeruli (Fig. 7.1).

Therefore the interpretation of the biopsy should account for the number of glomeruli obtained. A typical biopsy sample will contain 10 to 15 glomeruli and will be diagnostically useful. Nonetheless, it must be appreciated that because of the sampling issue, a biopsy sample of this size will occasionally be unable to diagnose focal diseases and at best will provide imprecise guidance on the extent of glomerular involvement.

An adequate biopsy also should provide samples for immunohistologic examination and electron microscopy (EM). Immunohistologic examination is performed by either immunofluorescence on frozen material or immunoperoxidase on fixed tissue, according to local protocols and expertise. It is helpful for the biopsy cores to be viewed under an operating microscope immediately after being taken to ensure that they contain cortex and that when the cores are divided, the immunohistologic and EM samples both contain glomeruli.

If the material obtained for a complete pathologic evaluation is insufficient, a discussion with the pathologist should address how best

The prebiopsy evaluation identifies issues that may compromise the safety and success of the procedure (Fig. 7.2). It will determine whether the patient has two normal-sized unobstructed kidneys, sterile urine, controlled blood pressure, and no bleeding diathesis. A thorough history should be taken to identify evidence of a bleeding diathesis, such as previous prolonged surgical bleeding, spontaneous bleeding, family history of bleeding, and ingestion of medication that increases bleeding risk, including antiplatelet agents and anticoagulants.

Important clinical history also relates to patients’ previous experiences of biopsies as well as psychological conditions and level of comprehension.11

An ultrasound scan should be performed to assess kidney size and identify significant anatomic abnormalities, such as solitary kidney, polycystic or simple cystic kidneys, malpositioned kidneys, horseshoe kidneys, small kidneys, and hydronephrosis.

We recommend hematology studies prebiopsy including platelet count and coagulation profile with prothrombin time and activated partial thromboplastin time. The value of the bleeding time (BT) and thromboelastography (TEG) for predicting bleeding risk after kidney biopsy is unclear. Retrospective studies, however, demonstrated a three- to fivefold increase in bleeding complications after kidney biopsy in patients with prolonged BT. Prospective studies of percutaneous liver biopsy patients showed a fivefold increase in bleeding complications in those with uncorrected BT.12 A consensus document concluded that the BT is a poor predictor of postsurgical bleeding, but it does correlate with clinical bleeding episodes in uremic patients.13 TEG provides an overall measure of the coagulation, platelet, and fibrinolytic systems in one assay and thus may be more predictive of clinical bleeding.14 A more recent study of 417 patients indicated that TEG abnormalities in patients with renal dysfunction are variable and fail to predict bleeding after kidney biopsy.15 The role of TEG in the patient undergoing native kidney biopsy requires further evaluation.

Management of Bleeding Risk

Several approaches to the management of bleeding risk have been adopted.

Aspirin

Patients should ideally discontinue aspirin 7 days prior to kidney biopsy. However, because cardiovascular disease is very common in

Workup for Kidney Biopsy

Assessments

Renal imaging
Two normal size,
unscarred,
unobstructed
kidneys

Blood pressure
Systolic BP
< 140 mm Hg
Diastolic BP
< 90 mm Hg

Urine culture
Sterile

Coagulation status
Drug therapy: Stop aspirin and clopidogrel 7 days before biopsy (unless high cardiovascular risk; see text)
Stop warfarin and DOACs 5 days before biopsy (may require bridging anticoagulation plan if high thrombotic risk)
Platelet count > 100×109/L
Prothrombin time <1.2 times control
Activated partial thromboplastin time <1.2 times control

Renal biopsy

Fig. 7.2 Workup for Kidney Biopsy. BP, Blood pressure; DOACs, direct oral anticoagulants.

subjects with kidney disease, aspirin discontinuation policies have led to increased cardiac events of recurrent myocardial infarction of 40% and stroke increase three- to fourfold.16 Although there is an associated increased risk of minor bleeding but not major bleeding, aspirin should be continued in the setting of active cardiovascular risk (e.g., ongoing angina, recent coronary angioplasty, transient ischemic attack).17

Clopidogrel

There is very limited data examining safety of continuing clopidogrel at the time of biopsy, so most guidelines suggest cessation 7 days prior to biopsy. Platelet transfusion also can be used to reverse clopidogrelinduced platelet dysfunction when the kidney biopsy is urgent.

Warfarin and Direct Oral Anticoagulants

Warfarin and direct oral anticoagulants (DOACs) should be stopped 5 days prior to biopsy. In low-risk patients, there is no need to have bridging anticoagulation,18 but in individuals with a mechanical valve, antiphospholipid syndrome, high-risk thrombophilia, or venous thromboembolism within 3 months, bridging low-molecular-weight or unfractionated heparin should be used.17

Procoagulants

The use of desmopressin (DDAVP) has been suggested in a small study with minimal clinically significant effect19 as a strategy to lessen minor and major bleeding because it is a synthetic analog of vasopressin and increases platelet adhesion to the blood vessel wall by releasing factor VII and von Willebrand factor. Because of its increased side effect profile (hyponatremia, hypotension, tachycardia, facial flushing, nausea, and abdominal pain) and minimal clinical evidence supporting its use, it is no longer recommended.17

Contraindications to Kidney Biopsy

The contraindications to percutaneous kidney biopsy are listed in Box 7.2. The major contraindication is a bleeding diathesis. If the disorder cannot be corrected and the biopsy is deemed indispensable, alternative approaches can be used, such as open biopsy, laparoscopic biopsy, or transvenous (usually transjugular) biopsy. Inability of the patient to comply with instructions during kidney biopsy is another major contraindication. Sedation or, in extreme cases, general anesthesia may be necessary.

BOX 7.2

Contraindications to Kidney Biopsy

Kidney Status
Multiple cysts
Solitary kidney
Acute pyelonephritis
Perinephric abscess
Kidney neoplasm
Patient Status
Uncontrolled bleeding diathesis
Uncontrolled blood pressure
Uremia
Obesity
Uncooperative patient
Most contraindications are relative rather than absolute. Clinical circumstances that necessitate urgent kidney biopsy may be overridden, except for uncontrolled bleeding diathesis.

Hypertension (>140/90 mm Hg), hypotension, perinephric abscess, pyelonephritis, hydronephrosis, severe anemia, large kidney tumors, and cysts are relative contraindications to kidney biopsy. When possible, these should be corrected before the biopsy is undertaken.
The presence of a solitary functioning kidney has been considered a contraindication to percutaneous biopsy, and some argue that the risk of biopsy is reduced by direct visualization at open biopsy. However, the postbiopsy nephrectomy rate of 1 in 2000 to 1 in 5000 is comparable to the mortality rate associated with the general anesthetic required for an open procedure. Therefore in the absence of risk factors for bleeding, percutaneous biopsy of a solitary functioning kidney can be justified if there is a clinically important indication for kidney biopsy.

KIDNEY BIOPSY TECHNIQUE

Percutaneous Kidney Biopsy

Native Kidney Biopsy

At our centers, the kidney biopsy is performed by nephrologists with continuous (real-time) ultrasound guidance and disposable automated biopsy needles. We use 16-gauge needles as a compromise between the greater tissue yield of larger needles and the trend toward fewer bleeding

Fig. 7.4 Kidney Biopsy Procedure. The biopsy needle is introduced at an angle of approximately 70 degrees to the skin and is guided by continuous ultrasound. The operator is shown wearing a surgical gown. This is not strictly necessary; sterile gloves and maintenance of a sterile field are sufficient.

Fig. 7.3 Computed Tomography Through the Left Kidney. The angle of approach of the needle is demonstrated. Note the relative adjacency of the lower pole of the kidney to other structures, particularly the large bowel.

complications of smaller needles as recommended by recent guidelines.17 For most patients, premedication or sedation is not required as long as there is adequate education and informed consent provided. A history of anxiety may require prebiopsy counseling and intraprocedural relation therapy.11 The patient is prone, and a pillow is placed under the abdomen at the level of the umbilicus to straighten the lumbar spine and splint the kidneys. Fig. 7.3 shows the anatomic relationships of the left kidney. Ultrasound is used to localize the lower pole of the kidney where the biopsy will be performed (usually the left kidney). An indelible pen mark is used to indicate the point of entry of the biopsy needle. The skin is sterilized with povidone-iodine (Betadine) or chlorhexidine solution. A sterile fenestrated sheet is placed over the area to maintain a sterile field. Local anesthetic (2% lidocaine [lignocaine]) is infiltrated into the skin at the point previously marked. While the anesthetic takes effect, the ultrasound probe is covered in a sterile sheath. Sterile ultrasound jelly is applied to the skin and, under ultrasound guidance, a 10-cm, 21-gauge needle is guided to the renal capsule and further local anesthetic infiltrated into the perirenal tissues, then along the track of the needle on withdrawal. A stab incision is made through the dermis to ease passage of the biopsy needle. This is passed under ultrasound guidance to the kidney capsule (Fig. 7.4). As the needle approaches the capsule, the patient is instructed to take a breath until the kidney is moved to a position such that the lower pole rests just under the biopsy needle, and then to stop breathing. The biopsy needle tip is advanced to the kidney capsule, and the trigger mechanism is released, firing the needle into the kidney (Fig. 7.5). The needle is immediately withdrawn, the patient is asked to resume breathing, and the contents of the needle are examined (Fig. 7.6). We examined the tissue core under an operating microscope to ensure that kidney cortex has been obtained (Fig. 7.7). A second pass of the needle is usually necessary to obtain additional tissue for immunohistologic examination and EM. If insufficient tissue is obtained, further passes of the needle are made. In our experience, however, passing the needle more than four times is associated with a modest increase in the postbiopsy complication rate.

Fig. 7.5 Kidney Biopsy Imaging. Ultrasound scan shows the needle entering the lower pole of the left kidney. Arrows indicate the needle track, which appears as a fuzzy white line.

No single fixative has been developed that allows good-quality light microscopy, immunofluorescence, and EM to be performed on the same sample. Therefore the kidney tissue is often divided into three samples and placed in formalin for light microscopy, normal saline for subsequent snap-freezing in liquid nitrogen for immunofluorescence, and glutaraldehyde for EM. Some centers can produce satisfactory light microscopy, immunohistochemistry, and EM on formalin-fixed biopsy material, although this depends on the expertise of individual laboratories.

The percutaneous kidney biopsy technique has several variations. Whereas most biopsies are guided by ultrasound, some operators use ultrasound only to localize the kidney and determine the depth and angle of approach of the needle and perform the biopsy without further ultrasound guidance. The success and complication rates appear to be no different from those seen with continuous ultrasound guidance. For technically challenging biopsies, computed tomography (CT) can be used to guide the biopsy needle.

For obese patients and patients with respiratory conditions who find the prone position difficult, the supine anterolateral approach recently has been described.[20] This technique provides good access to the lower pole of the kidney, is better tolerated than the prone position by these patients, and has a diagnostic yield and safety profile comparable to that of the standard technique for native kidney biopsy.

Kidney Transplant Biopsy

Biopsy of the transplant kidney is facilitated by the proximity of the kidney to the anterior abdominal wall and the lack of movement on respiration. It is performed under real-time ultrasound guidance with use of an automated biopsy needle. It is important to confirm that the transplanted kidney is in the normal extraperitoneal position—occasionally it will be intraperitoneal (simultaneous pancreas and kidney transplants in particular), and bowel injury becomes a potential hazard.

In most patients, the kidney transplant biopsy is performed to identify the cause of acute allograft dysfunction. In these circumstances, the goal is to identify acute rejection, and therefore the diagnosis can be made on a formalin-fixed sample alone for light microscopy. If vascular rejection is suspected, a snap-frozen sample for C4d immunostaining also should be obtained (although some laboratories can detect C4d on formalin-fixed material). If recurrent or de novo GN is suspected in patients with chronic allograft dysfunction, additional samples for EM and immunohistologic examination should be collected.

Fig. 7.6 Kidney Biopsy Sample. A core of kidney tissue is demonstrated in the sampling notch of the biopsy needle.

A

Special Situations

Pregnancy. In the setting of pregnancy, the risk of biopsy must be weighed against any potential benefit of diagnosis and treatment, especially considering that treatment options may be limited due to teratogenicity. Biopsy has been shown safe in all stages of pregnancy, but often after 32 weeks the baby is delivered first. A lateral position is undertaken to be able to perform the biopsy safely. A recent review study in which biopsy was performed for suspected glomerulonephritis or preeclampsia reported that therapy was altered in 66% of cases, suggesting it is useful in selected cases.[21]

Pediatrics. Renal biopsy in the pediatric setting has the added difficulty of much smaller kidneys and the need for a general anesthetic due to patient cooperation. Multiple cohort studies report that ultrasound-guided, percutaneous biopsies with a spring-loaded device and 18-gauge needle are safe with a complication rate of 4.1% and are successful in 99% of cases,[22] thus with a reduced number of passes resulting in similar complication rates. Kidney biopsy in pediatric kidney transplantation for surveillance has also been shown to have the same safety profile as in adults.[23]

Postbiopsy Monitoring

After the biopsy, the patient is placed supine and subjected to strict bed rest for 6 to 8 hours. The blood pressure is monitored frequently, the urine examined for visible hematuria, and the skin puncture site examined for excessive bleeding. If there is no evidence of bleeding after 6 hours, the patient is sat up in bed and subsequently allowed to ambulate. If visible hematuria develops, bed rest is continued until the bleeding settles. We advise minimal activity for 48 hours after biopsy and avoidance of contact sports and activities requiring straining for 2 weeks.

Conventionally, patients have been observed for complications in the hospital for 24 hours after biopsy. However, outpatient kidney biopsy with same-day discharge after 6 to 12 hours of observation has become increasingly popular for both native and kidney transplant biopsies. We recommend 6 hours for low-risk and 12 hours for high-risk biopsies (patients with significant renal impairment, patients undergoing biopsy for AKI, patients with elevated blood pressure prebiopsy, patients aged more than 70 years, and patients with abnormal bleeding profile or requiring early recommencement of

B

Fig. 7.7 Kidney Biopsy Micrographs. Appearance of kidney biopsy material under the operating microscope. (A) Low-power view shows two good-sized cores. (B) Higher magnification view shows the typical appearance of glomeruli (arrows).

anticoagulation).[17] Some studies suggest that as much as one-third of serious bleeding complications requiring transfusion may occur after 8 hours postbiopsy, whereas up to 91% occur within 12 hours.[24]

Early identification of postbiopsy bleeding is potentially useful in patients with stable observations and no clinical symptoms of bleeding. Ultrasound scanning 1 hour after biopsy has been investigated as a method to predict bleeding complications.[25,26] In the older study the absence of hematoma predicted an uncomplicated course, but identifying a hematoma did not reliably predict adverse outcomes; identification of hematoma at 1 hour had a 95% negative predictive value and 43% positive predictive value for a significant complication. The role of postbiopsy imaging in the wider clinical setting remains to be determined given the additional expense of routine scanning and the uncertainty about how best to manage findings that are detected only by ultrasound—an issue that was not addressed in the more recent study.[26]

Alternatives to the Percutaneous Approach

postprocedure complications, but the risk of general anesthesia and the delayed recovery time have prevented its widespread adoption. Open biopsy still may be performed, however, when a kidney biopsy is required in patients who are otherwise undergoing abdominal surgery.

Laparoscopic Kidney Biopsy

Laparoscopic renal biopsy requires general anesthesia and two laparoscopic ports in the posterior and anterior axillary lines to gain access to the retroperitoneal space. Laparoscopic biopsy forceps are used to obtain cortical biopsy samples, and the biopsy sites are coagulated with laser and packed to prevent hemorrhage. In the largest study of laparoscopic kidney biopsy, adequate tissue was obtained in 96% of 74 patients.[29] Significant bleeding occurred in three patients, the colon was injured in one, and a biopsy was performed inadvertently on the spleen and liver, respectively, in two others. Inadvertent biopsy was subsequently averted using intraoperative ultrasound in difficult cases.

When the percutaneous approach is contraindicated, other approaches to kidney biopsy have been described. The choice of technique depends on the safety, morbidity, recovery period, and adequacy of the technique, but mainly on the local expertise available.

COMPLICATIONS OF KIDNEY BIOPSY

Transvenous (Transjugular or Transfemoral) Kidney Biopsy

Pain

Transvenous sampling of the kidney is theoretically safer than the percutaneous approach because the needle passes from the venous system into the renal parenchyma and is directed away from large blood vessels. Any bleeding that occurs should be directed back into the venous system, and if capsular perforation develops, significant bleeding points can be immediately identified and controlled by coil embolization. Others argue that coil embolization of the punctured vein is unhelpful because significant bleeding into a perirenal hematoma or the urine indicates an arterial breach that requires selective angiography and arterial embolization.

Transvenous kidney biopsy cannot be regarded as routine because it involves specialist skills and additional time and expense compared with the percutaneous approach. The main indication for this approach is an uncontrollable bleeding diathesis. It also has been advocated for patients receiving artificial ventilation in the intensive care unit; the need to obtain tissue from more than one organ, including the kidney, liver, or heart; large-volume ascites that preclude the prone position; uncontrolled hypertension; morbid obesity; severe respiratory insufficiency; solitary kidney; failed percutaneous approach; and coma.

The patient lies supine, and the right internal jugular vein is cannulated. A guidewire is passed into the inferior vena cava (IVC), and a catheter is passed over the guidewire and selectively into the right renal vein, which is shorter and enters the IVC at a more favorable angle than the left renal vein. A sheath is passed over the catheter to a suitable peripheral location in the kidney with the aid of contrast enhancement. Finally, the biopsy device (usually a side-cut biopsy needle system) is passed through the sheath, and samples are taken. Contrast is then injected into the biopsy track to identify capsular perforation, and embolization coils are inserted if brisk bleeding is identified.

The quality of kidney tissue obtained by transjugular biopsy is variable, although studies report diagnostic yields of more than 90%.27 The complication rate appears comparable to that seen with percutaneous kidney biopsy, which is reassuring given that these are high-risk patients.

Patients should be informed about the inevitable dull ache around the needle entry site when the local anesthetic wears off after renal biopsy. Simple analgesia with acetaminophen (paracetamol) or acetaminophen-codeine combinations usually suffices. More severe pain in the loin or abdomen on the side of the biopsy suggests significant perirenal hemorrhage. Opiates may be necessary for pain relief, with appropriate investigation to clarify the severity of the bleed. Patients with visible hematuria may develop clot colic and describe the typical severe pain associated with ureteral obstruction.

Open Kidney Biopsy

Open kidney biopsy is useful when percutaneous biopsy is contraindicated. In a series of 934 patients, tissue adequacy was 100% with no major complications.28 This is an effective approach with minimal

The complication rates compiled from large series of kidney biopsies are shown in Table 7.1 30

Hemorrhage

A degree of perirenal bleeding accompanies every kidney biopsy. The mean decrease in hemoglobin after a biopsy is approximately 1 g/dL.31 Significant perirenal hematomas are almost invariably associated with severe loin pain, although some hematomas are asymptomatic. Both visible hematuria and painful hematoma are seen in 3% to 4% of patients after biopsy.

The initial management is strict bed rest and maintenance of normal coagulation indices. If bleeding is brisk and associated with hypotension or prolonged and fails to settle with bed rest, renal angiography should be performed to identify the source of bleeding. Coil

Complications in 118,064 Native Kidney Biopsies

TABLE 7.1

Complication	Percentage
Hematoma	11

Pain

4.3

Visible hematuria

3.5

Need for blood transfusion

1.6

Need for intervention to control bleeding

0.3

Death

0.06 (0.03 for outpatient biopsies)

Data from Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373(9):823–833.

embolization can be performed during the same procedure, and this has largely eliminated the need for open surgical intervention and nephrectomy.

Arteriovenous Fistula

Most postbiopsy arteriovenous fistulas are detected by Doppler ultrasound or contrast-enhanced CT and, when looked for specifically, can be found in as many as 18% of patients. Because most are clinically silent and more than 95% resolve spontaneously within 2 years, fistulas should not be routinely sought. In a small minority of patients, arteriovenous fistulas can lead to visible hematuria (typically recurrent, dark red, and often with blood clots), hypertension, and renal impairment, which requires embolization.

Other Complications

A variety of rare complications have been reported, including biopsy performed on other organs (liver, spleen, pancreas, bowel, gallbladder), pneumothorax, hemothorax, calyceal-peritoneal fistula, dispersion of carcinoma, and Page kidney (compression of kidney by perirenal hematoma leading to renin-mediated hypertension).

Death

Death resulting directly from kidney biopsy is much less common in recent biopsy series compared with earlier reports. Most deaths are the result of uncontrolled hemorrhage in high-risk patients, particularly those with severe kidney impairment.

SELF-ASSESSMENT QUESTIONS

1. A 68-year-old woman with nonnephrotic proteinuria of unknown cause attended the outpatient unit for a kidney biopsy. She had a history of hypertension, chronic alcohol abuse, and osteoarthritis. Which of the following would be a contraindication to renal biopsy for this patient?
A. Ingestion of naproxen 24 hours earlier
B. Blood pressure of 162/94 mm Hg
C. Dipstick urinalysis positive for nitrites and leukocytes
D. Presence of simple cysts in both kidneys (four in left, three in right)
E. Body mass index of 36 kg/m^2

2. A 32-year-old woman was referred to the Kidney-obstetric clinic for evaluation of kidney disease. Which is a recognized indication for kidney biopsy during pregnancy?
A. Isolated proteinuria, ratio of protein to creatinine of 320 mg/mmol
B. Asymptomatic proteinuria with nonvisible hematuria
C. Episodic visible hematuria
D. Symptomatic nephrotic syndrome after 32 weeks of gestation
E. Unexplained deterioration in kidney function before 32 weeks of gestation

3. A 75-year-old man was admitted as an emergency with AKI. He had been unwell for 4 months with myalgia, arthralgia, and generalized fatigue. More recently, he had developed epistaxis and a nonblanching leg rash. Six months earlier, he had a myocardial infarction followed by right coronary artery angioplasty and stenting. He was taking aspirin (75 mg), clopidogrel (75 mg), bisoprolol (5 mg), ramipril (5 mg), and atorvastatin (40 mg). On examination, his blood pressure was 148/86 mm Hg, and he was euvolemic. A purpuric rash was present on both lower legs. Test results were as follows:

✓ •✓ Serum creatinine: 523 μmol/L (60–110)

✓
✓
✓
✓
✓

• ✓
• ✓
• ✓
• ✓
• ✓

Serum C-reactive protein: 25 mg/L (<10)
Urine dipstick: 3+ blood, 2+ protein, 0 nitrites, 0 leukocytes
Antinuclear antibodies: negative
Anti–neutrophil cytoplasmic antibodies: negative
Anti–glomerular basement membrane antibodies: negative
An urgent kidney biopsy is requested to determine the cause of AKI.
What should be done to minimize the risk for postbiopsy bleeding?
A. Undertake a transjugular kidney biopsy
B. Transfuse platelets before the biopsy
C. Administer DDAVP
D. Stop aspirin and clopidogrel and wait 24 hours before performing the biopsy
E. Administer vitamin K and proceed if international normalized ratio and activated partial thromboplastin time ratio are normal

4. A 32-year-old man was seen in the nephrology clinic with proteinuria. He has a history of type 1 diabetes mellitus and hypertension.
He was treated with lisinopril (10 mg), amlodipine (5 mg), aspirin (75 mg), simvastatin (40 mg), and insulin. On examination, he was overweight (body mass index: 30 kg/m2), blood pressure was 146/84 mm Hg, and edema was present to midcalf level bilaterally.
Test results were as follows:
✓ • ✓ Serum creatinine: 123 µmol/L (60–110)
✓ • ✓ Serum albumin: 28 g/L (37–49)
✓ • ✓ Urinary protein/creatinine ratio: 460 mg/mmol (<15)
Which additional feature would provide justification for undertaking a kidney biopsy?
A. Presence of diabetic retinopathy
B. Duration of diabetes of 12 years
C. Presence of nonselective proteinuria
D. Negative dipstick urinalysis 4 months earlier
E. Hemoglobin A1c of 7.2%

REFERENCES

1. Iversen P, Brun C. Aspiration biopsy of the kidney. 1951. J Am Soc Nephrol. 1997;8:1778–1787. discussion 1778-1786.
2. Alwall N. Aspiration biopsy of the kidney, including i.a. a report of a case of amyloidosis diagnosed through aspiration biopsy of the kidney in 1944 and investigated at an autopsy in 1950. Acta Med Scand. 1952;143:430–435.
3. Kark RM, Muehrcke RC. Biopsy of kidney in prone position. Lancet. 1954;266:1047–1049.
4. Bobart SA, DeVriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. Kidney Int. 2019;95:429–438.
5. Li C, Li H, Wen Y-b, Li X-M., Li X-W.. Analysis of predictive factors for immunosuppressive response in anti-phospholipidase A2 receptor antibody positive membranous nephropathy. BMC Nephrol. 2018;19:354–359.
6. Li Y, Wan J, Chen Y, Pan Y. Serum anti-phospholipase A2 receptor (PLA2R) antibody detected at diagnosis as a predictor for clinical remission in patients with primary membranous nephropathy. BMC Nephrol. 2019;20:360–369.
7. Topham PS, Harper SJ, Furness PN, et al. Glomerular disease as a cause of isolated microscopic haematuria. Q J Med. 1994;87:329–335.
8. Kropp KA, Shapiro RS, Jhunjhunwala JS. Role of renal biopsy in end stage renal failure. Urology. 1978;12:631–634.
9. Turner MW, Hutchinson TA, Barre PE, et al. A prospective study on the impact of the renal biopsy in clinical management. Clin Nephrol. 1986;26:217–221.
10. Richards NT, Darby S, Howie AJ, et al. Knowledge of renal histology alters patient management in over 40% of cases. Nephrol Dial Transplant. 1994;9:1255–1259.
11. Gutman T, Lopez-Vargars P, Manera KE, et al. Identifying and integrating patient and caregiver perspectives in clinical practice guidelines for percutaneous renal biopsy. Nephrology. 2019;24(4):395–404.
12. Boberg KM, Brosstad F, Egeland T, et al. Is a prolonged bleeding time associated with an increased risk of hemorrhage after liver biopsy? Thromb Haemost. 1999;81:378–381.
13. Peterson P, Hayes TE, Arkin CF, et al. The preoperative bleeding time test lacks clinical benefit: college of American Pathologists’ and American Society of Clinical Pathologists’ position article. Arch Surg. 1998;133:134–139.
14. Davis CL, Chandler WL. Thromboelastography for the prediction of bleeding after transplant renal biopsy. J Am Soc Nephrol. 1995;6:1250–1255.
15. Gal-Oz A, Papushado A, Kirgner I, et al. Thromboelastography versus bleeding time for risk of bleeding post native kidney biopsy. Ren Fail. 2020;42(1):10–18.

16. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndrome. Circulation. 2004;110:2361–2367.
17. MacGinley R, Champion De Crespigny PJ, Gutman T, et al. KHA-CARI Guideline recommendations for renal biopsy. Nephrology (Carlton). 2019;24(12):1205–1213.
18. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373(9):823–833.
19. Manno C, Bonifati C, Torres DD, et al. Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized control trial. Am J Kidney Dis. 2011;57:850–855.
20. Gesualdo L, Cormio L, Stallone G, et al. Percutaneous ultrasoundguided renal biopsy in supine antero-lateral position: a new approach for obese and non-obese patients. Nephrol Dial Transplant. 2008;23:971–976.
21. Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy:

evidence for counselling? a systematic narrative review. BJOG. 2013;120:412–427.
22. Franke M, Kramarczyk A, Taylan C, Maintz D, Hoppe B, Koerber F. Ultrasound-guided percutaneous renal biopsy in 295 children and adolescents: role of ultrasound and analysis of complications. PLoS One. 2014:1–16.
23. Rose EM, Kennedy SE, Mackie FE. Surveillance biopsies after pediatric kidney transplantation: a review. Pediatr Transplant. 2016;20:748–755.
24. Whittier WL, Korbet SM. Timing of complications in percutaneous renal biopsy. J Am Soc Nephrol. 2004;15:142–147.
25. Waldo B, Korbet SM, Freimanis MG, Lewis EJ. The value of post-biopsy ultrasound in predicting complications after percutaneous renal biopsy of native kidneys. Nephrol Dial Transplant. 2009;24:2433–2439.
26. Prasad N, Kumar S, Manjunath R, et al. Real-time ultrasound-guided percutaneous renal biopsy with needle guide by nephrologists decreases post-biopsy complications. Clin Kidney J. 2015;8:151–156.
27. See TC, Thompson BC, Howie AJ, et al. Transjugular renal biopsy: our experience and technical considerations. Cardiovasc Intervent Radiol. 2008;31:906–918.
28. Nomoto Y, Tomino Y, Endoh M, et al. Modified open renal biopsy: results in 934 patients. Nephron. 1987;45:224–228.
29. Shetye KR, Kavoussi LR, Ramakumar S, et al. Laparoscopic renal biopsy: a 9-year experience. BJU Int. 2003;91:817–820.
30. Poggio ED, McClelland RL, Blank KN, et al. Systematic review and metaanalysis of native kidney biopsy complications. Clin J Am Soc Nephrol. 2020;15:1595–1602.
31. Burstein DM, Korbet SM, Schwartz MM. The use of the automatic core biopsy system in percutaneous renal biopsies: a comparative study. Am J Kidney Dis. 1993;22:545–552.

8

Disorders of Extracellular Volume

David H. Ellison

EXTRACELLULAR FLUID COMPARTMENT

Water makes up 60% of a typical man’s body weight and 50% of a woman’s body weight. Total body water (TBW) is distributed in two compartments: the intracellular fluid (ICF) compartment (55%–65% of TBW) and extracellular fluid (ECF) compartment (35%–45% of TBW). The ECF is further subdivided into two spaces: the interstitial space, which accounts for about 75% of the ECF, and the intravascular space, which represents the remaining 25% (Fig. 8.1).

Water diffuses freely between the intracellular space and the extracellular spaces in response to gradients in effective osmolality, where effective osmolality (tonicity) is the product of the solute concentration and its reflection coefficient (similar to the inverse of permeability). Therefore, the amount of water in different compartments depends primarily on the quantity of effective osmoles in that compartment. The major cation in the ECF is sodium ion (Na^+), and the major intracellular cation is potassium ion (K^+); the number of cations always equals the number of anions in fluid. This uneven ion distribution is maintained by active transport through the Na^+/K^+-adenosine triphosphate (ATP)-dependent pumps on the cell membrane, which determines the relative volume of different compartments. Because sodium is the predominant extracellular cation, the ECF volume is determined primarily by the sodium content of the body. Total body sodium largely depends on salt intake and kidney excretion; the latter is tightly regulated.

Fluid movement between the intravascular and interstitial spaces of the ECF occurs across the capillary wall and is governed by Starling forces: the capillary hydrostatic pressure and colloid osmotic pressure. Unlike cell membranes, capillary membranes are highly permeable to small solutes, such as Na^+, rendering small molecules incapable of generating transcapillary water movement. Plasma proteins, especially albumin, play special roles in retaining fluid within capillaries because proteins are poorly permeable across capillary membranes. The outward transcapillary hydrostatic pressure gradient exceeds the corresponding inward oncotic pressure gradient, thereby favoring movement of plasma ultrafiltrate into the interstitial space.

Titze and colleagues[1] suggest that this model is oversimplified. They emphasize that not all fluid compartments are in osmotic equilibrium and not all extracellular sodium is osmotically active. Accordingly, sodium can be stored in compartments such as the skin (whether osmotically silent[2] or osmotically active[3] is not clear) and then released in a rhythmic manner that is independent of ECF volume.[4] The existence of such compartments has been recognized for many years; for example, in cartilage, glycosaminoglycans attract sodium to generate a hypertonic environment into which water movement is resisted by rigid collagen,[5] and a “gel phase” containing glycosaminoglycans was incorporated into the well-known model generated by Guyton and colleagues.[6] Immune cells contribute to the skin sodium storage, which may help determine the ability of skin to resist microbial pathogens. Sodium homeostasis relies on the crucial role of the lymphatics in returning sodium to the circulation. Despite these important caveats to the concept of a uniform interstitial environment, treating edema removes fluid primarily from an “interstitial” (nonplasma) compartment, indicating that most extravascular fluid is in osmotic equilibrium with plasma.[7]

The ECF volume determines the adequacy of the circulation and, in turn, the adequacy of delivery of oxygen, nutrients, and other substances needed for organ functions; it is also necessary for removal of waste products. This is achieved despite day-to-day variation in the intake of sodium and water, with the ECF volume varying by only 1% to 2%.

REGULATION OF EXTRACELLULAR FLUID HOMEOSTASIS

Circulatory stability depends on homeostatic mechanisms that include an afferent sensing limb, involving volume and stretch detectors distributed throughout the vascular bed, and an efferent effector limb (Table 8.1). Adjustments in the effector mechanisms occur in response to afferent stimuli by sensing-limb detectors to modify circulatory parameters. Disorders of either sensing mechanisms or effector mechanisms can lead to failure of adjustment of sodium handling by the kidney, with resultant hypertension or edema formation in the patient with positive sodium balance or hypotension and hypovolemia in the patient with negative sodium balance.

Afferent (Sensor) Limb

Afferent limb (sensing) sites include low-pressure cardiopulmonary receptors (atrial, ventricular, and pulmonary stretch receptors), highpressure arterial baroreceptors (carotid, aortic arch, and kidney sensors), central nervous system (CNS) receptors, and hepatic receptors.

The cardiac atria possess the distensibility and compliance needed to monitor changes in intrathoracic venous volume. Atrial distention and a sodium load cause release of atrial natriuretic peptide (ANP), a polypeptide normally stored in secretory granules within atrial myocytes.

The closely related brain natriuretic peptide (BNP) is stored primarily

Body Fluid Composition
200
Na^+

mEq/L

HCO_3

150
Na^+

HCO_3

HCO_3

HCO_3
A

A
100
Na^+

Na^+

K^+
CI

50

A
K^+

CI

CI

HPO_4

CI
K^+
0
Plasma
ECF
RBC
ICF

Fig. 8.1 Gamblegram of Body Composition. A 70-kg man contains 42 L (60%) of water, whereas a 60-kg woman contains 36 L (50%) of water. Of water, two-thirds is intracellular (ICF) and one-third is extracellular (ECF). The osmolality in compartments is similar, even though solute concentrations differ, owing to valence of ions. RBC, Red blood cell; A, Other anions.

Homeostatic Mechanisms in Extracellular Fluid Volume

TABLE 8.1

Afferent (Sensing)

Efferent (Effector)

Cardiopulmonary receptors
有•有 Atrial
有•有 Ventricular
有•有 Pulmonary
High-pressure baroreceptors
有•有 Carotid
有•有 Aortic
有•有 Kidney
有 •有 Pressure sensorsa
有 •有 Glomerular afferent
有 •有 Juxtaglomerular apparatus
Central nervous system receptors
Hepatic receptors

Renin-angiotensin-aldosterone system
Prostaglandins
Arginine vasopressin
Natriuretic peptides
有•有 Atrial
有•有 Brain
有•有 C-type
Other hormones
有•有 Nitric oxide
有•有 Endothelin
有•有 Kallikrein-kinin system

aPressure

sensors are unspecified receptors contributing to pressure natriuresis.

in ventricular myocardium and is released when ventricular diastolic pressure rises. An increase in left atrial pressure also sends signals to the hypothalamus that can suppress the release of antidiuretic hormone (ADH), also called arginine vasopressin (AVP). These atrial-renal and atrial-hypothalamic reflexes enhance kidney sodium and water excretion on sensing of a distended left atrium.

The sensitive arterial stretch receptors in the carotid artery and in the aortic arch respond to a decrease in arterial pressure. Information from these nerve endings is carried by the vagal and glossopharyngeal nerves to vasomotor centers in the medulla and brainstem. In a normal situation, these receptors exert a tonic restraining effect on the heart and circulation by inhibiting the sympathetic outflow and augmenting parasympathetic activity. In addition, changes in transmural pressure across the arterial vessels and the atria also influence the secretion of AVP and renin and the release of ANP. Activation of the arterial receptors signals the kidney to retain sodium and water through increases in sympathetic activity and vasopressin release. Stimulation of the sympathetic nervous system (SNS) also enhances the renin-angiotensinaldosterone system (RAAS). A rise in arterial pressure elicits the opposite response, resulting in decreased catecholamine release and natriuresis.

Kidney-sensing mechanisms include the juxtaglomerular apparatus (JGA), which is involved in the generation and release of renin from the kidney and in tubuloglomerular feedback (TGF) (see later discussion). Renin secretion is inversely related to perfusion pressure and directly related to intrarenal tissue pressure. Solute delivery to the macula densa is also an important determinant of renin release; an increase in sodium chloride entry into macula densa cells inhibits renin release, whereas a decrease in entry stimulates it. Kidney nerve stimulation through activation of β-adrenergic receptors of the JGA directly enhances renin release. Other receptors reside in the CNS and hepatic circulation but have been less well defined.

Kidney Hemodynamics and Sodium Excretion

Increases or decreases in glomerular filtration rate (GFR) lead to parallel changes in NaCl reabsorption (Fig. 8.2), the phenomenon of glomerulotubular balance (GTB), so that GFR is not a major determinant of net solute excretion. A second process, TGF, senses NaCl at the macula densa to adjust GFR. High luminal NaCl concentration at the macula densa occurs during high loop segment flow rates and volume expansion. This leads to constriction of the nearby afferent arteriole.

Mechanisms of ECF Volume Regulation
Glomerulotubular Balance

Proximal
Reabsorption

A

Tubuloglomerular Feedback

GFR

GFR

B

GFR Autoregulation

GFR

LP Flow

Pressure Natriuresis

Sodium
Excretion

C
D
MAP
MAP

Fig. 8.2 Overall Mechanisms of Extracellular Fluid (ECF) Volume Regulation. (A) Proximal reabsorption rises with increased glomerular filtration rate (GFR) (glomerulotubular balance). (B) Relationship between late proximal (LP) flow and GFR (tubuloglomerular feedback). (C) GFR is autoregulated across mean arterial pressure (MAP). (D) Sodium excretion increases, as MAP increases, the pressure natriuresis. Boxes indicate typical operating ranges.

This process reduces GFR (see Fig. 8.2) and therefore proximal flow, tending to keep solute excretion rates constant. Although functionally independent of GTB, the sequential arrangement of GTB and TGF means they work in concert and are remarkably effective at maintaining NaCl excretion rates in the face of changing GFR.[8]

The importance of TGF for kidney health has been emphasized recently by the introduction of sodium glucose cotransporter 2 inhibitors. These drugs inhibit glucose and sodium reabsorption along the proximal tubule and were developed as treatments for diabetes mellitus. Nevertheless, they have shown a remarkable ability to slow the progression of chronic kidney disease (CKD), not only when caused by diabetes, but also from other causes.[9] Although the mechanisms are likely pleiotropic, they strongly activate TGF by delivering more sodium to the macula densa, thereby reducing intraglomerular pressure, an effect similar to that observed with angiotensin-converting enzyme (ACE) inhibitors.[10]

Pressure Natriuresis

Both kidney blood flow and GFR are autoregulated (see Fig. 8.2), meaning they are relatively insensitive to variations in arterial pressure, within a range of typical pressure values. In contrast, urinary Na+ excretion is strongly affected by even modest variations in pressure, with a rise in pressure increasing kidney Na+ excretion (see Fig. 8.2). This process appears to be intrinsic to the kidney, but the shape of the relationship is strikingly altered by the RAAS. This phenomenon, termed pressure natriuresis, likely results from the adjustment of Na+ reabsorption by several segments of the nephron, via pathways that remain incompletely defined. The dominant importance of pressure natriuresis, at least under sodium retentive conditions, is clear from experimental models. Natriuretic sensitivity to natriuretic peptides in heart failure can be restored[11] by a rise in kidney perfusion pressure (RPP). Conversely, escape from the sodium retentive effects of aldosterone[12] or angiotensin II (Ang II)[13] also requires a rise in RPP.

Efferent (Effector) Limb

The stimulation of the effector limb of the ECF volume homeostasis leads to activation of effector mechanisms (see Table 8.1). These effector mechanisms aim predominantly at modulation of kidney sodium and water excretion to preserve circulatory stability.

Renin-Angiotensin-Aldosterone System

Renin secretion from the JGA increases in response to depletion of the ECF volume as a result of the processes described previously. Renin converts angiotensinogen to Ang I, which is then converted to Ang II by the action of the ACE; Ang II can subsequently affect circulatory stability and ECF volume homeostasis. Ang II is a vasoconstrictor that stimulates sodium retention and aldosterone release, which all maintain arterial pressure when ECF volume is low. Ang II has complex effects on GFR and kidney plasma flow (RPF), but when the ECF volume is low, it preferentially increases kidney efferent arteriolar tone, thus tending to preserve GFR. Ang II also increases the filtration fraction by altering Starling forces across the glomerulus, which leads to enhanced proximal sodium and water retention.[14]

Ang II also augments sympathetic neurotransmission and enhances the TGF mechanism. In addition to these indirect mechanisms, Ang II directly enhances proximal tubular volume reabsorption by activating apical membrane sodium-hydrogen (Na^+-H^+) exchangers. Ang II also enhances sodium absorption by stimulating aldosterone secretion, which, in turn, increases sodium reabsorption in the aldosteronesensitive distal nephron.

Sympathetic Nervous System

Sympathetic nerves that originate in the prevertebral celiac and paravertebral ganglia innervate cells of the afferent and efferent arterioles, JGA, and kidney tubule. Sympathetic nerves alter kidney sodium and water handling by direct and indirect mechanisms.[15] Increased nerve stimulation indirectly stimulates proximal tubular sodium reabsorption by altering preglomerular and postglomerular arteriolar tone, thereby influencing filtration fraction. Kidney nerves directly stimulate proximal tubular fluid reabsorption through receptors on the basolateral membrane of the proximal convoluted tubule cells. These effects on sodium handling are further amplified by the ability of the sympathetic nerves to stimulate renin release, which leads to the formation of Ang II and aldosterone.

Natriuretic Peptides

ANP and BNP augment sodium and water excretion by increasing GFR, possibly by dilating the afferent arteriole and constricting the efferent arteriole. Furthermore, they inhibit sodium reabsorption in the cortical collecting tubule and inner medullary collecting duct, reduce renin and aldosterone secretion, and oppose the vasoconstrictive effects of Ang II.[16] Circulating levels of ANP and BNP are elevated in congestive heart failure (CHF) and in cirrhosis with ascites but do not overcome the sodium-retaining effects of low RPP.

Prostaglandins

Prostaglandins are derived from arachidonic acid and modulate kidney blood flow and sodium handling. Important kidney prostaglandins include prostaglandin I_2, which mediates baroreceptor (but not β-adrenergic) stimulation of renin release. Prostaglandin E_2 is stimulated by Ang II and has vasodilatory properties. Increased levels of Ang II, AVP, and catecholamines stimulate synthesis of prostaglandins, which, in turn, act to dilate the kidney vasculature, inhibit sodium and water reabsorption, and stimulate renin release. In situations of ECF or effective arterial blood volume (EABV) depletion, the combination of prostaglandin-mediated afferent arteriolar dilation and Ang II–mediated efferent arteriolar constriction plays a central role in autoregulatory maintenance of GFR. Often, in these situations, interference with efferent vasoconstriction (e.g., ACE inhibition), and with afferent vasodilation (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) leads to a precipitous decline in GFR, manifested as acute kidney injury (AKI).

Arginine Vasopressin

The polypeptide AVP is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and is secreted by the posterior pituitary gland. Hypertonicity is the predominant stimulus for AVP release under typical conditions. Substantial reductions in EABV, however, act as a second, nonosmotic regulatory pathway.17 AVP release is suppressed in response to ECF volume overload sensed by increased afferent impulses from arterial baroreceptors and atrial receptors, whereas decreased ECF volume has the opposite effect. AVP release leads to antidiuresis via V2 receptors and, at higher concentrations, to systemic vasoconstriction through the V1 receptors.18 The antidiuretic action of AVP results from the effect on the principal cell of the collecting duct through activation of the V2 receptor. AVP increases the synthesis and provokes the insertion of aquaporin 2 (AQP2) water channels into the luminal membrane, thereby allowing water to be reabsorbed down the favorable osmotic gradient generated by the countercurrent multiplier system. AVP also enhances Na+ reabsorption via the epithelial sodium channel, ENaC, and thereby K+ secretion. AVP appears to have synergistic effects with aldosterone on sodium transport in the cortical collecting duct.19 AVP stimulates potassium secretion by the distal nephron, and this preserves potassium balance during ECF depletion, when circulating levels of vasopressin are high and tubular delivery of sodium and fluid is reduced. It should be noted, however, that states of excess AVP secretion are manifested primarily by excess water, and not salt, accumulation, because of offset physiologic control mechanisms.

Other Hormones

Other hormones that contribute to kidney sodium handling and ECF volume homeostasis include nitric oxide (NO), endothelin, and the kallikrein-kinin system. NO is an endothelium-derived mediator that participates in the natriuretic responses to increases in blood pressure or ECF volume expansion. Endothelins, in addition to their potent actions to constrict vascular smooth muscle, are natriuretic factors. Endothelin 1, via the endothelin B (ETB) receptor, increases NO production, which tends to increase urinary salt excretion. Kinins are potent vasodilator peptides, but their physiologic roles are not yet fully defined.

Terms Useful for Disorders of Extracellular Fluid Volume

In clinical practice, it is helpful to view disorders of ECF volume as distinct from disorders of water balance. The latter reflect gain or loss of electrolyte-free water, typically resulting in changes in plasma osmolality (hyponatremia or hypernatremia); when losses or gains are substantial, detectable changes in ECF volume can occur. Changes in ECF volume, however, often termed volume contraction or volume expansion, reflect gain or loss of NaCl. Water is often retained or lost secondarily.

Loss of salt and water produces true depletion of ECF volume, but there are many pathologic conditions (e.g., heart failure [HF]; cirrhosis) in which ECF volume is expanded but the kidneys behave as if it is contracted. To account for this discrepancy, the term EABV is used to describe the blood volume detected by the sensitive arterial baroreceptors. The EABV can change independently of the total ECF volume. The state of the EABV is often inferred from the behavior of the kidneys.

EXTRACELLULAR FLUID VOLUME CONTRACTION

Contraction of ECF volume typically results from sodium losses that exceed intake. Losses may be in the kidney or extrarenal through the gastrointestinal (GI) tract, skin, and lungs or by sequestration in potential spaces in the body (e.g., abdomen, muscle) that are not in hemodynamic equilibrium with the ECF (Table 8.2). The reduction in ECF volume occurs from both the interstitial and intravascular compartments. The loss of solute-free water (e.g., diabetes insipidus [DI]) has a lesser effect on intravascular volume because water is lost from

Major Causes of Extracellular Fluid Volume Depletion

TABLE 8.2

Kidney

Extrarenal

- Diuretic use
- Tubular disorders
  - Genetic
    - Bartter and Gitelman syndromes
    - Pseudohypoaldosteronism type 1
  - Acquired tubular disorders
    - Acute kidney injury
    - Recovery phase of oliguric kidney injury
    - Release of urinary tract obstruction
- Hormonal and metabolic disturbances
  - Mineralocorticoid deficiency or resistance
    - Primary adrenal insufficiency
    - Hyporeninemic hypoaldosteronism
    - Diabetes mellitus
    - Chronic interstitial kidney diseases
  - Solute diuresis
- Kidney water loss
  - Diabetes insipidus

- Gastrointestinal losses
  - Vomiting
  - Gastrointestinal suctioning
- Diarrhea
  - Ileostomy and colostomy secretions
- Dermal losses
  - Sweat
  - Exudative skin disease
- Third-space sequestration
  - Ascites
  - Pleural effusion, hydrothorax
  - Intestinal obstruction
- Retroperitoneal collection
- Hemorrhage
  - Internal
  - External

all aqueous spaces in the body, and the body’s solute content remains unchanged. Thus, in this case of disordered water balance, hypertonicity—rather than ECF volume contraction—predominates.

Extrarenal Causes

Gastrointestinal Losses

Approximately 3 to 6 L of fluids and digestive juices are secreted daily throughout the GI tract, and most of this fluid is reabsorbed along more distal portions. Vomiting or nasogastric suction may cause volume loss that is usually accompanied by metabolic alkalosis, whereas diarrhea may result in volume depletion that is accompanied by metabolic acidosis. This results from abnormal loss of bicarbonate or salts of organic anions in the stool. An exception to this general principle is the rare syndrome known as congenital chloride-wasting diarrhea, in which, because of mutations in a protein that exchanges chloride for bicarbonate in the colon,20 infants typically present with diarrhea and metabolic alkalosis.

Dermal Losses

Sweat is typically hypotonic, leading to more water loss than salt loss. Sweat production can be excessive in high ambient temperature or with prolonged exercise in hot, humid climates and may lead to volume depletion. Loss of the skin barrier with superficial burns and exudative skin lesions may lead to significant ECF volume depletion.

Third-Space Sequestration

Body fluid accumulation in potential spaces that are not in hemodynamic equilibrium with the ECF compartment can cause volume depletion. This pathologic accumulation, often called third-space sequestration, includes ascites, hydrothorax, and intestinal obstruction, with fluid collecting in the peritoneal cavity, pleural space, and intestines, respectively, and leading to significant ECF volume loss. Severe pancreatitis may result in retroperitoneal fluid collections.

Hemorrhage

Hemorrhage occurring internally (e.g., from bleeding esophageal varices) or externally (e.g., trauma) may lead to significant volume loss.

Kidney Losses

In health, approximately 25,000 mmol of sodium is filtered every day. The small quantities of sodium excreted in urine relative to the filtered load depend on intact tubular reabsorptive mechanisms to adjust urinary sodium excretion to maintain ECF homeostasis. Impairment in the integrity of these mechanisms can result in significant volume depletion.

Diuretic Use

Most of the widely used diuretic medications inhibit sodium transport pathways along the nephron (see later discussion). Diuretics may cause sodium wasting by the kidney with volume contraction and metabolic acid-base disturbances.

Genetic and Acquired Tubular Disorders

Tubular sodium reabsorption may be disrupted in several genetic disorders that include Bartter syndrome and Gitelman syndrome; these are often called “tubulopathies.” They are caused by mutations of sodium, potassium, or chloride transporters or in regulatory factors. Although they result in sodium wasting and volume contraction, they typically present with hypokalemic metabolic alkalosis. They are discussed in more detail in Chapter 49. Pseudohypoaldosteronism type 1 (PHA1) is another rare inherited disorder characterized by sodium wasting and hyperkalemic metabolic acidosis and is caused by mutations in either the epithelial sodium channel (ENaC) or the mineralocorticoid receptor. Acquired tubular disorders that may be accompanied by salt wasting include AKI, during the recovery phase of oliguric AKI, or urinary obstruction (see Chapters 61 and 74). Sjögren syndrome may cause a phenotype resembling Gitelman syndrome, as may treatment with cisplatin.

Hormonal and Metabolic Disturbances

Mineralocorticoid deficiency and resistance states often lead to sodium wasting. This may occur in the setting of primary adrenal insufficiency

(Addison disease) and PHA1. Salt wasting also can be seen in chronic tubular and interstitial kidney diseases. Severe hyperglycemia or high levels of blood urea during release of urinary tract obstruction can lead to obligatory kidney sodium and water loss secondary to glycosuria or urea diuresis, respectively.

Water Loss via the Kidney

DI represents a spectrum of diseases resulting from AVP deficiency (central DI) or tubular resistance to AVP (nephrogenic DI). The most common causes of polyuria from nephrogenic DI in adults are chronic lithium ingestion, hypercalcemia, and, less frequently, hypokalemia (see Chapter 9). In these disorders the tubular reabsorption of solutefree water is impaired. This generally results in a lesser effect on ECF volume because, in contrast to sodium, there is a relatively smaller amount of the TBW in the ECF compartment compared with the ICF compartment.

Clinical Evaluation of Extracellular Fluid Volume Depletion

BOX 8.1

Mild to Moderate Volume Loss
- Thirst
- Delay in capillary refill
- Postural dizziness, weakness
- Dry mucous membranes and axillae
- Cool, clammy extremities and collapsed peripheral veins
- Tachypnea
- Tachycardia with pulse rate >100 beats/min or postural pulse increment of 30 beats/min or more
- Postural hypotension (systolic blood pressure decrease >20 mm Hg on standing)
- Low jugular venous pulse
- Oliguria

Severe Volume Loss and Hypovolemic Shock
- Depressed mental status (or loss of consciousness)
- Peripheral cyanosis
- Reduced skin turgor (in young patients)
- Marked tachycardia, low pulse volume
- Supine hypotension (systolic blood pressure <100 mm Hg)

Clinical Manifestations of Extracellular Fluid Volume Contraction

The spectrum of the clinical manifestations of volume contraction (Box 8.1) depends on the amount and rate of ECF volume loss and on the vascular and kidney responses to that loss. The history and physical examination are usually the key factors in evaluating the presence and causes of hypovolemia because laboratory testing may appear normal. Symptoms are usually nonspecific and can range from mild postural symptoms, thirst, muscle cramps, and weakness to drowsiness and disturbed mentation with profound volume loss. Physical examination may reveal tachycardia, cold clammy skin, postural or recumbent hypotension, and reduced urine output, depending on the degree of volume loss. Low jugular venous pressure (JVP; ≤5) is consistent with volume depletion. However, the JVP may be elevated in patients with pulmonary hypertension or when the EABV is low. The lack of symptoms or discernible physical findings does not preclude volume depletion, and hemodynamic monitoring and administration of a fluid challenge may be necessary.

Laboratory Tests

Hemoconcentration and increased serum albumin concentration may be seen early with hypovolemia, but anemia or hypoalbuminemia caused by a concomitant disease may confound interpretation of these laboratory values. In healthy individuals, the ratio of blood urea nitrogen (BUN) to serum creatinine is approximately 10:1 to 20:1 (measured in milligrams per deciliter). In volume-contracted states, this ratio may increase because of an associated differential increase in urea reabsorption in the collecting duct. Several clinical conditions affect this ratio. Upper GI tract hemorrhage and administration of corticosteroids increase urea production, and hence the ratio of BUN to creatinine increases. Malnutrition and liver disease diminish urea production, making the ratio less helpful.

Urine osmolality and specific gravity may be elevated in hypovolemic states but may be altered by an underlying kidney disease that leads to kidney sodium wasting, concomitant intake of diuretics, or a solute diuresis. Hypovolemia normally promotes avid kidney sodium reabsorption, resulting in low urine sodium concentration and low fractional excretion of sodium. Urine chloride follows a similar pattern because sodium and chloride are generally reabsorbed together.

Volume depletion with metabolic alkalosis (e.g., with vomiting) is an exception because of the need to excrete the excess bicarbonate in conjunction with sodium to maintain electroneutrality; in this case, urine chloride concentration is a better index of ECF volume contraction.

The fractional excretion of sodium (FENa) is calculated by the following formula:

$$FENa = [U_{Na} \times P_{creat} / U_{creat} \times P_{Na}] \times 100$$

where UNa and Ucreat are urinary sodium and creatinine concentrations, respectively, and PNa and Pcreat are plasma sodium and creatinine concentrations, respectively. In an oliguric patient with AKI, FENa less than 1% is consistent with volume depletion; FENa greater than 1% is more consistent with acute tubular necrosis, although the sensitivity and specificity of this test are limited.[21]

Therapy of Extracellular Fluid Volume Contraction

The goal of treatment is to replace the fluid deficit and ongoing losses with a fluid that resembles the lost fluid. The first step is to determine the urgency of the hypovolemic condition. In severe hypovolemia or hypovolemic shock, immediate treatment should be initiated, typically with 1 to 2 L of isotonic crystalloid. The adequacy of repletion can then be monitored clinically with central venous pressure monitoring or, in the intensive care unit (ICU), with respiratory variation in the arterial pressure tracing. Estimating the magnitude of volume deficit is imprecise; thus a key component of successful treatment is frequent monitoring and adjustment of therapy.

Mild volume contraction usually can be corrected orally. It is important to note, however, that unlike oral rehydration solutions used for childhood diarrhea (50–90 mmol/L sodium), sports drinks typically contain very little NaCl (7–20 mmol/L) and do not replace substantial sodium losses, although normal kidneys can typically adjust for the discrepancy when losses are mild.

Crystalloid solutions (isotonic or slightly hypotonic) with sodium as the principal cation are effective because they distribute primarily in the ECF. One-third of an infusate of isotonic saline (0.9% NaCl) remains in the intravascular compartment, whereas two-thirds distributes into the interstitial compartment. Colloid-containing solutions include human albumin (5% and 25%) and hetastarch (6% hydroxyethyl starch [HES]), which remain within the vascular compartment (provided the transcapillary barrier is intact and not disrupted by capillary leak states such as often occurs with multiorgan failure). The solutions augment the plasma oncotic pressure and thus expand the plasma volume by counteracting the capillary hydraulic pressure.

Colloid-containing solutions have not shown an advantage in the treatment of hypovolemic states. A large multicenter trial that randomized medical and surgical critical patients to receive fluid resuscitation with 4% albumin or normal saline showed similar mortality, morbidity, and hospitalization rates in the two groups.[22] Another study randomly assigned ICU patients with severe sepsis to fluid resuscitation with either 6% HES or Ringer acetate solution.[23] Patients who received HES had increased mortality and were more likely to receive kidney replacement therapy. Consequently, artificial colloids should be avoided in patients with severe sepsis or at risk for developing AKI.[24]

Isotonic saline or a balanced salt solution (e.g., lactated Ringer’s solution) is usually the preferred initial choice in volume-depleted patients with normal serum [Na+] and most of those with low serum [Na+]. Furthermore, isotonic saline is the preferred fluid to restore ECF volume in hypovolemic patients with hypernatremia. Once euvolemia is established, hypotonic (0.45% NaCl) saline should be delivered to gradually correct tonicity. Administration of large volumes of isotonic saline may result in the development of hyperchloremic metabolic acidosis or AKI. Although a smaller randomized trial of patients admitted to the ICU did not detect a difference in AKI,25 a recent large pragmatic trial of critically ill patients found that the use of balanced salt solutions was associated with an improved composite outcome of death, new kidney replacement therapy, or persistent kidney dysfunction compared with subjects receiving isotonic saline.26

Hypovolemic shock may be accompanied by lactic acidosis resulting from tissue hypoperfusion. Fluid resuscitation restores tissue oxygenation and will decrease the production of lactate, but lactated Ringer solution is inappropriate because the infused lactate will not be converted to bicarbonate. Correction of acidosis with sodium bicarbonate ($NaHCO_3$) has the potential for increasing tonicity, expanding volume, worsening intracellular acidosis from increased carbon dioxide production, and not improving hemodynamics compared with isotonic saline. Whether $NaHCO_3$ effectively corrects the impaired cardiac contractility associated with lactic acidosis has not been well documented by clinical studies. Therefore, $NaHCO_3$ to manage lactic acidosis in the setting of volume depletion is often avoided unless the arterial pH is less than 7.1.

EXTRACELLULAR FLUID VOLUME EXPANSION

Expansion of ECF volume usually results from kidney sodium and water retention. Generalized edema results from an apparent increase in the interstitial fluid volume, most often in response to HF, cirrhosis with ascites, and nephrotic syndrome. Weight gain of several kilograms usually precedes clinically apparent edema. Localized excess fluid may accumulate in the peritoneal and pleural cavities, leading to ascites and pleural effusion, respectively.

Pathogenesis

Kidney sodium and water retention secondary to arterial underfilling leads to an alteration in capillary hemodynamics that favors fluid movement from the intravascular compartment into the interstitium. In general, these two processes account for edema formation.

Capillary Hemodynamic Disturbances

According to the Starling equation, the exchange of fluid between the plasma and the interstitium is determined by the hydrostatic and oncotic pressures in each compartment. Interstitial fluid excess results from a decrease in plasma oncotic pressure or an increase in capillary hydrostatic pressure. In other words, edema is a result of an increase in fluid movement from the intravascular compartment to the interstitial space or a decrease in fluid movement from the interstitial space to the intravascular compartment, or both. Thus, the degree of interstitial fluid accumulation as determined by rate of fluid removal by the lymphatic vessels is a determinant of edema.

The capillary hydrostatic pressure is relatively insensitive to alterations in arterial pressure. The stability of the capillary pressure is a result of variations in the precapillary sphincter, which governs how much arterial pressure is transmitted to the capillary, a locally controlled response called autoregulation. In contrast, the venous end is not similarly well regulated. Therefore, when the blood volume expands, as in HF and kidney disease, capillary hydrostatic pressure increases and edema ensues. Venous obstruction works by the same

Major Causes of Extracellular Fluid Volume Expansion

TABLE 8.3

Primary Kidney Sodium Retention

Secondary Kidney Sodium Retention[a]

Acute kidney injury
Advanced chronic kidney disease
Glomerular diseases

Cardiac failure
Cirrhosis
Nephrotic syndrome
Idiopathic edema
Drug-induced edema
Pregnancy

[a] Secondary to reduced effective arterial blood volume depletion (arterial underfilling).

mechanism to cause edema, as exemplified by ascites formation in liver cirrhosis and by acute pulmonary edema after sudden impairment in cardiac function (e.g., myocardial infarction). In hepatic cirrhosis and nephrotic syndrome, another factor in edema formation is reduction in plasma oncotic pressure, with fluid transudation into the interstitial space. Even normal conditions favor net filtration into the interstitium because capillary hydrostatic pressure exceeds the plasma colloid pressure in several tissues throughout the capillary. In these tissues, a substantial amount of filtered fluid is returned to the circulation through lymphatic channels, which minimizes edema formation.

Kidney Sodium Retention

The mechanism for maintenance of ECF volume expansion and edema formation is kidney sodium retention, which can be primary or secondary in response to reduction in EABV (Table 8.3).

Primary sodium retention by the kidney. A primary defect in kidney sodium excretion can occur with AKI, CKD, or glomerular disease. Patients with AKI have limited ability to excrete sodium and water. Advanced CKD may lead to sodium and water retention by GFR reduction, although in the absence of proteinuria, frank edema is uncommon. Primary sodium retention by the kidney characterizes some forms of glomerulonephritis and occurs through incompletely understood mechanisms in the presence of a relatively suppressed RAAS but frequently with decreased GFR. Filtered proteases may cleave and activate the sodium channel, ENaC, in these situations.[27]

Mineralocorticoid excess or enhanced mineralocorticoid activity are associated with sodium retention. However, because of mineralocorticoid escape (discussed previously), the clinical manifestation is generally hypertension rather than hypervolemia. In normal individuals, administration of a high-dose mineralocorticoid initially increases kidney sodium retention so that ECF volume is increased. However, kidney sodium retention then ceases, spontaneous natriuresis ensues, sodium balance is reestablished, and there is no detectable edema. This escape from mineralocorticoid-mediated sodium retention explains why edema is not a characteristic feature of primary hyperaldosteronism. The pathophysiologic mechanism of mineralocorticoid escape involves an increase in GFR and reduction of proximal tubular sodium and water reabsorption. This leads to an increase in sodium and water delivery to the distal nephron site of aldosterone action, which overrides the sodium reabsorption of aldosterone. Other contributing mechanisms include decreased expression of distal tubular thiazide-sensitive NaCl cotransporters,28 increased secretion of ANP,29 and pressure natriuresis. Regardless of the mechanisms involved, RPP must rise to enable the escape process12; because this can occur during primary kidney salt retention, these states are typically characterized by hypertension and not edema.

Mechanisms of Sodium Retention in Heart Failure

HFPEF or HFREF

ECF volume expansion

Effective arterial volume low
(BP below set point)

AVP
(vasopressin)

Water retention

RAAS

SNS

Salt retention

High renal perfusion
pressure and
natriuretic peptides

Escape (diuresis)

Fig. 8.3 Mechanisms of Sodium Retention in Heart Failure. Heart failure, from reduced ejection fraction (HFREF) or preserved ejection fraction (HFPEF), activates neurohormonal systems, which lead to sodium and water retention, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and arginine vasopressin (AVP). Ensuing ECF volume expansion increases natriuretic peptide secretion. Low kidney perfusion pressure (blood pressure below set point) causes resistance to natriuretic peptides and prevents escape from sodium and water retention from aldosterone, angiotensin II, and AVP.

Secondary sodium retention by the kidneys. An estimated 85% of blood circulates on the low-pressure venous side of the circulation, and 15% in the high-pressure arterial circulation. Thus, an increase in total blood volume could occur, even when there is underfilling of the arterial circulation, if the increase in total blood volume is primarily caused by expansion of the venous compartment. Underfilling of the arterial circulation could result from a decrease in cardiac output, as occurs in low-output cardiac failure, or from systemic arterial vasodilation, which occurs early in cirrhosis as a result of decreased systemic vascular resistance (SVR) in the splanchnic circulation.[30] Because arterial pressure is determined by the product of cardiac output and SVR, both states would be characterized by a decline in arterial pressure below the kidney’s set point. This model proposes that kidney sodium retention triggered by arterial underfilling (arterial pressure less than pressure set point) is a compensatory response necessary to restore arterial circulatory integrity.

If there is arterial underfilling from decreased cardiac output or systemic arterial vasodilation, the hypotension is sensed by the arterial stretch receptors. This leads to activation of the efferent limb of body fluid volume homeostasis. Specifically, a decrease in glossopharyngeal and vagal tone from the carotid and aortic receptors to the CNS leads to a rapid increase in sympathetic activity with associated activation of the RAAS axis. If it is severe enough, the underfilling also leads to nonosmotic release of vasopressin. Additionally, a decrease in pressure at the kidney baroreceptors and decreased NaCl delivery to the macula densa increase renin secretion and thereby Ang II and aldosterone.

The resultant increase in SVR and kidney sodium and water retention attenuates the arterial underfilling, through the Frank-Starling mechanism, and tends to restore arterial perfusion. Together, these actions maintain the arterial circulatory integrity and restore perfusion to vital organs at the expense of expanded ECF volume and edema.

Sodium and Water Retention in Heart Failure

HF can occur with reduced or preserved ejection fraction (HFREF and HFPEF, respectively), but the mechanisms involved in kidney sodium and water retention appear to involve similar mediators.31 Decreased cardiac output with arterial underfilling leads to reduced stretch of arterial baroreceptors and reduced perfusion pressure in the kidney. In the case of HFPEF, this often involves a decrease below a hypertensive baseline or below a baseline raised by CKD. This results in increased sympathetic discharge from the CNS and activation of the RAAS. Adrenergic stimulation and increased Ang II activate receptors on the proximal tubular epithelium that enhance sodium reabsorption. The kidney vasoconstriction of the glomerular efferent arteriole by Ang II in HF also alters net Starling forces in the peritubular capillary in a direction to enhance sodium reabsorption.32 Thus, Ang II and α adrenergic stimulation increase sodium reabsorption in the proximal tubule by a direct effect on the proximal tubule epithelium and secondarily by kidney vasoconstriction. This subsequently leads to decreased sodium delivery to the collecting duct, which impairs escape from both aldosterone and natriuretic peptides.11 33 This failure of escape explains why sodium retention and ECF volume expansion occur in HF (Fig. 8.3). Accordingly, patients with HF may have substantial natriuresis when spironolactone, a competitive mineralocorticoid receptor antagonist (MRA), is given in adequate doses to compete with increased endogenous aldosterone levels.34

The atrial-renal reflexes, which normally enhance kidney sodium excretion, are also impaired because plasma levels of ANP do not increase further when patients with dilated cardiomyopathy and mild HF receive a saline load, and the natriuretic response is also blunted. Autonomic dysfunction and blunted arterial baroreceptor sensitivity in HF are associated with increased circulating catecholamines and increased kidney sympathetic activity. There is also evidence for parasympathetic withdrawal in HF, in addition to the increase in sympathetic drive.

Another outcome of the neurohumoral activation that occurs in HF is the baroreceptor-mediated nonosmotic release of AVP.35 This nonosmotic AVP stimulation overrides the osmotic regulation of AVP and is the major factor leading to the hyponatremia associated with end-stage HF.36 AVP causes antidiuresis by activating V2 receptors on the basolateral surface of the principal cells in the collecting duct.37 Activation of these receptors initiates a cascade of intracellular signaling events by means of the adenylyl cyclase–cyclic adenosine monophosphate (cAMP) pathway, leading to an increase in AQP2 water channel protein expression and its trafficking to the apical membrane of the collecting duct. This sequence of events leads to increased water reabsorption and can cause hyponatremia, which is an ominous prognostic indicator in patients with HF.38 Concurrently, increased nonosmotic AVP release stimulates V1 receptors on vascular smooth muscle

Hemodynamics Associated With Cirrhosis
Sinusoidal and portal hypertension

Splanchnic arterial vasodilation

Decreased effective arterial blood volume

High-pressure baroreceptor-mediated activation of
renin-angiotensin-aldosterone and sympathetic
nervous systems and arginine vasopressin

Sodium and water retention
Adequate to normalize
circulatory homeostasis

Increase in plasma volume

Normalization of the activity
of sodium and water
retaining systems

Inadequate to normalize
circulatory homeostasis

Persistent activation of sodium
and water retaining systems

Normal sodium and
water excretion

Continuous sodium and
water retention

Renal vasoconstriction

No ascites

Ascites formation

Hepatorenal syndrome

Fig. 8.4 Pathogenesis of Functional Kidney Abnormalities and Ascites Formation in Cirrhosis. (Modified from Ginés P, Cardenas A, Sola E, Schrier RW. Liver disease and the kidney. In: Coffman TM, Falk RJ, Molitoris BA, et al, eds. Schrier's Diseases of the Kidney. Wolters Kluwer; 2012:1965–1996.)

cells and thereby may increase SVR. This adaptive vasoconstrictive response may become maladaptive and contribute to cardiac dysfunction in patients with severe HF.

Sodium and Water Retention in Cirrhosis

Many pathogenetic aspects of sodium and water retention are similar in cirrhosis and HF (Fig. 8.4). However, arterial underfilling in cirrhosis occurs secondary to splanchnic arterial vasodilation, with resultant water and sodium retention. Ascites formation in cirrhosis is likely initiated by sinusoidal and portal hypertension[39] from distortion of hepatic architecture, increased hepatic vascular tone, or increased splenohepatic flow. Decreased intrahepatic bioavailability of NO and increased production of vasoconstrictors (Ang II, endothelin) also are responsible for increased resistance in the hepatic vasculature.40 Portal hypertension caused by increased sinusoidal pressure activates vasodilatory mechanisms in the splanchnic circulation.41 These mechanisms, mediated at least partly by NO and carbon monoxide (CO) overproduction, lead to splanchnic and peripheral arteriolar vasodilation. In advanced stages of cirrhosis, arteriolar vasodilation causes underfilling of the systemic arterial vascular space. This event, through a decrease in EABV, leads to a fall in arterial pressure. Consequently, baroreceptor-mediated activation of the RAAS, SNS stimulation, and nonosmotic release of ADH occur to restore the blood volume homeostasis.42 This involves compensatory vasoconstriction as well as kidney sodium and water retention. However, splanchnic vasodilation also increases splanchnic lymph production, which exceeds the lymph-transporting capacity, and thus lymph leakage into the peritoneal cavity occurs with ascites development.43 Persistent kidney sodium and water retention (along with lymph leakage into the peritoneal cavity from increased splanchnic vascular permeability) play the major role in sustained ascites formation.

Sodium and Water Retention in Nephrotic Syndrome

Unlike HF and liver cirrhosis, in which the kidneys are structurally normal, the nephrotic syndrome is characterized by diseased kidneys. Many nephrotic patients have a higher arterial blood pressure, higher GFR, and less impairment of sodium and water excretion than patients with HF and cirrhosis. Two mechanisms, underfill and overfill, may account for nephrotic edema; components of each mechanism may exist in different edematous conditions (Fig. 8.5). The underfill theory suggests that reduced plasma oncotic pressure from proteinuria increases fluid movement from the vascular to interstitial compartment. The resultant arterial underfilling culminates in activation of homeostatic mechanisms involving the SNS and the RAAS. The overfill theory implicates primary kidney sodium and water retention that translates into elevated total plasma volume, hypertension, and suppressed RAAS. Distinguishing between the two mechanisms is important because it influences the approach to diuretic use in nephrotic patients.

The following observations support the underfill theory for edema formation. Plasma volume, systemic arterial blood pressure, and cardiac output are diminished in some nephrotic patients, especially in

Pathogenesis of Edema in Nephrotic Syndrome
Nephrotic syndrome

Underfill theory

Overfill theory

Proteinuria

- Decreased GFR
- Interstitial inflammation
- Increased abundance and/or targeting of sodium channels in the connecting tubules

Reduced serum albumin

Reduced serum oncotic pressure

Reduced effective arterial blood volume

Primary renal sodium retention

Activation of renin-angiotensin-aldosterone and sympathetic nervous systems

Expanded extracellular fluid volume

Renal sodium and water retention

Edema

Fig. 8.5 Underfill and Overfill Mechanisms in Pathogenesis of Edema in Nephrotic Syndrome. The ratio of underfill and overflow likely varies depending on the cause of the nephrotic syndrome. GFR, Glomerular filtration rate.

children with minimal change disease (MCD; see Chapter 18). The Starling forces governing the fluid movement across the capillary wall equal the difference of the hydrostatic pressure and the oncotic pressure gradients. The gradual decrease in the plasma albumin concentration and the plasma oncotic pressure is mitigated by the reduced entry of albumin into the interstitial space and a concurrent decline in interstitial oncotic pressure. Consequently, less ECF volume expansion and edema formation is noted unless hypoalbuminemia is severe.44 Thus, nephrotic patients who are underfilled and are predisposed to AKI despite generalized edema generally have serum albumin concentration of less than 2 g/dL (20 g/L). However, serum albumin concentration may not be the primary driver of ECF volume expansion because either spontaneous or steroid-induced remission of minimal change leads to natriuresis before albumin rises45; this suggests that other mechanisms, in addition to low oncotic pressure, must be involved. Observations supporting the overfill theory include studies of adults with MCD who have increased blood volume and blood pressure. After remission induced by corticosteroids, plasma volume and blood pressure decline, with an increase in plasma renin activity. However, evaluation of intravascular volume is somewhat unreliable because the afferent stimulus for edema formation appears to be a dynamic process, with different results at different phases of edema formation.44 Also supporting primary kidney sodium retention, experimental studies in animals with unilateral nephrotic syndrome demonstrate that sodium retention occurs secondary to increased reabsorption in the collecting tubules.46 Increased abundance and apical targeting of ENaC subunits may be mediated, in part, by proteolytic cleavage of the channel by filtered proteases.47–49 In summary, nephrotic patients with arterial underfilling are more likely to have MCD with severe hypoalbuminemia, preserved GFR, and low blood pressure or postural hypotension. Other glomerular diseases, especially those involving kidney inflammation, are more often associated with an overfill picture with volume expansion, raised blood pressure, and a decline in GFR. It has been postulated that interstitial inflammatory cells, a feature of some glomerular diseases other than MCD, may facilitate an increase in sodium retention and hypertension by releasing mediators that cause vasoconstriction.50

Drug-Induced Edema

Although they are no longer commonly used, systemic vasodilators such as minoxidil and diazoxide induce arterial underfilling and subsequent retention of sodium with water (causing edema) through mechanisms similar to those in HF or cirrhosis. Dihydropyridine calcium channel blockers may cause peripheral edema, which is related to redistribution of fluid from the vascular space into the interstitium, possibly induced by preferential dilation of resistance arterioles in the absence of an appropriate microcirculatory myogenic reflex. This facilitates transmission of the systemic pressure to the capillary circulation.51 Fluid retention and HF exacerbation may be seen with thiazolidinedione therapy in patients with type 2 diabetes mellitus, involving activation of peroxisome proliferator–activated receptor γ (PPARγ). Although this can simulate sodium reabsorption by the sodium channels in collecting tubule cells,52 additional effects are likely involved, including effects on vascular smooth muscle to reduce arterial pressure.53 NSAIDs can exacerbate volume expansion in HF and cirrhotic patients by decreasing vasodilatory prostaglandins in the afferent arteriole of the glomerulus.54

Idiopathic Edema

This poorly defined syndrome occurs most often in premenopausal women and is characterized by intermittent edema secondary to sodium and water retention. Patients often complain of face and hand edema, leg swelling, and variable weight gain55 and often misuse diuretics or laxatives, which may chronically stimulate the RAAS. The diagnosis of idiopathic edema is usually made by exclusion of other causes after history, physical examination, and sometimes diuretic screening.

Sodium and Water Retention in Pregnancy

In the first trimester of normal pregnancy, systemic arterial vasodilation and a decrease in blood pressure occur in association with a compensatory increase in cardiac output.56 The lower arterial pressure activates the RAAS, contributing to the kidney sodium and water retention and expanding the plasma volume (10%–30%).57 Decreased plasma osmolality, stimulated thirst, and persistent nonosmotic vasopressin release are other features of normal pregnancy. In contrast to diseases such as HF and cirrhosis, pregnancy is associated with an increase in GFR and kidney blood flow. The increased GFR leads to higher filtered load and increased distal sodium delivery in pregnancy, which contributes to the better escape from the sodium-retaining effect of aldosterone and attenuates edema formation. See Chapter 44 for more details.

Clinical Manifestations of Extracellular Fluid Volume Expansion

A history of an underlying disease, such as coronary artery disease, hypertension, or liver cirrhosis, can pinpoint the underlying mechanism of edema formation. Patients with left HF may present with exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients with right-sided HF or biventricular failure may exhibit weight gain and lower limb swelling. Physical examination reveals increased JVP, pulmonary crackles, a third heart sound, or dependent peripheral edema that may be elicited in the ankles or sacrum.

Nephrotic patients may present with periorbital edema, especially when caused by minimal change disease. However, those with severe disease may exhibit marked generalized edema with anasarca. Patients with cirrhosis present with ascites and lower limb edema caused by portal hypertension and hypoalbuminemia. Physical examination may reveal stigmata of chronic liver disease and splenomegaly.

Diagnostic and Therapeutic Approach to Extracellular Volume Expansion

Management of ECF volume expansion consists of recognizing and treating the underlying cause and attempting to achieve negative sodium balance by dietary sodium restriction and administration of diuretics. Before embarking on diuretic therapy, it is imperative to appreciate that ECF volume expansion may have occurred to compensate for arterial underfilling, as in HF and cirrhosis. A judicious approach is therefore necessary to avoid a precipitous fall in cardiac output and tissue perfusion. Nevertheless, it has become clear that diuresis of 3 to 5 L/day is typically tolerated safely in patients with acute decompensated HF, and that a modest rise in serum creatinine concentration should be accepted, as long as decongestion is taking place.58

Moderate dietary sodium restriction (2–3 g Na+/day; 86–130 mmol/day) should be encouraged. Salt substitutes contain potassium chloride and should not be used in patients with advanced kidney impairment or those taking potassium-sparing diuretics. Restriction of total fluid intake is usually necessary only for patients with hyponatremia. Medications that promote sodium retention (e.g., NSAIDs) should be discontinued. Diuretics are the cornerstone of therapy to remove excess volume. Other measures can be used in patients with inadequate response or lack of response to diuretics. In those with liver cirrhosis, large-volume paracentesis with albumin infusion provides symptomatic relief and is commonly included as part of the treatment regimen. Although extracorporeal fluid removal by ultrafiltration can be used in patients with acute decompensated HF accompanied by kidney impairment or diuretic resistance, a randomized controlled trial did not indicate benefit.59

Although salt and fluid removal is a central feature of the treatment of HF, there are a number of other approaches that have been shown to ameliorate symptoms and prolong life. ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists have been shown to be useful in those with HFREF.

Recently, SGLT2 inhibitors, which have a modest diuretic effect, have also been shown to improve mortality in patients with HF.

Diuretics

Principles of Action

Diuretics are the mainstays of therapy for edematous states, with five classes based on the predominant sites of diuretic action along the nephron (Fig. 8.6). Most diuretics work from the tubule lumen and reach this site by secretion across the proximal tubule epithelium. All diuretics except osmotic agents have a high degree of protein binding, which limits glomerular filtration and traps them in vascular spaces, allowing them to be delivered to the proximal convoluted tubule for secretion.[60] Most diuretics either act by inhibiting sodium reabsorption with an accompanying anion, usually chloride (loop diuretics or thiazides), or inhibit sodium reabsorption through channels in the luminal membrane (amiloride directly or aldosterone antagonists, indirectly). The resultant natriuresis decreases the ECF volume.

Loop diuretics, which are used commonly to treat edematous conditions, have relatively short half-lives, and each dose is followed by a phase of natriuresis and a phase of antinatriuresis (often referred to as postdiuretic Na^+ retention). A low-salt diet can ensure that postdiuretic Na^+ retention does not overcome effective diuresis. A second type of adaptation occurs during chronic treatment. During continued administration of a diuretic, the magnitude of each natriuretic response declines, so daily salt excretion once again equals daily salt intake. This is known as the braking phenomenon; mechanisms include activation of the SNS and RAAS, decreased systemic and kidney arterial blood pressure, hypertrophy of the distal nephron cells with increased expression of epithelial transporters, and perhaps alterations in natriuretic hormones (e.g., ANP).[60]

Classes of Diuretics

Loop diuretics. Loop diuretics such as furosemide, bumetanide, and torsemide act by blocking the Na^+-K^+-Cl^- cotransporters at the luminal surface of thick ascending limb (TAL) cells, thereby diminishing net reabsorption.[61] These agents are the most potent of all diuretics, inhibiting the reabsorption of 25% of filtered sodium, which normally occurs along the TAL. Moreover, the nephron segments past the TAL typically do not possess the capacity to reabsorb completely the volume of fluid exiting the TAL. Thus, a substantial percentage of the solute rejected from the TAL is excreted.

The oral bioavailability of furosemide averages 50%, but varies between 10% and 100%; the oral bioavailabilities of bumetanide and torsemide are higher (~80%). Loop diuretics have short elimination half-lives, so the dosing interval needs to be short to maintain adequate levels in the lumen. Excessive prolongation of dosing interval provides more time for postdiuretic sodium retention to overcome natriuresis. This is the reason that loop diuretics are typically given twice daily. When escalating diuretics in congested hospitalized patients, several algorithms recommend repeating furosemide doses as frequently as every 6 hours, given the short intravenous (IV) half-life of furosemide and bumetanide.[62] For oral use, torsemide has a longer half-life than bumetanide or furosemide, permitting it to be used once daily in some cases.

The intrinsic potency of a diuretic is defined by its dose-response curve, which is generally sigmoidal. The steep dose-response is the reason that loop diuretics are often referred to as threshold drugs. This is exemplified by furosemide, which can initiate diuresis in a person with normal kidney function with an IV dose of 10 mg, and a maximal effect

Sites of Salt and Water Transport and Actions of Diuretics

Proximal
convoluted
tubule

NaCl
NaHCO3

NaCl Mg2+

Ca2+
(+PTH)

Distal convoluted
tubule

4

1
Proximal
straight
tubule

K+
Glomerulus
2
H2O

Cortex

4

K+
Ca2+
Mg2+
Na+
K+
Cl–

H+

3

Outer medulla

Thin
descending
limb

Diuretics
1 Acetazolamide and SGLT2 Inhibitors

H2O

2

2 Osmotic agents (mannitol)

NaCI
(+aldosterone)

5

Thick
ascending
limb

H+

H_2O
(+ADH)
Thin
ascending
limb

3 Loop agents (e.g., furosemide)

K+

2

Collecting
duct

4 Thiazides
5 Aldosterone antagonists and ENaC blockers
Inner medulla

Loop of
Henle

Fig. 8.6 Sites of Salt and Water Transport and Actions of Diuretics. Specific sites are indicated by numbers. (Modified from Ives HE. Diuretic agents. In: Katzung BG, ed. Basic and Clinical Pharmacology. McGrawHill Medical; 2006:237.)

is seen with 40 mg. A larger dose provides minimal or no extra increase in natriuresis, and side effects may increase. In contrast, the effective diuretic dose is often substantially higher in patients with HF, advanced cirrhosis, and kidney failure; guidelines are available for diuretic dosing in these situations.62 Patients who respond poorly to intermittent doses of a loop diuretic may receive continuous IV infusion, which might enhance the response by virtue of maintaining an effective amount of drug at the site of action.63 A Cochrane review suggested that continuous infusions led to greater diuresis and a better safety profile, but the quality of the evidence is poor.64 A randomized trial in acute decompensated HF found no difference in the primary end points—the global assessment of symptoms over the course of 72 hours and the change in serum creatinine from baseline to 72 hours—for continuous versus bolus infusion of furosemide. A higher dose of diuretic was more effective without clinically important negative effects on kidney function.65 Despite this negative result, this study did not include diuretic-resistant patients or those with significant kidney dysfunction, and so continuous infusion is still employed in some cases.

Although pharmacologically similar to other loop diuretics, ethacrynic acid has greater ototoxic potential and therefore is reserved for patients allergic to other agents.

Distal convoluted tubule diuretics. Thiazide and thiazidelike diuretics (chlorothiazide, hydrochlorothiazide, chlorthalidone,

metolazone, and indapamide) inhibit NaCl absorption in the distal convoluted tubule, where up to 5% of filtered sodium and chloride is reabsorbed, and are therefore less potent than loop diuretics. Thiazides have a relatively longer half-life and can be administered once or twice daily. Metolazone has pharmacologic characteristics similar to classical thiazide diuretics and is more often used in conjunction with other classes of diuretics.

Thiazides are used commonly to treat hypertension (see Chapter 37). For edema, they are occasionally used alone in patients with mild HF, but more often they are used in combination to synergize the effect of loop diuretics by blocking multiple nephron segment sites. Because thiazide diuretics must reach the lumen to be effective, higher doses are required in patients with impaired kidney function. Thiazides as sole agents (possibly excluding the thiazide-like diuretics metolazone and indapamide) lose some effectiveness at GFR less than 30 mL/min but may still be useful in some patients.66 Regardless, thiazide diuretics still enhance the diuretic effect of loop diuretics when coadministered with loop diuretics to overcome diuretic resistance. If used, such combination therapy should be closely monitored because of a risk for hypokalemia and excessive ECF depletion.

Collecting duct diuretics. Amiloride, triamterene, and the mineralocorticoid receptor antagonists spironolactone and eplerenone act on the collecting duct. Amiloride and triamterene act primarily in the connecting tubule and cortical collecting duct (the aldosteronesensitive distal nephron) by interfering with sodium reabsorption through the apical sodium channel ENaC; this inhibits potassium secretion by dissipating the electronegative gradient (normally created by sodium reabsorption) that favors potassium secretion. Spironolactone and eplerenone are competitive antagonists of aldosterone and cause natriuresis and potassium retention. Finerenone is a new nonsteroidal mineralocorticoid receptor antagonist, which has properties that appear to differ from those of spironolactone and eplerenone; it appears to block the mineralocorticoid receptor as a bulky, passive agonist. It was recently approved by the US Food and Drug Administration (FDA) to slow progression of CKD in the setting of diabetes mellitus.[67] Potassium-sparing diuretics are considered weak diuretics because they block only about 3% of the filtered sodium load reaching their site of action and thus are most often used with other diuretics to augment diuresis or preserve potassium. If combination therapy is used, careful monitoring is essential to prevent dangerous hyperkalemia. Vulnerable patients include those with underlying kidney dysfunction, those with HF, patients with diabetes, and those concurrently taking ACE inhibitors, ARBs, NSAIDs, or β-blockers. Collecting duct diuretics are considered first-line agents in certain conditions. For example, spironolactone is used in patients with liver cirrhosis with ascites and amiloride in the treatment of Liddle syndrome, a rare autosomal dominant condition characterized by a primary increase in ENaC function (see Chapter 47).

Proximal tubule diuretics. A substantial component of sodium reabsorption along the proximal tubule is mediated by a luminal Na^+-H^+ exchanger. The activity of this transporter depends on both the generation of protons inside the cell and their elimination in the luminal brush border. Both actions are catalyzed by carbonic anhydrase. Acetazolamide inhibits carbonic anhydrase, thereby reducing proton secretion in the proximal tubule lumen, thus increasing sodium bicarbonate excretion. Acetazolamide is a weak diuretic because distal segments reabsorb much of the inhibited Na^+ and because proximal inhibition activates the TGF to reduce Na^+ filtration.[8] Acetazolamide generates hyperchloremic metabolic acidosis, particularly with prolonged use. It also may cause hypokalemia because of increased distal sodium delivery; it may cause hypophosphatemia, but the mechanism of this is not well understood. Rarely used as a single agent, acetazolamide is most frequently used with other diuretics, in treatment of metabolic alkalosis accompanied by edematous states, and in chronic obstructive pulmonary disease. It is also used in acute and chronic high-altitude sickness because of its ability to stimulate ventilation as a compensatory response to the metabolic acidosis, although unpleasant paresthesias may occur.

Osmotic diuretics. Osmotic diuretics such as mannitol are inert substances that are freely filtered at the glomerulus but are poorly reabsorbed. Mannitol is used intravenously and produces diuresis by increasing the osmotic pressure within the lumen of the proximal tubule and loop of Henle. This causes enhanced water diuresis and to a lesser extent sodium and potassium excretion. Mannitol is not used for edematous states but rather to treat cerebral edema induced by trauma or neoplasms and to reduce intraocular pressure. Mannitol is also used in the treatment of dialysis disequilibrium syndrome, preventing the brisk decline in serum osmolality that would otherwise occur with dialysis. This helps prevent a shift of fluid into the brain that may occur with rapid rate of solute removal by dialysis, which is thought to be responsible for the symptoms.

Aquaretics. The “vaptans” are drugs that block either V2 receptors alone or V1 and V2 receptors together and increase electrolyte-free water excretion. They are used in electrolyte disorders, such as the syndrome of inappropriate antidiuretic hormone secretion, but have also been approved to slow CKD progression in autosomal dominant polycystic kidney disease. Because they have little effect on urinary sodium excretion, they are not typically effective in addressing edema.

SGLT2 inhibitors. SGLT2 inhibitors, initially introduced as drugs to control hyperglycemia, have pleiotropic effects that improve kidney and cardiovascular outcomes, even in the absence of diabetes mellitus. Although not marketed as diuretics, these agents cause a mild diuresis, both by inhibiting sodium glucose cotransport along the proximal tubule and by inhibiting the Na+-H+ exchanger. Sodium glucose cotransport and sodium proton antiport appear to be coupled functionally along the proximal tubule. These drugs induce a mild but sustained reduction in ECF volume that may contribute to their beneficial effects.68

Adverse Effects

Many common diuretics are derived from sulfanilamide and may therefore induce allergy in susceptible patients, manifested as hypersensitivity reactions, usually as a rash or, rarely, acute interstitial nephritis. The most serious and common adverse effects of diuretics, however, are electrolyte disturbances.

Loop diuretics impair tubular reabsorption by inhibiting the Na/K/2Cl cotransporter along the luminal membrane of thick ascending limb cell. This transporter lies in parallel with a potassium channel that permits potassium to diffuse back into the lumen. Coupled with basolateral chloride exit, this drives an electrical potential difference oriented with the lumen positive with respect to blood. This drives magnesium and calcium reabsorption. Loop diuretics eliminate this potential difference and can, therefore, increase calcium and magnesium excretion. Thiazide diuretics exert the same effect on magnesium, although the mechanism is different. In a recent study of communitydwelling subjects, the use of a thiazide was associated with prevalent hypomagnesemia, whereas loop diuretic use was not.69 Unlike loop diuretics, thiazide diuretics decrease urinary calcium losses and are therefore preferred in the treatment of hypercalciuric states and in patients with osteoporosis. Thiazide diuretics interfere with urinediluting mechanisms by blocking sodium reabsorption at the distal convoluted tubule, an effect that may contribute to hyponatremia.70

Acutely, loop and thiazide diuretics increase the excretion of uric acid, whereas chronic administration results in reduced uric acid excretion. The chronic effect is likely caused by enhanced absorption in the proximal convoluted tubule secondary to volume depletion. Other adverse effects with large doses may include ototoxicity with loop diuretics, particularly with aminoglycoside coadministration, and gynecomastia, which may develop with spironolactone.

Approach to Diuretic Treatment of Extracellular Fluid Volume Expansion

Although the mechanisms underlying expansion of the ECF volume are similar in the different clinical syndromes, some evidence-based differences in diuretic approach are recommended. For HF, either HFREF or HFPEF, initial treatment involves loop diuretics. A starting dose of 20 to 40 mg furosemide, or an equivalent, is typical, and may be effective, but it may be necessary to increase, or double, subsequent doses if the initial dose does not elicit a diuresis. Such a diuresis should occur promptly after drug administration and be notable to the patient. This approach is based on the threshold nature of the loop diuretic dose response curve. It is often necessary to use loop diuretics twice daily, but it is always important to ensure that each dose is above the threshold. The pharmacokinetic profile of torsemide is more favorable than that of furosemide; some clinicians prefer this drug, but solid evidence to support this choice is lacking currently.

For cirrhotic ascites, patients are typically started on a combination of spironolactone and furosemide, at a fixed ratio (100 mg spironolactone to 40 mg furosemide).71 Single-agent spironolactone can be used but causes more potassium imbalance. Doses can be titrated retaining the same ratio of spironolactone and furosemide.

For nephrotic syndrome and CKD, loop diuretics are indicated, but higher doses than used for HF are typically required because both CKD and nephrotic syndrome are diuretic-resistant conditions.

Diuretic Resistance

Diuretic resistance typically refers to edema that has become refractory to maximal doses of loop diuretics. Apparent resistance may be the result of drug interactions. NSAIDs block prostaglandinmediated increases in kidney blood flow and natriuresis and can precipitate HF exacerbations.54 Arterial underfilling in cirrhosis and HF increases proximal tubular sodium reabsorption, which reduces delivery of sodium to the distal nephron segment sites of diuretic action. Yet in HF, resistance most commonly results from activation of distal nephron transport.72 This problem can be addressed by combining loop and thiazide diuretics because the latter block the distal nephron sites responsible. To prevent loop diureticinduced renin-angiotensin-aldosterone effects, many patients are treated with aldosterone antagonists, especially because these agents are essential parts of the treatment regimen for HFREF. If other approaches fail, a thiazide diuretic can be added. In nephrotic syndrome, the filtered protein in tubular fluid may contain serine proteases, which cleave and activate ENaC, thereby promoting excess sodium reabsorption.49 ENaC can be inhibited with amiloride.

SELF-ASSESSMENT QUESTIONS

1. A 58-year-old woman with a history of alcohol dependence and known chronic liver disease presents to the emergency department with increasing breathlessness and distended abdomen. Vital signs reveal temperature of 36.9°C (98.5°F), respiratory rate of 17 breaths/min, oxygen saturation of 93% on room air, pulse rate of 76 beats/min, and blood pressure of 93/58 mm Hg without significant orthostatic change. Physical examination reveals scleral icterus, and JVP is flat. Cardiac auscultation is normal; breath sounds are decreased at the bases. Her abdomen is distended with a fluid wave and a positive shifting dullness. The patient has bilateral pitting edema to the mid-calves and intact peripheral pulses. Which of the following is the primary mechanism responsible for maintaining volume excess in this patient?

A. Reduction in plasma oncotic pressure resulting from synthetic hypoalbuminemia causing an increase in fluid movement from the vascular to the interstitial compartment.

B. Underfilling of the arterial circulation resulting from splanchnic venous dilation causing neurally and hormonally mediated kidney sodium retention.

C. Primary kidney sodium and water retention that results in elevated total plasma volume.

D. Decrease in plasma osmolality with stimulation of thirst and persistent release of antidiuretic hormone.

2. Laboratory investigations of the patient described in question 1 reveal serum sodium of 128 mmol/L, potassium of 3.7 mmol/L, chloride of 101 mmol/L, bicarbonate of 23 mg/dL, BUN of 56 mg/dL, and creatinine of 1.0 mg/dL. Albumin is 3.0 g/dL. Reasonable initial approaches to remove excess volume in this patient include all of the following except:

A. Prescribe a diet restricted to 2.3 g (100 mmol) of sodium daily to mitigate kidney retention of sodium and prevent diuretic resistance.

B. Perform a large-volume paracentesis with albumin infusion to rapidly decompress the abdomen.

C. Administer spironolactone up to 400 mg/day, with a loop diuretic to increase sodium excretion.

D. Administer intravenous mannitol to increase osmotic pressure within the tubule and thus sodium and water reabsorption.

3. Over the next 3 days, the patient previously described becomes febrile, with a temperature of 37.8°C (100°F), and confused. Her pulse rate is 120 beats/min with blood pressure of 88/52 mm Hg. The JVP is now near the angle of the jaw when the patient is sitting at 45 degrees. Hemoglobin is 7.6 g/dL, total white blood cell (WBC) count 15,000 (85% polymorphonuclear leukocytes), and platelet count 81,000 × 109 cells/L. Analysis of the ascitic fluid reveals 100 RBCs/µL and 450 WBCs/µL, but no organisms on Gram stain. BUN is 48 mg/dL, serum creatinine is 1.7 mg/dL, and urine sodium is 65 mEq/L, with a fractional sodium excretion of 1.4%. Appropriate immediate measures for the patient at this time would include which of the following?

A. Administer 50 g of albumin, with the goal of improving her hemodynamic profile.

B. Administer fluid resuscitation with 6% hydroxyethyl starch to expand extracellular fluid compartment rapidly and restore blood pressure.

C. Treat for presumptive bacterial peritonitis.

D. Insert jugular venous dialysis access for urgent initiation of dialysis.

REFERENCES

1. Titze J. A different view on sodium balance. Curr Opin Nephrol Hypertens. 2015;24(1):14–20.
2. Titze J. Water-free sodium accumulation. Semin Dial. 2009;22(3):253–255.
3. Jantsch J, Schatz V, Friedrich D, et al. Cutaneous Na + storage strengthens the antimicrobial barrier function of the skin and boosts macrophagedriven host defense. Cell Metab. 2015;21(3):493–501.
4. Rakova N, Juttner K, Dahlmann A, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab. 2013;17(1):125–131.
5. Maroudas AI. Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature. 1976;260(5554):808–809.
6. Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. Annu Rev Physiol. 1972;34:13–46.
7. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail. 2014;2(3):298–305.
8. Palmer LG, Schnermann J. Integrated control of Na transport along the nephron. Clin J Am Soc Nephrol. 2015;10(4):676–687.
9. Salah HM, Al’Aref SJ, Khan MS, et al. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomesSystematic review and meta-analysis of randomized placebo-controlled trials. Am Heart J. 2021;232:10–22.
10. Anders HJ, Davis JM, Thurau K. Nephron protection in diabetic kidney disease. N Engl J Med. 2016;375:2096–2098.
11. Redfield MM, Edwards BS, Heublein DM, Burnett Jr JC. Restoration of renal response to atrial natriuretic factor in experimental low-output heart failure. Am J Physiol. 1989;257:R917–R923.
12. Hall JE, Granger JP, Smith Jr MJ, Premen AJ. Role of renal hemodynamics and arterial pressure in aldosterone “escape. Hypertension. 1984;6(2 Pt 2):I183–I192.
13. Hall JE, Granger JP, Hester RL, et al. Mechanisms of escape from sodium retention during angiotensin II hypertension. Am J Physiol. 1984;246(5 Pt 2):F627–F634.
14. Anders HJ, Davis JM, Thurau K. Nephron protection in diabetic kidney disease. N Engl J Med. 2016;375(21):2096–2098.
15. DiBona GF. Physiology in perspective: the Wisdom of the Body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 2005;289(3):R633–R641.
16. Akabane S, Matsushima Y, Matsuo H, et al. Effects of brain natriuretic peptide on renin secretion in normal and hypertonic saline-infused kidney. Eur J Pharmacol. 1991;198(2–3):143–148.
17. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol. 1979;236(4):F321–F332.
18. Goldsmith SR. Vasopressin as a vasopressor. Am J Med. 1987;82:1213–1219.
19. Schafer JA, Hawk CT. Regulation of Na + channels in the cortical collecting duct by AVP and mineralocorticoids. Kidney Int. 1992;41:255–268.
20. Konishi KI, Mizuochi T, Yanagi T, et al. Clinical features, molecular genetics, and long-term outcome in congenital chloride diarrhea: a nationwide study in Japan. J Pediatr. 2019;214:151–157.e6.
21. Perazella MA, Coca SG. Traditional urinary biomarkers in the assessment of hospital-acquired AKI. Clin J Am Soc Nephrol. 2012;7:167–174.
22. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–2256.
23. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer’s acetate in severe sepsis. N Engl J Med. 2012;367(2):124–134.
24. Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients.

Intensive Care Med. 2012;38(3):368–383.

25. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314(16):1701–1710.
26. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378:829–839.
27. Hinrichs GR, Jensen BL, Svenningsen P. Mechanisms of sodium retention in nephrotic syndrome. Curr Opin Nephrol Hypertens. 2020;29:207–212.
28. Wang XY, Masilamani S, Nielsen J, et al. The renal thiazide-sensitive NaCl cotransporter as mediator of the aldosterone-escape phenomenon. J Clin Invest. 2001;108(2):215–222.
29. Yokota N, Bruneau BG, Kuroski de Bold ML, de Bold AJ. Atrial natriuretic factor significantly contributes to the mineralocorticoid escape phenomenon. Evidence for a guanylate cyclase-mediated pathway. J Clin Invest. 1994;94(5):1938–1946.
30. Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. Ann Intern Med. 1990;113:155–159.
31. Buglioni A, Burnett Jr JC. Pathophysiology and the cardiorenal connection in heart failure. Circulating hormones: biomarkers or mediators. Clin Chim Acta. 2015;443:3–8.
32. Sparks MA, Stegbauer J, Chen D, et al. Vascular type 1A angiotensin II receptors control BP by regulating renal blood flow and urinary sodium excretion. J Am Soc Nephrol. 2015;26(12):2953–2962.
33. Khraibi AA, Granger JP, Haas JA, et al. Intrarenal pressures during direct inhibition of sodium transport. Am J Physiol Regul Integr Comp Physiol. 1992;263:R1182–R1186.
34. Hensen J, Abraham WT, Durr JA, Schrier RW. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. Am J Nephrol. 1991;11(6):441–446.
35. Schrier RW, Cadnapaphornchai MA, Ohara M. Water retention and aquaporins in heart failure, liver disease and pregnancy. J R Soc Med. 2001;94(6):265–269.
36. Szatalowicz VL, Arnold PE, Chaimovitz C, et al. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med. 1981;305:263–266.
37. Birnbaumer M, Seibold A, Gilbert S, et al. Molecular cloning for the receptor for human antidiuretic hormone. Nature. 1992;357:333–335.
38. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation. 1986;73(2):257–267.
39. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361(13):1279–1290.
40. Hernandez-Guerra M, Garcia-Pagan JC, Bosch J. Increased hepatic resistance: a new target in the pharmacologic therapy of portal hypertension. J Clin Gastroenterol. 2005;39(4 suppl 2):S131–S137.
41. Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. N Engl J Med. 2004;350(16):1646–1654.
42. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;8:1151–1157.
43. Arroyo V, Gines P. Mechanism of sodium retention and ascites formation in cirrhosis. J Hepatol. 1993;17(suppl 2):S24–S28.
44. Koomans HA, Geers AB, Dorhout Mees EJ, Kortlandt W. Lowered tissue-fluid oncotic pressure protects the blood volume in the nephrotic syndrome. Nephron. 1986;42(4):317–322.
45. Oliver WJ, Owings CL. Sodium excretion in the nephrotic syndrome: relation to serum albumin concentration, glomerular filtration rate, and aldosterone secretion rate. Am J Dis Child. 1967;113:352–362.
46. Ichikawa I, Rennke HG, Hoyer JR, et al. Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest. 1983;71:91–103.
47. Andersen H, Friis UG, Hansen PB, et al. Diabetic nephropathy is

associated with increased urine excretion of proteases plasmin, prostasin and urokinase and activation of amiloride-sensitive current in collecting duct cells. Nephrol Dial Transplant. 2015;30(5):781–789.
48. Svenningsen P, Bistrup C, Friis UG, et al. Plasmin in nephrotic urine activates the epithelial sodium channel. J Am Soc Nephrol. 2009;20(2):299–310.

References

49. Svenningsen P, Friis UG, Versland JB, et al. Mechanisms of renal NaCl retention in proteinuric disease. Acta Physiol (Oxf). 2013;207(3):536–545.
50. Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Interstitial inflammation, sodium retention, and the pathogenesis of nephrotic edema: a unifying hypothesis. Kidney Int. 2002;62(4):1379–1384.
51. Gustafsson D. Microvascular mechanisms involved in calcium antagonist edema formation. J Cardiovasc Pharmacol. 1987;10(suppl 1):S121–S131.
52. Guan Y, Hao C, Cha DR, et al. Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. Nat Med. 2005;11(8):861–866.
53. Kleinhenz JM, Murphy TC, Pokutta-Paskaleva AP, et al. Smooth muscle-targeted overexpression of peroxisome proliferator activated receptor-gamma disrupts vascular wall structure and function. PLoS One. 2015;10(10):e0139756.
54. Heerdink ER, Leufkens HG, Herrings RMC, et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med. 1998;158:1108–1112.
55. Streeten DH. Idiopathic edema. Pathogenesis, clinical features, and treatment. Endocrinol Metab Clin North Am. 1995;24(3):531–547.
56. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Int. 1998;54(6):2056–2063.
57. West CA, Sasser JM, Baylis C. The enigma of continual plasma volume expansion in pregnancy: critical role of the renin-angiotensin-aldosterone system. Am J Physiol Renal Physiol. 2016;311(6):F1125–F1134.
58. Parikh CR, Coca SG. “Permissive AKI” with treatment of heart failure. Kidney Int. 2019;96:1066–1068.
59. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367(24):2296–2304.
60. Ellison DH, Hoorn EJ, Wilcox CS. Diuretics. In: Taal MW, Chertow GM, Marsden PA, et al., eds. Brenner and Rector’s the Kidney. 9th ed. Vol. 2. Philadelphia: Elsevier; 2012:1879–1916..
61. Schlatter E, Greger R, Weidtke C. Effect of ‘high ceiling’ diuretics on active salt transport in the cortical thick ascending limb of Henle’s loop of rabbit kidney. Pflugers Arch. 1983;396:210–217.

62. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(10):1178–1195.
63. Rudy DW, Voelker JR, Greene PK, et al. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern Med. 1991;115:360–366.
64. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005;3:CD003178.
65. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.
66. Sinha AD, Agarwal R. Thiazide diuretics in chronic kidney disease. Curr Hypertens Rep. 2015;17:13.
67. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219–2229.
68. Vallon V, Verma S. Effects of SGLT2 inhibitors on kidney and cardiovascular function. Annu Rev Physiol. 2021;83:503–528.
69. Liamis G, Rodenburg EM, Hofman A, et al. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med. 2013;126(3):256–263.
70. Leung AA, Wright A, Pazo V, et al. Risk of thiazide-induced hyponatremia

in patients with hypertension. Am J Med. 2011;124(11):1064–1072.
71. Runyon BA, American Association for the Study of Liver Diseases, Practice Guidelins Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49(6):2087–2107.
72. Ter Maaten JM, Rao VS, Hanberg JS, et al. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. Eur J Heart Fail. 2017;19(8):1014–1022.
73. Ginés P, Cardenas A, Sola E, Schrier RW. Liver disease and the kidney. In: Coffman TM, Falk RJ, Molitoris BA, et al., eds. Schrier’s Diseases of the Kidney. Philadelphia: Wolters Kluwer; 2012:1965–1996.
74. Ives HE. Diuretic agents. In: Katzung BG, ed. Basic and Clinical Pharmacology. Columbus: McGraw-Hill Medical; 2006:237.

9

Disorders of Water Metabolism

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PHYSIOLOGY OF WATER BALANCE

The maintenance of the tonicity of body fluids within a narrow physiologic range is made possible by homeostatic mechanisms that control the intake and excretion of water. Vasopressin, known as arginine vasopressin (AVP) or antidiuretic hormone (ADH), governs the excretion of water by its effect on the renal collecting system. Osmoreceptors located in the hypothalamus control the secretion of vasopressin in response to changes in tonicity.

In the steady state, water intake matches water losses. Water intake is regulated by the need to maintain a physiologic serum osmolality of 285 to 290 mOsm/kg H_2O. Despite major fluctuations of solute and water intake, the total solute concentration (i.e., the tonicity) of body fluids is maintained virtually constant. The ability to dilute and to concentrate the urine allows wide flexibility in urine flow (see Chapter 2). During water loading, the diluting mechanisms permit excretion of 20 to 25 L of urine daily, and during water deprivation, the urine volume may be as low as 0.5 L/day.[1–3]

VASOPRESSIN

AVP plays a critical role in determining the concentration of urine: It is a 9-amino acid cyclic peptide, synthesized and secreted by the supraoptic and paraventricular magnocellular nuclei in the hypothalamus. AVP has a half-life of 15 to 20 minutes and is rapidly metabolized in the liver and the kidney.

Osmotic Stimuli for Vasopressin Release

Substances restricted to the extracellular fluid (ECF), such as hypertonic saline and mannitol, decrease cell volume by acting as effective osmoles and enhancing osmotic water movement from the cell. This stimulates vasopressin release; in contrast, urea and glucose readily cross cell membranes and thus do not cause changes in cell volume. The “osmoreceptor” cells, located close to the supraoptic nuclei in the anterior hypothalamus, are sensitive to changes in serum osmolality as small as 1% and bring about the release of AVP by a pathway that involves the activation of transient receptor potential (TRPV4) channels.[4] In humans, the osmotic threshold for AVP release is 280 to 290 mOsm/kg H_2O[5] (Fig. 9.1). This system is so efficient that serum osmolality usually does not vary by more than 1% to 2% despite wide fluctuations in water intake.

Nonosmotic Stimuli for Vasopressin Release

Decreased effective circulating volume (e.g., heart failure, cirrhosis, vomiting) causes discharge from parasympathetic afferent nerves in the carotid sinus baroreceptors and increases AVP secretion. Much higher vasopressin levels can be achieved with hypovolemia than with hyperosmolality, although a large (7%) decrease in blood volume is required before this response is elicited. Other nonosmotic stimuli include nausea, pain, pregnancy, and fructose (such as from sugary beverages).[6] AVP levels (as reflected by elevation of serum copeptin, a surrogate marker) are also elevated in patients with metabolic syndrome and in patients with chronic kidney disease (CKD) compared with healthy individuals. The function of the V1a and V1b receptors in human disease are still being evaluated, although a recent study suggests that V1b may have a role in driving fat in response to fructose, possibly as a means for increasing metabolic water reserves.[6]

Mechanism of Vasopressin Action

AVP binds three types of receptors coupled to G proteins: the V1a (vascular and hepatic), V1b (anterior pituitary and pancreatic islet), and V2 (renal) receptors. The V2 receptor is primarily localized in the collecting duct and leads to an increase in water permeability through aquaporin 2 (AQP2), a member of a family of cellular water transporters (Fig. 9.2).
AQP1 is localized in the apical and basolateral region of the proximal tubule epithelial cells and the descending limb of the loop of Henle and accounts for the high water permeability of these nephron segments.
AQP1 is constitutively expressed, and not subject to regulation by AVP.7
AQP2 is localized exclusively in apical plasma membranes and intracellular vesicles in the collecting duct principal cells. AVP affects both the short-term and the long-term regulation of AQP2. The short-term regulation, also described as the shuttle hypothesis, explains the rapid and reversible increase (within minutes) in collecting duct water permeability after AVP administration. This involves the insertion of water channels from subapical vesicles into the luminal membrane. Long-term regulation relates to AVP-mediated increases in the transcription of genes involved in AQP2 production and occurs if AVP levels are elevated for 24 hours or more. An increased number of AQP2 channels per cell elevates the maximal water permeability of the collecting duct epithelium.7
Aquaporins 3 and 4 are located on the basolateral membranes of the collecting duct (Fig. 9.2) and are probably involved in water exit from the cell. AQP3 is expressed along the entire collecting duct, whereas AQP4 is found in the inner medullary collecting duct. AQP4 is also found in the hypothalamus and is a candidate osmoreceptor for the control of AVP release.7
AVP also stimulates urea transporters in the inner medullary collecting duct.
Urea transporter A1 (UT-A1) is found exclusively in apical plasma membranes and intracellularly in inner medullary collecting ducts.
UT-A3 is found predominantly in the basolateral plasma membrane in inner medullary collecting ducts. Urea reabsorption into the inner medullary interstitium is important for increasing inner medullary tonicity and the driving force for water reabsorption.8

Thirst and Water Balance

Hypertonicity is the most potent stimulus for thirst, with a change of only 2% to 3% in serum osmolality producing a strong desire to drink.

the concentration of solutes in serum. The free water clearance (Cwater) is the volume of water that has been added to (positive Cwater) or subtracted from (negative Cwater) isotonic urine (Cosm) to create either hypotonic or hypertonic urine.
Urine volume flow (V) includes the isotonic portion of urine (Cosm) plus the free water clearance (Cwater).

The osmotic threshold for thirst usually occurs at 290 to 295 mOsm/kg H2O and is greater than the threshold for vasopressin release (see Fig. 9.1). This osmolality closely approximates the level at which maximal concentration of urine is achieved. Hypovolemia, hypotension, and angiotensin II (Ang II) are also stimuli for thirst. Between the limits imposed by the osmotic thresholds for thirst and AVP release, serum osmolality may be regulated more precisely by small, osmoregulated adjustments in urine flow and water intake. The exact level at which balance occurs depends on insensible losses, water intake, and water generated from metabolism.

$V = Cosm + Cwater$
Therefore:
$Cwater = V - Cosm$

QUANTITATION OF RENAL WATER EXCRETION

The Cosm solute clearance is determined by urine flow, urine osmolality, and serum osmolality Posm as follows:
(
)
Uosm × V
Cosm =
Posm

Urine volume can be considered as having two components. The osmolar clearance (Cosm) is the volume needed to excrete solutes at

5.0
4.0

Maximally effective
vasopressin levels

1200
1100
900
700
500
300
150

3.0
2.0
1.0

Thirst

Therefore:
Cwater = V −

Urinary osmolality (mOsm/L)

Serum vasopressin (ng/L)

Response to Changes in Serum Osmolality
Urine osmolality
Thirst
Vasopressin

(

Uosm × V
Posm

)

(
)
Uosm
=V 1−
Posm

This relationship reflects the following:

1. In hypotonic urine (Uosm < Posm), Cwater is positive.
2. In isotonic urine (Uosm = Posm), Cwater is zero.
3. In hypertonic urine (Uosm > Posm), Cwater is negative (i.e., water is retained).

If excretion of free water in a polyuric patient is unaccompanied by water intake, the patient becomes hypernatremic. Conversely, failure to excrete free water with increased water intake can cause hyponatremia.

A limitation of the previous equation is that it fails to predict clinically important alterations in serum tonicity and serum sodium concentration (serum [Na+]) because urea is included in the calculation of urine osmolality. Urea is an important component of urinary osmolality; however, urea equilibrates across most cell membranes in the body and does

280
284 288
292
296
Serum osmolality (mOsm/L)

Fig. 9.1 Mechanisms Maintaining Serum Osmolality. Thirst, vasopressin levels, and urinary osmolality in response to changes in serum osmolality. (Modified from Narins RG, Krishna GC. Disorders of water balance. In: Stein JH, ed. Internal Medicine. Little, Brown; 1987:794.)

Cellular Mechanism of Vasopressin Action

UT-A3
Urea

P

UT-A3

Apical membrane

UT-A1

P
PKA

P

Urea

P

P
cAMP

AC

AVP
V2R

AQP2

Basolateral membrane

UT-A1

P
H2O

AQP2

109

H2O
AQP3/4

Fig. 9.2 Cellular Mechanism of Vasopressin Action. Arginine vasopressin (AVP) binds to V2 receptors (V2R) on the basolateral membrane and activates G proteins, stimulates adenylyl cyclase (AC), and initiates a signaling cascade (cAMP, PKA) resulting in aquaporin 2 (AQP2) and urea transporter A1 (UT-A1) phosphorylation (P) and accumulation in the apical membrane. Water exits the cell through AQP3 and AQP4 in the basolateral membrane. Urea exits the cell through urea transporter A3 (UT-A3) in the basolateral membrane.
cAMP, Cyclic adenosine monophosphate; PKA, protein kinase A.

Plasma Osmolality and Dysnatremias

Decrease

Suppression
of thirst

Plasma
osmolality
280–290
mOsm/kg H_2O
Suppression
of vasopressin
release

Increase

Stimulation
of thirst

Disorder involving
urine dilution with
water intake

Stimulation
of vasopressin
release

Disorder involving
urine concentration
with inadequate
water intake
Concentrated
urine

Dilute
urine

Hypernatremia

Hyponatremia

Fig. 9.3 Maintenance of serum osmolality and pathogenesis of dysnatremias. (Modified from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady HR, Wilcox CS, eds. Therapy in Nephrology and Hypertension. Saunders; 1999:257–269.)

not cause water movement between fluid compartments. Therefore, urea does not influence serum Na^+ concentration or the release of vasopressin, and changes in serum [Na^+] are better predicted by electrolyte free water clearance [$C_{water(e)}$]. The equation can be modified, replacing P_{osm} by serum [Na^+] (P_{Na}), and the urine osmolality by urine [Na^+] and urine [K^+], potassium concentration, ($U_{Na} + U_K$):

$$C_{water(e)} = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$

If $U_{Na} + U_K$ is less than P_{Na}, then $C_{water(e)}$ is positive and serum [Na^+] increases. If $U_{Na} + U_K$ is greater than P_{Na}, then $C_{water(e)}$ is negative and serum [Na+] decreases. In the clinical setting, it is more appropriate to use the equation for electrolyte free clearance to predict if a patient’s serum [Na+] will increase or decrease in the face of the prevailing water excretion. For example, in a patient with high urea excretion, the original equation would predict negative water excretion and a decrease in serum [Na+], but, in fact, [Na+] increases, which is accurately predicted by the latter equation.

SERUM SODIUM CONCENTRATION, OSMOLALITY, AND TONICITY

The kidney’s countercurrent mechanism, which allows urinary concentration and dilution, acts in concert with the hypothalamic osmoreceptors through AVP secretion to maintain serum [Na+] and tonicity within a very narrow range[9] (Fig. 9.3). A defect in the urine-diluting capacity coupled with excess water intake leads to hyponatremia. A defect in urineconcentrating ability with inadequate water intake leads to hypernatremia.

Serum [Na+] along with its accompanying anions accounts for nearly all the osmotic activity of the serum. Calculated serum osmolality is given by 2[Na+] mmol/L + BUN (mg/dL)/2.8 + glucose (mg/dL)/18, where BUN is blood urea nitrogen and 2.8 and 18 represent correction factors based on molecular weights of the respective molecules so as to unify the equation units to mmol/L. The addition of other solutes to ECF results in an increase in measured osmolality (Table 9.1). Solutes that are permeable across cell membranes do not cause water movement and therefore yield hypertonicity without cellular dehydration, as in uremia or ethanol intoxication. By contrast, in diabetic ketoacidosis, when glucose cannot freely cross cell membranes in the absence of insulin, water moves from the cells to the ECF, leading to cellular dehydration and lowering serum [Na+]. This can be viewed as translocational because the decrease in serum [Na+] does not reflect a change in total body water but rather the movement of water from intracellular to extracellular space. Therefore, serum [Na+] can be corrected by 1.6 mmol/L for every 100 mg/dL (5.6 mmol/L) increase in serum glucose, although this may somewhat underestimate the impact of glucose to decrease serum [Na+].

Effects of Osmotically Active Substances on Serum Sodium (Na +) Levels

TABLE 9.1

Substances That Increase Osmolality Without Changing Serum Na+
Urea
Ethanol
Ethylene glycol
Isopropyl alcohol
Methanol

Substances That Increase Osmolality and Decrease Serum Na+ (Translocational Hyponatremia)
Hyperglycemia
Mannitol
Glycine
Maltose

Pseudohyponatremia occurs when the solid phase of serum (usually 6%–8%) is increased by large increments in either lipids or proteins (e.g., in hypertriglyceridemia and paraproteinemias). Serum osmolality is normal in pseudohyponatremia. This false result occurs because the usual method, indirect ion-selective potentiometry, measures the concentration of sodium in whole serum and not just the liquid phase, in which the concentration of sodium is 150 mmol/L. Many laboratories use direct ion-selective potentiometry, giving the true aqueous sodium-related osmolality, so if there is a divergence in the plasma sodium between the indirect and direct methods of measurement, a diagnosis of pseudohyponatremia becomes probable. In the absence of a direct-reading potentiometer, an estimate of serum water may be obtained from the following formula10:

$\text{Serum water content (\%)} = 99\ 1 - (0\ 1 \times L) - (0\ 07 \times P)$

where L and P refer to the total lipid and protein concentration (in g/L), respectively. For example, if the formula reveals that serum water is 90% of the serum sample rather than the normal 93% (which yields a serum sodium concentration of 140 mmol/L as 150 × 0.93 = 140), the concentration of measured sodium would be expected to decrease to 135 mmol/L (150 × 0.90).

ESTIMATION OF TOTAL BODY WATER

In normal individuals, total body water is approximately 60% of body weight (50% in females and obese individuals). With hyponatremia or hypernatremia, the change in total body water can be calculated from the serum [Na+] by the following formula:

Water excess = 0 6W ×

Water

6W ×

1−
Na+

Na+

obs

140
obs

140

−1

Mechanisms of Urine Dilution
Na^+/Cl^- Na^+/Cl^-

Glomerular
filtration

Diminished by:
age, renal disease,
Proximal
congestive heart
tubule
failure, cirrhosis,
nephrotic syndrome,
volume depletion

Na^+/Cl^- reabsorption
reduced by:
thiazide diuretics

Cortical
diluting
segment
H_2O
Na^+/Cl^-
Thick ascending
limb
Na^+/Cl^-

Na^+/Cl^-
H_2O
H_2O

Delivery of H_2O
determined by:
glomerular
filtration rate,
proximal tubule
H_2O, and Na^+/Cl^-
reabsorption

Distal convoluted
tubule

Na^+/Cl^-

H_2O

Collecting duct
(impermeable to H_2O in
absence of vasopressin
or other antidiuretic
substances)
Permeability
increased by:
vasopressin, drugs

Na^+/Cl^-

Na^+/Cl^-
reabsorption

reduced by:
loop diuretics,
osmotic
diuretics,
interstitial
renal disease

H_2O

Loop of
Henle

Fig. 9.4 Mechanisms of Urine Dilution. Normal determinants of urinary dilution and disorders causing hyponatremia. (Modified from Cogan MC. Normal water homeostasis. In: Cogan MC, ed. Fluid and Electrolytes. Lange; 1991:98–106.)

Solute concentration

where $[Na^+]_{obs}$ is observed sodium concentration (in mmol/L) and W is body weight (in kilograms). By use of this formula, a change of 10 mmol/L in the serum $[Na^+]$ in a 70-kg individual is equivalent to a change of 3 L in free water.

Etiology and Classification of Hyponatremia

Once the patient is ascertained as being hypo-osmolar, the next step is to determine whether the individual is hypovolemic, euvolemic, or hypervolemic (Fig. 9.5).

HYPONATREMIC DISORDERS

Hypovolemia: Hyponatremia Associated With Decreased Total Body Sodium

Hyponatremia is defined as serum $[Na^+]$ of less than 135 mmol/L. If translocational and pseudohyponatremia are not responsible for the hyponatremia, the decrease in serum sodium concentration reflects a low serum osmolarity, also designated as hypotonicity. The underlying cause of hypotonic hyponatremia is a disturbance in the urinary diluting mechanism.11 Fig. 9.4 depicts the normal diluting process and the sites at which it can be disrupted so as to impair water excretion, causing its retention and culminating in hyponatremia. A diminished glomerular filtration rate (GFR) and/or an increase in proximal tubular fluid reabsorption decrease distal delivery of filtrate to the diluting segments of the nephron, quantitatively limiting maximal water excretion. Also, hyponatremia may result from a decrement in Na^+-Cl transport from the thick ascending limb of the loop of Henle [TAL] or distal convoluted tubule, critical processes in the generation of a dilute tubular fluid. Most frequently, hyponatremia results from nonosmotic vasopressin secretion despite the presence of serum hypo-osmolality. This renders the collecting duct water permeable, thereby not allowing for the excretion of a maximally dilute urine.

A patient with hypovolemic hyponatremia has both a total body Na^+ and a water deficit, with the Na^+ deficit exceeding the water deficit. This occurs in patients with high gastrointestinal (GI) and renal losses of water and solute accompanied by free water or hypotonic fluid intake. The underlying mechanism is the nonosmotic release of vasopressin stimulated by volume contraction, which maintains vasopressin secretion despite the hypotonic state. Measurement of urine $[Na^+]$ is a useful tool in helping to diagnose these conditions (see Fig. 9.5).

Gastrointestinal and third-space sequestered losses. The kidney responds to volume contraction by conserving Na^+ and Cl . A similar response is observed in burn patients and patients with sequestration of fluids in third spaces, as in the peritoneal cavity with peritonitis or pancreatitis or in the bowel lumen with ileus. In all these, urine [Na+] is usually less than 10 mmol/L, and the urine is hyperosmolar. An exception occurs in patients with vomiting and metabolic alkalosis. Here, increased bicarbonate ion (HCO_3) excretion obligates simultaneous cation excretion, resulting in a urine [Na+] that may exceed 20 mmol/L despite severe volume depletion; however, the urine [Cl] remains less than 10 mmol/L. Sodium

Diagnostic Approach in Hyponatremia
Hyponatremia

Assess volume status

Hypovolemia
Total body water ↓
Total body Na+ ↓↓

Euvolemia (no edema)
Total body water ↑
No change in total body Na+
(>20 mmol/L urinary Na+)

Hypervolemia
Total body water ↑↑
Total body Na+ ↑

Measure
urinary [Na+]
≥20 mmol/L

Renal losses
Diuretic excess
Mineralocorticoid
deficiency
Salt-losing nephropathy
Bicarbonaturia with
renal tubular acidosis
and metabolic alkalosis
Ketonuria
Osmotic diuresis
Cerebral salt wasting

Measure
urinary [Na+]
≥20 mmol/L

<20 mmol/L

Extrarenal losses
Vomiting
Diarrhea
Third spacing of fluids
in burns, pancreatitis,
trauma

Glucocorticoid deficiency
Hypothyroidism
Stress
Drugs (see Table 9.2)
Syndrome of inappropriate
ADH secretion (SIADH)

Acute or chronic
kidney injury

<20 mmol/L

Nephrotic syndrome

Cirrhosis
Cardiac failure

Fig. 9.5 Algorithm for diagnostic assessment of the patient with hyponatremia. (Modified from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady HR, Wilcox CS, eds. Therapy in Nephrology and Hypertension. Saunders; 1999:257–269.)

conservation is also impaired in CKD that may also result in high urine [Na+] despite volume depletion.

Diuretics. Diuretic use is one of the most common causes of hypovolemic hyponatremia associated with a high urine [Na+]. Loop diuretics inhibit Na+-Cl reabsorption in the thick ascending limb (TAL), impairing the generation of a hypertonic medullary interstitium. Therefore, despite increased AVP secretion, responsiveness to AVP is diminished and free water is excreted. In contrast, thiazide diuretics act in the distal tubule where they interfere with urine dilution, limiting free water excretion. Hyponatremia usually occurs within 14 days of initiation of therapy, with manifestation in approximately one-third of patients within 5 days. Underweight women and elderly patients are most susceptible. Postulated mechanisms for diuretic-induced hyponatremia include the following:

✓•✓ Hypovolemia-stimulated AVP release and decreased fluid delivery to the diluting segment

✓•✓ Impaired water excretion through interference with maximal urinary dilution in the cortical diluting segment

✓•✓ K+ depletion, directly stimulating water intake by alterations in osmoreceptor sensitivity and increasing thirst

Water retention can mask the physical findings of hypovolemia, making the patients with diuretic-induced hyponatremia appear euvolemic.

Salt-losing nephropathy. A salt-losing state may occur in patients with advanced CKD (GFR < 15 mL/min), particularly from interstitial disease. It is characterized by hyponatremia and hypovolemia. In proximal (type 2) renal tubular acidosis, there is renal Na+ and K+ wasting despite only moderately reduced GFR and bicarbonaturia further obligating urine Na+ excretion.

Mineralocorticoid deficiency. Mineralocorticoid deficiency is characterized by hyponatremia with ECF volume contraction, urine [Na+] greater than 20 mmol/L, and high serum K+, urea, and creatinine. Decreased ECF volume provides the nonosmotic stimulus for AVP release.

Osmotic diuresis. An osmotically active, nonreabsorbable solute obligates the renal excretion of Na+ and results in volume depletion. In the face of continuing water intake, the diabetic patient with severe glycosuria, the patient with a urea diuresis after relief of urinary tract obstruction, and the patient with mannitol diuresis all undergo urinary losses of Na+ and water, leading to hypovolemia and hyponatremia. Urine [Na+] is typically greater than 20 mmol/L. The ketone bodies β-hydroxybutyrate and acetoacetate also obligate urinary electrolyte losses and aggravate the renal Na+ wasting seen in diabetic ketoacidosis, starvation, and alcoholic ketoacidosis.

Cerebral salt wasting. Cerebral salt wasting is a syndrome described primarily in patients with subarachnoid hemorrhage. The primary defect is salt wasting from the kidneys with subsequent volume contraction, which stimulates vasopressin release. The exact mechanism is not understood, but it is postulated that brain natriuretic peptide increases urine volume and Na+ excretion. Serum uric acid is often low, similar to that observed in syndrome of inappropriate antidiuretic hormone (SIADH; see later). The diagnosis requires evidence of inappropriate sodium losses and reduced effective blood volume, usually with signs of orthostatic hypotension. These criteria are rarely fulfilled, suggesting that cerebral salt wasting is overdiagnosed.

Aquaporin 2 Expression in Various Disorders
Water retention

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AQP2 expression
(fraction of control levels)

Polyuria
3.5
3
2.5
2
1.5
1
0.5
0

Fig. 9.6 Changes In Aquaporin 2 (Aqp2) Expression Seen in Association With Different Water Balance Disorders. Levels are expressed as a fraction (percentage) of control levels. AQP2 expression is reduced, sometimes dramatically, in a wide range of hereditary and acquired forms of diabetes insipidus (DI) characterized by different degrees of polyuria. Conversely, congestive heart failure and pregnancy are conditions associated with increased expression of AQP2 levels and excessive water retention. (Modified from Nielsen S, Knepper MA, Kwon TH. Regulation of water balance. Urine concentration and dilution. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 8th ed. Lippincott Williams & Wilkins; 2007:96–123.)

Hypervolemia: Hyponatremia Associated With Increased Total Body Sodium

Hyponatremia can also develop in hypervolemic states, such as congestive heart failure (CHF), nephrotic syndrome, and cirrhosis, in which the total body water is increased more than total body Na+ (see Fig. 9.5 and Chapter 8).

Congestive heart failure. Edematous patients with CHF have reduced effective intravascular volume as a result of decreased systemic mean arterial pressure (MAP) and cardiac output. This reduction is sensed by aortic and carotid baroreceptors activating nonosmotic pathways, resulting in vasopressin release. In addition, the relative “hypovolemic” state stimulates the renin-angiotensin axis and increases norepinephrine production, which, in turn, decreases GFR. This causes an increase in proximal tubular reabsorption and a decrease in water delivery to the distal tubule.

The neurohumorally mediated decrease in delivery of tubular fluid to the distal nephron and an increase in vasopressin secretion mediate hyponatremia by limiting Na+-Cl and water excretion. In addition, low cardiac output and high Ang II levels are potent stimuli of thirst. There is also excessive intracellular targeting of AQP2 to the apical cell membrane of the collecting duct, most likely from high AVP levels (Fig. 9.6).12

As cardiac function improves with afterload reduction, plasma vasopressin decreases, with concomitant improvement in water excretion. The degree of hyponatremia has also been correlated with the severity of cardiac disease and with patient survival; serum [Na+] less than 125 mmol/L reflects severe CHF.

Hepatic failure. Patients with cirrhosis and hepatic insufficiency also have increased ECF volume (ascites, edema). Because of splanchnic venous dilation, they have increased plasma volume. Cirrhotic patients have an increased cardiac output because of multiple arteriovenous fistulas in their alimentary tract, lungs, and skin. Vasodilation and arteriovenous fistulas cause a decrease in MAP. As the severity of cirrhosis increases, there are progressive increases in plasma renin, norepinephrine, AVP, and endothelin, and an associated decline in MAP and serum [Na+]. In experimental models, expression of AQP2 is upregulated in collecting ducts.7

Nephrotic syndrome. In some patients with nephrotic syndrome, especially those with minimal change disease, low plasma oncotic pressure from hypoalbuminemia alters Starling forces, leading to intravascular volume contraction and stimulation of AVP with hyponatremia. In contrast, most nephrotic patients have a renal defect in sodium excretion resulting in increased effective circulating volume. Hyponatremia may still occur in these latter conditions. In experimental models of nephrotic syndrome, expression of AQP2, AQP3, and UT-A1 are downregulated in the collecting duct (which would have countering effects), but so are the sodium transporters, NKCC2, NHE3, and Na-K-ATPase, in the TAL, resulting in hyponatremia.7

Advanced chronic kidney disease. Patients with severely reduced GFR, either acute or chronic, have a profound increase in fractional excretion of Na+ to maintain normal salt balance given the overall decreased number of functioning nephrons. Edema usually develops when the Na+ ingested exceeds the capacity of the kidneys to excrete this load. Likewise, if water intake exceeds threshold, there is positive water balance and hyponatremia. At a GFR of 5 mL/min, only 7.2 L of filtrate is formed daily. Approximately 30%, or 2.2 L, of this filtered fluid will reach the diluting segment of the nephron, which is therefore the maximum solute-free water that can be excreted daily. As GFR progressively declines, a defect in renal concentration precedes a disorder in urinary dilution. The excretion of free water as a function of remaining glomeruli is well maintained until kidney failure is very advanced.13

Older age. Aging results in 20% reduction in maximum urine osmolality in people older than 60 years. The concentrating defect is not related to a decrease in GFR or an abnormality in AVP secretion.

Euvolemia: Hyponatremia Associated With Normal Total Body Sodium

Euvolemic hyponatremia is the most common dysnatremia in hospitalized patients. These patients have no physical signs of increased or decreased total body Na+

Glucocorticoid deficiency. Cortisol exhibits a negative feedback on ACTH and vasopressin production so primary or secondary glucocorticoid deficiency leads to impaired water excretion from excess circulating vasopressin. This can be corrected by physiologic doses of corticosteroids but not by volume expansion. Hyponatremia may be enhanced by reduced renal blood flow and decreased distal fluid delivery to the diluting segments of the nephron.

Hypothyroidism. Hyponatremia occurs in patients with severe hypothyroidism, who usually meet the clinical criteria for myxedema coma. A decrease in cardiac output leads to nonosmotic release of AVP. A reduction in GFR leads to diminished free water excretion through decreased distal delivery to the distal nephron. The exact mechanisms are unclear. In patients with untreated hypothyroidism who have moderately severe disease, a vasopressin-independent mechanism is suggested by normal suppression of vasopressin after water loading. However, in patients with more advanced hypothyroidism, elevated vasopressin levels are reported in the basal state and after a water load. Hyponatremia is readily reversed by hormonal replacement treatment.

Psychosis. Patients with acute psychosis may develop hyponatremia. Psychogenic drugs, particularly selective serotonin reuptake inhibitors (SSRIs), are associated with hyponatremia, but psychosis can cause hyponatremia independently.14 The pathophysiologic process involves an increased thirst perception, a mild defect in osmoregulation that causes vasopressin to be secreted at lower osmolality, and an enhanced renal response to vasopressin. Individuals with self-induced water intoxication may also be more prone to rhabdomyolysis.

Postoperative hyponatremia. Postoperative hyponatremia mainly is a result of excessive infusion of electrolyte-free water (hypotonic saline or 5% dextrose in water) and the presence of AVP, which prevents water excretion. Hyponatremia can also occur despite infusion with nearisotonic (normal) saline within 24 hours of induction of anesthesia.15 Young premenstrual girls are at higher risk of acute postoperative hyponatremia accompanied by cerebral edema. The mechanism has not been fully elucidated, and the patients at highest risk cannot be prospectively identified. Nevertheless, hypotonic fluids should be avoided after surgery, isotonic fluids minimized, and serum [Na+] checked if hyponatremia is suspected (e.g., symptoms of headache or nausea).

Exercise-induced hyponatremia. Hyponatremia is seen in longdistance runners. A study at a marathon race associated increased risk of hyponatremia with body mass index less than 20 kg/m2, running time exceeding 4 hours, and greatest weight gain.16 A study in ultramarathon runners showed elevated AVP despite normal or low serum [Na+]. The mechanism may be because of an exuberant AVP response in relation to exercise-induced dehydration.

Drugs causing hyponatremia. Drug-induced hyponatremia is becoming the most common cause of hyponatremia.14 Thiazide diuretics and SSRIs are the most commonly implicated medications. Hyponatremia can be mediated by AVP analogs, such as desmopressin (DDAVP, 1-desamino-d-arginine AVP), that enhance AVP release and agents potentiating the action of AVP. In other cases, the mechanism is unknown (Table 9.2). Desmopressin for nocturia in elderly patients and enuresis in young persons has caused hyponatremia in some of these subjects, so it is not routinely used to treat these conditions. Desmopressin for nocturia should be used only when the number of voidings are not tolerable and are debilitating (>2/night). Upon awakening, the drug is likely to be still active for several more hours, requiring great attention to water restriction. Hyponatremia may also result from use of intravenous immunoglobulin (IVIG).17 The mechanism of IVIG-associated hyponatremia is multifactorial, involving pseudohyponatremia (because of increases in serum protein concentration), translocation (because of sucrose in the solution), and true dilutional hyponatremia (because of the retention of water, particularly when associated with acute kidney injury [AKI]).17

Drugs Associated With
Hyponatremiaa

TABLE 9.2

Vasopressin Analogs

Drugs That Potentiate Renal
Action of Vasopressin

Desmopressin (DDAVP)
Oxytocin

Chlorpropamide
Cyclophosphamide
Nonsteroidal anti-inflammatory drugs
(NSAIDs)
Acetaminophen

Drugs That Enhance
Vasopressin Release

Drugs That Cause Hyponatremia
by Unknown Mechanisms

Chlorpropamide
Clofibrate
Carbamazepine-oxcarbazepine
Vincristine
Nicotine
Narcotics
Antipsychotics/antidepressants
(SSRIs)
Ifosfamide

Haloperidol
Fluphenazine
Amitriptyline
Thioridazine
Fluoxetine
Methamphetamine (MDMA, “ecstasy”)
Intravenous immunoglobulin (IVIG)

Terms in italics are the most common causes.
aNot including diuretics.
MDMA, 3,4-Methylenedioxymethamphetamine; SSRIs, selective serotonin reuptake inhibitors.
From Liamis G, Elisaf M. Hyponatremia induced by drugs. In: Simon E, ed. Hyponatremia: Springer; 2013:111–126.

Syndrome of inappropriate antidiuretic hormone secretion.
Despite being the most common cause of hyponatremia in hospitalized patients, SIADH is a diagnosis of exclusion. A defect in osmoregulation causes AVP to be inappropriately stimulated, leading to urine concentration (Table 9.3). A few causes deserve special mention. Central nervous system (CNS) disturbances such as hemorrhage, tumors, infections, and trauma cause SIADH by excess AVP secretion. Small cell lung cancers, cancer of the duodenum and pancreas, and olfactory neuroblastoma cause ectopic production of AVP. Idiopathic cases of SIADH are unusual except in elderly patients, in whom hyponatremia is frequently multifactorial,18 but in whom as many as

10% have abnormal AVP secretion without known cause.

Several patterns of abnormal AVP release have emerged from studies of patients with clinical SIADH[19] and have now been reproduced employing the simpler, more reliable, and more stable copeptin assay.[20]

In one-third of patients with SIADH, AVP release varies appropriately with serum [Na+] but begins at a lower threshold of serum osmolality, implying a “resetting of the osmostat.” Ingestion of free water then leads to water retention to maintain the serum [Na+] at a new lower level, usually 125 to 130 mmol/L. In two-thirds of patients, AVP release does not correlate with serum [Na+], but a solute-free urine cannot be excreted. Therefore, ingested water is retained, giving rise to moderate nonedematous volume expansion and dilutional hyponatremia. In about 10% of patients, AVP levels are not measurable, suggesting that the syndrome of inappropriate antidiuresis (SIAD) is a more accurate term.[19] It was suggested that such patients may have a nephrogenic syndrome of antidiuresis, and a gain-of-function mutation in the AVP receptor. However, none of the six patients who had unmeasurable copeptin (a surrogate marker for AVP) levels had an identifiable gain of function mutation.[20]

The diagnostic criteria for SIADH are summarized in Box 9.1 1

Plasma AVP may be in the “normal” range (up to 10 ng/L), but this

TABLE 9.3

Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Carcinomas

Pulmonary Disorders

Nervous System Disorders

Bronchogenic carcinoma
Carcinoma of duodenum
Carcinoma of pancreas
Thymoma
Carcinoma of stomach
Lymphoma
Ewing sarcoma
Carcinoma of bladder
Carcinoma of prostate
Oropharyngeal tumor
Carcinoma of ureter

Viral pneumonia
Bacterial pneumonia
Pulmonary abscess
Tuberculosis
Aspergillosis
Positive-pressure ventilation
Asthma
Pneumothorax
Mesothelioma
Cystic fibrosis

Encephalitis (viral, bacterial)
Human immunodeficiency virus (HIV)
Meningitis (viral, bacterial, tuberculous, fungal)
infection; acquired immunodeficiency
Head trauma
syndrome (AIDS)
Brain abscess
Idiopathic (elderly)
Brain tumors
Prolonged exercise
Guillain-Barré syndrome
Acute intermittent porphyria
Subarachnoid hemorrhage or subdural hematoma
Cerebellar and cerebral atrophy
Cavernous sinus thrombosis
Neonatal hypoxia
Hydrocephalus
Shy-Drager syndrome
Rocky Mountain spotted fever
Delirium tremens
Cerebrovascular accident (stroke; cerebral
thrombosis or hemorrhage)
Acute psychosis
Peripheral neuropathy
Multiple sclerosis

Other

Terms in italics are the most common causes.
From Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Saunders; 2008:337–352.

BOX 9.1 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

Essential Diagnostic Criteria

- Decreased extracellular fluid effective osmolality (270 mOsm/kg H2O)
- Inappropriate urine concentration (>100 mOsm/kg H2O)
- Clinical euvolemia
- Elevated urine Na+ concentration under conditions of normal salt and water intake
- Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use

Supplemental Criteria

- Abnormal water-load test result (inability to excrete at least 90% of a 20mL/kg water load in 4 hours and/or failure to dilute urine osmolality to <100 mOsm/kg)
- Serum vasopressin level inappropriately elevated relative to the serum osmolality
- No significant correction of serum Na+ level with volume expansion, but improvement after fluid restriction
- Hypouricemia and elevated fractional excretion of uric acid

Modified from Verbalis J. The syndrome of inappropriate antidiuretic hormone secretion and other hypo-osmolar disorders. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 9 ed. Philadelphia: Lippincott Williams & Wilkins; 2013:2012-54.

is inappropriate given the hypo-osmolar state. The measurement of plasma AVP is rarely needed because the urinary osmolality provides an excellent surrogate bioassay. Thus, a hypertonic urine (>300 mOsm/kg H2O) provides strong evidence for the presence of AVP in the circulation because such urinary tonicities are unattainable in its absence. Likewise, a urinary osmolality lower than 100 mOsm/kg H2O reflects the virtual absence of the hormone. Urinary osmolarities in

the range of 100 to 300 mOsm/kg H2O can occur in the presence or absence of AVP. A decrease in serum uric acid concentration associated with a high fractional excretion (>10%) is frequently encountered in the patient with SIADH.

Clinical Manifestations of Hyponatremia

Most patients with serum [Na+] greater than 125 mmol/L are asymptomatic. In patients with less than 125 mmol/L, but more specifically less than 120 mmol/L, which is typically the definition of “severe hyponatremia,” headache, yawning, lethargy, nausea, reversible ataxia, psychosis, seizures, and coma may occur as a result of cerebral edema. Neurologic symptoms in a hyponatremic patient call for immediate attention and treatment.

“Moderate hyponatremia” and “mild hyponatremia” are normally defined with ranges from 120 to 129 mmol/L and 130 to 134 mmol/L, respectively. In the setting of nonsevere disease, complications are less frequently manifested.

The catastrophic consequence of significant hyponatremia is cerebral edema so severe that there is increased intracerebral pressure, tentorial herniation, respiratory depression, and death. These events occur with rapid development of hyponatremia, usually in hospitalized postoperative patients receiving diuretics or hypotonic fluids.

Untreated severe hyponatremia has a mortality rate as high as 50%, and it is in this group where the complications from not only the hyponatremia itself but also its overcorrection are most commonly seen.

Cerebral Edema

The development of cerebral edema largely depends on the cerebral adaptation to hypotonicity. Decreases in extracellular osmolality cause movement of water into cells, increasing intracellular volume and causing tissue edema. The water channel AQP4 appears to play a key role in the movement of water across the blood-brain barrier. AQP4 knockout mice are protected from hyponatremic brain

Brain Volume Adaptation to Hyponatremia
Losses in response
to swelling
ECF hypo-osmolality

Acute hyponatremia

Acute Cerebral Edema

K^+, Na^+, H_2O↑
Edema

[↓Na^+]

Movement down
osmotic gradient
Losses in response
to swelling
ECF hypo-osmolality
[↓Na^+]

Persons at Risk for Neurologic
Complications With Hyponatremia

TABLE 9.4

Chronic hyponatremia

K^+, Na^+, H_2O↑
osmolytes

Brain adapted
to new osmotic
equilibrium

Fig. 9.7 Brain Volume Adaptation to Hyponatremia. During acute hyponatremia, water enters the brain to establish osmotic equilibrium with the ECF. As an acute adaptive change, NaCl exits from the brain interstitial space, followed by loss of potassium from cells several hours later. In chronic hyponatremia, the brain loses osmolytes, which lead to further water losses from the brain and an almost full restoration of brain water to levels marginally greater than baseline. (Modified from Verbalis J. The syndrome of inappropriate antidiuretic hormone secretion and other hypo-osmolar disorders. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 9th ed. Lippincott Williams & Wilkins; 2013:2012–2054.)

swelling, whereas animals overexpressing AQP4 have exaggerated brain swelling.21 Cellular edema within the fixed confines of the cranium increases intracranial pressure, leading to the neurologic syndrome. In most hyponatremic patients, mechanisms of volume regulation prevent cerebral edema.

Within 1 to 3 hours after hyponatremia develops, a decrease in cerebral extracellular volume occurs by movement of fluid into the cerebrospinal fluid, which is then shunted back into the systemic circulation. Loss of extracellular solutes Na^+ and Cl can occur as early as 30 minutes after the onset of hyponatremia (Fig. 9.7). If hyponatremia persists for longer than 3 hours, the brain adapts by losing cellular osmolytes, including K^+ and organic solutes, which tends to lower the osmolality of the brain, resulting in water losses. Thereafter, if hyponatremia persists, other organic osmolytes, such as phosphocreatine, myoinositol, and amino acids (e.g., glutamine, taurine), are lost, greatly decreasing cerebral swelling. As a result of these adaptations, most patients have minimal symptoms despite severe hyponatremia ($[Na^+] < 120$ mmol/L).

Certain patients are at increased risk for development of acute cerebral edema in the course of hyponatremia[12] (Table 9.4). Hospitalized premenstrual girls with hyponatremia are more symptomatic and more likely to have complications of therapy than postmenopausal women or men. This increased risk of cerebral edema is independent of the rate of development or the magnitude of hyponatremia. The best management of these patients is to avoid the administration of hypotonic fluids in the postoperative setting. Children are particularly vulnerable to the development of acute cerebral edema, perhaps because of a relatively high ratio of brain to skull volume.

Postoperative menstruating women
Elderly women taking thiazides
Children
Patients with polydipsia secondary to psychiatric disorders
Hypoxemic patients
Marathon runners

Osmotic Demyelination Syndrome (Central Pontine Myelinolysis)
Liver transplant recipients
Alcoholic patients
Malnourished patients
Hypokalemic patients
Burn patients
Elderly women taking thiazides
Hypoxemic patients
Severe hyponatremia ($[Na^+] < 105$ mmol/L)

Patient groups at risk for acute cerebral edema and central pontine myelinolysis (osmotic demyelination).
From Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Elsevier; 2008:337–352.

Osmotic Demyelination

Another neurologic syndrome can occur in hyponatremic patients as a complication of correction of hyponatremia. Osmotic demyelination most often affects the central pons and is therefore also termed central pontine myelinolysis (CPM). It occurs at all ages; Table 9.4 lists patients at highest risk. Osmotic demyelination syndrome is especially common after liver transplantation, with a reported incidence of 13% to 29% at autopsy. The risk of CPM is related to the severity and chronicity of the hyponatremia. It rarely occurs with serum $[Na^+]$ greater than 120 mmol/L or a short duration of hyponatremia (<48 hours).

The symptoms are biphasic. Initially, there is a generalized encephalopathy associated with rapid correction of serum $[Na^+]$. At 2 to 3 days after correction, the patient displays behavioral changes, cranial nerve palsies, and progressive weakness, culminating in quadriplegia and a “locked-in” syndrome. T2-weighted magnetic resonance imaging shows nonenhancing and hyper-intense pontine and extrapontine lesions. These lesions may not appear until 2 weeks after development, so a diagnosis of myelinolysis should not be excluded if the imaging is initially normal.

The pathogenesis of osmotic demyelination syndrome is uncertain; one suggestion is that sodium-coupled amino acid transporters (e.g., SNAT2) are downregulated by hypotonicity, thereby delaying the return of osmolytes to the brain, rendering it more sensitive to the correction of hyponatremia.22 Although [Na+] and [K+] return to normal in a few hours, osmotically active solutes require several days to return to normal levels. This temporary imbalance causes cerebral dehydration and can lead to a potential breakdown of the bloodbrain barrier. Astrocytes appear to be an early target of the disease, activating microglial cells resulting in the expression of proinflammatory cytokines.23

Although CPM was originally considered to be uniformly fatal, a substantial number of patients can have some neurologic recovery, even with severe symptoms at onset, suggesting there are reversible forms of osmotic demyelination.

Treatment of Hyponatremia

Symptoms and duration of hyponatremia determine treatment. Acutely hyponatremic patients (developing within 48 hours) are at great risk for permanent neurologic sequelae from cerebral edema if the hyponatremia remains uncorrected. Patients with chronic

Treatment of Patient With Symptomatic Hyponatremia
Symptomatic

Asymptomatic

Acute
Duration <48 h

Chronic
Duration >48 h
or unknown

Chronic
Rarely <48 h

Emergency correction needed
- Hypertonic saline (3%) at 1–2 mL/kg/h
- Coadministration of furosemide

Some immediate correction needed
- Hypertonic saline at 1–2 mL/kg/h (if seizures), otherwise isotonic saline
- Coadministration of furosemide (20 mg IV)
- Change to water restriction upon 10% increase of $[\mathrm{Na}^+]$, or if symptoms resolve

No
immediate
correction
needed

Perform frequent measurement of serum and urine electrolytes
Do not correct serum $[\mathrm{Na}^+]$ >12 mmol/L/24 h
Goal of correction 8 mmol/L in 24 h

Long-term management
- Identification and treatment of reversible causes
- Water restriction
- Demeclocyline 300–600 mg bid (allow 2 weeks for full effect) or
- Urea 15–60 g daily
- V2 receptor antagonist

Fig. 9.8 Algorithm for management of the patient with symptomatic (and “asymptomatic”) hyponatremia. IV, Intravenous. (Modified from Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Elsevier; 2008:337–352.)

hyponatremia are at risk for osmotic demyelination if the hyponatremia is corrected too rapidly.

monitored carefully for changes in neurologic and pulmonary status, and serum electrolytes should be checked every 2 hours.

Acute Symptomatic Hyponatremia

Chronic Symptomatic Hyponatremia

Acute symptomatic hyponatremia with seizures or other neurologic manifestations almost always develops in hospitalized patients receiving hypotonic fluids (Fig. 9.8). Treatment should be prompt because the risk of acute cerebral edema far exceeds the risk of osmotic demyelination.

The cell volume adaptive response, whereby the brain decreases its water content in acute hyponatremia, may be inhibited by female hormones, possibly explaining the large female predominance. A contribution of hypoxia also may be important, because when hypoxia is combined with hyponatremia in experimental animals, the volume adaptive response is abrogated, resulting in brain edema and increased mortality.24 Because the neurologic complications associated with acute symptomatic hyponatremia are devastating, patients require prompt treatment with 3% NaCl.12 A rapid increment of 4 to 6 mmol/L within the first 6 hours appears to be sufficient to reverse cerebral edema; correction to normal levels is unnecessary.25 Initial treatment should entail an infusion of 3% NaCl 1 to 2 mL/kg over 60 minutes or a 100 mL bolus over 10 minutes followed by two further doses to raise the plasma sodium to the specified level. Administration of a loop diuretic enhances free water excretion and hastens the normalization of serum [Na+]. If the patient presents with severe neurologic symptoms, such as seizures, obtundation, or coma, 3% NaCl may be infused at higher rates (4–6 mL/kg/hr). Patients should be

If the hyponatremia has taken more than 48 hours to evolve or if the duration is not known, correction should be cautious (see Fig. 9.8). Controversy exists as to whether it is the rate of correction or the magnitude of correction of hyponatremia that predisposes to neurologic complications. It is difficult to dissociate these two variables because a rapid correction rate is usually accompanied by a greater absolute magnitude of correction during a given time. Three important principles guide treatment:

1. Because cerebral water is increased by approximately 10% in severe chronic hyponatremia, the goal is to increase the serum Na+ level by 10%, or about 10 mmol/L, in the first 24 hours.
2. A correction rate of 1.0 to 1.5 mmol/L in any given hour should not be exceeded.
3. The goal of treatment is an increase of 6 to 10 mmol/L every 24 hours but do not increase by more than 12 mmol/L every 24 hours and 18 mmol/L per 48 hours.

Numerous formulas have been used to assess the expected changes in serum sodium with various infusions, but the one proposed by Adrogue and Madias is the most widely employed.26 Although helpful in the initial treatment phase, it does not take into account ongoing renal and extrarenal losses, thus commonly resulting in correction larger than those predicted by the formula. The risk for overcorrection

TABLE 9.5

Treatment of Patients With Chronic Asymptomatic Hyponatremia

Treatment

Mechanism of Action

Dose

Advantages

Limitations

Fluid restriction

Decreases availability of free
water

Variable

Effective and inexpensive; not
complicated

Noncompliance

Unrestricted water intake

Polyuria, narrow therapeutic
range, neurotoxicity
Neurotoxicity, polyuria,
photosensitivity, nephrotoxicity
Limited clinical experience

Pharmacologic Inhibition of Vasopressin Action
Lithium
Inhibits kidney’s response to
900–1200 mg/day
vasopressin
Demeclocycline
Inhibits kidney’s response to
300–600 mg twice daily
vasopressin
Antagonizes vasopressin
—
V2 receptor antagonist
action

Effective; unrestricted water
intake
Addresses underlying
mechanisms

Increased Solute (Salt) Intake
With furosemide
Increases free water clearance

Effective

Ototoxicity, K+ depletion

Effective; unrestricted water
intake

Polyuria, unpalatable,
gastrointestinal symptoms

With urea

Osmotic diuresis

Titrate to optimal dose;
coadminister 2–3 g NaCl
30–60 g/day

can be mitigated by the coadministration of DDAVP, thus preventing the excretion of a hypotonic urine.27 If the aforementioned noted limits are exceeded, relowering of serum sodium can be achieved by the infusion of dextrose and water and the administration of DDAVP.27

Chronic “Asymptomatic” Hyponatremia

Patients with chronic hyponatremia are often asymptomatic. However, epidemiologic data consistently show higher mortality rates than matched controls with normal serum sodium levels.28 Formal neurologic testing frequently reveals subtle impairments, including gait disturbances that reverse with correction of the hyponatremia. This results in an increased risk for falls and fractures.29 Therefore, even “asymptomatic” patients should be treated in an attempt to restore serum sodium to near-normal levels, particularly if they display gait instability or have sustained a fall. These patients should also be evaluated for hypothyroidism, adrenal insufficiency, and SIADH and should have their medications reviewed.

Fluid restriction. Stopping any medication associated with hyponatremia and fluid restriction is the cornerstone of therapy in patients with chronic asymptomatic hyponatremia (Table 9.5). Intake of all fluids should be restricted, and fructose-containing fluids should be avoided because fructose stimulates vasopressin release independently of osmolarity. This approach is usually successful if patients are compliant. It involves a calculation of the fluid restriction that will maintain a specific serum $[Na^+]$. The daily osmolar load (OL) and the minimal urinary osmolality $(U_{osm})_{min}$ determine a patient’s maximal urine volume (V_{max}), as follows:

$$V_{max} = \frac{OL}{(U_{osm})_{min}}$$

The value of $(U_{osm})_{min}$ is a function of the severity of the diluting disorder. In the absence of circulating vasopressin, it can be as low as 50 mOsm/kg H_2O. In a normal North American diet, the daily osmolar load is approximately 10 mOsm/Kg (700 mOsm for a 70-kg person). Assuming that a patient with SIADH has Uosm that cannot be lowered to less than 500 mOsm/kg H_2O, the same osmolar load of 700 mOsm allows only 1.4 L of urine to be excreted daily. Therefore, if the intake exceeds 1.4 L/day, the serum Na^+ concentration will decrease. Measurement of urine $[Na^+]$ and $[K^+]$ can guide the required degree of water restriction.30 Unless the ratio of urine $[Na^+]$ plus $[K^+]$ over serum $[Na^+]$ is 0.5 or less, the needed water restriction is not likely to be complied with. Likewise, a urinary osmolality greater than 500 mOsm/kg also predicts poor response to water restriction.1 In a report from a hyponatremia registry, the increment in serum sodium observed in patients placed on water restriction did not achieve statistical significance compared with their baseline admission serum sodium.31 If the diluting defect is so severe that fluid restriction to less than 1 L is necessary or if the serum Na+ concentration remains low (<130 mmol/L), an alternative approach to treatment should be considered, such as increasing solute excretion or pharmacologic inhibition of AVP.

Increase solute excretion. If the patient remains unresponsive to fluid restriction, solute intake can be increased to facilitate an obligatory increase in excretion of solute and free water. This can be achieved by increasing oral salt and protein intake in the diet to increase the Cosm of the urine. Loop diuretics combined with high sodium intake (2–3 g of additional salt) are effective in the management of hyponatremia.

A single dose of a loop diuretic (e.g., 40 mg furosemide) is usually sufficient but should be doubled if the diuresis induced in the first 8 hours is less than 60% of the total daily urine output.

In patients with SIADH, urine osmolality is fixed. In the collecting duct, urea is an effective osmole that increases water loss, thereby decreasing water retention and sodium loss. This permits improvement in hyponatremia and without altering urine concentration. The dose of urea is usually 30 to 60 g/day. The limitations are GI distress and unpalatability.

Pharmacologic inhibition of vasopressin. Vaptans are novel oral V2 receptor antagonists that block vasopressin binding to the collecting duct tubular epithelial cells and increase free water excretion without significantly altering electrolyte excretion.32–34 Vaptans are effective in the treatment of hyponatremia in euvolemic and hypervolemic patients.35 Conivaptan, a V2 and V1a antagonist, is the only vaptan available for IV use,34 but treatment should be limited to 4 days because it is a potent cytochrome P-450 3A4 (CYP3A4) inhibitor and should generally be avoided in patients at risk for variceal bleeding, given that the antagonism of V1 receptors would tend to vasodilate existing varices. Tolvaptan, an oral V2 antagonist, is available at doses of 15 to 60 mg/day. In the tolvaptan trials (TEMPO) in patients with polycystic kidney disease, higher doses were used and some cases of hepatic toxicity, as well as rhabdomyolysis, were encountered. This has led to a Food and Drug Administration (FDA) warning requiring careful monitoring of liver function tests and creatine kinase (CK, CPK) levels. Although the recommendation is to use tolvaptan for less than 30 days, some clinicians are treating chronically for patients with severe SIADH using the lowest dose that can maintain normal serum osmolality so long as liver function tests remain normal. Several newer V2 selective vaptans (mozavaptan, satavaptan, and lixivaptan) have been made available, but tolvaptan remains the most extensively studied.

An alternative pharmacologic treatment is demeclocycline, 600 to 1200 mg/day given 1 to 2 hours after meals; calcium-, aluminum-, and magnesium-containing antacids should be avoided. Onset of action is usually 3 to 6 days after initiation of treatment. Dose should be titrated to the minimum that keeps serum [Na+] within the desired range with unrestricted water intake. Demeclocycline can cause photosensitivity or (in children) tooth or bone abnormalities. Polyuria leads to noncompliance, and nephrotoxicity may occur, especially in patients with underlying liver disease. Lithium was previously used to antagonize AVP action but has been superseded by the vaptans and demeclocycline.

Hypovolemic Hyponatremia

When thiazides are prescribed, especially in elderly women, serum [Na+] should be monitored and water intake restricted. If hyponatremia develops, the thiazide should be discontinued.

Neurologic syndromes directly related to hyponatremia are unusual in hypovolemic hyponatremia because loss of Na+ and water limits any osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids interrupts the nonosmotic release of AVP. AVP antagonists should not be used in these patients.35

Hypervolemic Hyponatremia

Congestive heart failure. In patients with CHF, sodium and water restriction is critical. Treatment with a combination of angiotensinconverting enzyme (ACE) inhibitors and loop diuretics increase cardiac output, thereby decreasing the neurohumoral mediators that impair water excretion. Loop diuretics also diminish the action of AVP on the collecting tubules. Thiazides should be avoided because they impair urinary dilution and may worsen hyponatremia. V2 antagonists increase serum [Na+] in patients with heart failure, and correction of serum [Na+] is associated with better long-term outcomes.35 However, in the much larger randomized controlled EVEREST trial in patients with decompensated heart failure, tolvaptan did not affect long-term clinical outcomes, but some improvement in secondary outcomes, such as urine output, dyspnea, and edema, were noted. In principle, a vaptan with V1 antagonist activity could have additional benefit in the CHF patient, but this remains unproven.

Cirrhosis. In patients with cirrhosis, water and sodium restriction is the mainstay of therapy. Loop diuretics increase Cwater. V2 antagonists increase water excretion and increase serum [Na+].35 The response to vaptans in cirrhosis is more attenuated than in patients with SIADH or CHF, which suggests that vasopressin-independent mechanisms may also contribute to the hyponatremia. The administration of V2 antagonists to patients with liver failure is not associated with decrements in blood pressure. Combined V1 and V2 antagonists (e.g., conivaptan) should not be used in these patients, and in view of the potential liver toxicity, the use of tolvaptan should probably be limited to management of serum hyponatremia before liver transplant.35

HYPERNATREMIC DISORDERS

Hypernatremia is defined as serum [Na+] greater than 145 mmol/L and reflects serum hyperosmolarity. The renal concentrating mechanism provides the first defense mechanism against water depletion and hyperosmolarity. The components of the normal concentrating mechanism are shown in Fig. 9.9. Disorders of urine concentration may result from decreased delivery of solute (with decreasing GFR) or the inability to generate interstitial hypertonicity because of decreased Na+ and Cl− reabsorption in the ascending limb of Henle’s loop (loop diuretics), decreased medullary urea accumulation (poor dietary intake), or alterations in medullary blood flow. Hypernatremia may also result from failure to release or respond to vasopressin. Thirst is the first and most important defense mechanism in preventing hypernatremia.

Etiology and Classification of Hypernatremia

Patients with hypernatremia fall into three broad categories based on volume status.13 A diagnostic algorithm is helpful in the evaluation of these patients (Fig. 9.10).

Hypovolemia: Hypernatremia Associated With Low Total Body Sodium

Patients with hypovolemic hypernatremia sustain losses of both Na+ and water but with a relatively greater loss of water. On physical examination, there are signs of hypovolemia, including orthostatic hypotension, tachycardia, flat neck veins, poor skin turgor, and altered mental status. Patients generally have hypotonic water loss from the kidneys or the GI tract; in the GI tract, the urine [Na+] will be low.

Hypervolemia: Hypernatremia Associated With Increased Total Body Sodium

Hypernatremia with increased total body Na+ is the least common form of hypernatremia. It results from the administration of hypertonic solutions such as 3% NaCl and NaHCO3 for the treatment of metabolic acidosis, hyperkalemia, and cardiorespiratory arrest. It may also result from inadvertent dialysis against a dialysate with a high Na+ concentration or from consumption of salt tablets. Therapeutic hypernatremia is also becoming common as hypertonic saline solutions have emerged as an alternative to mannitol for treatment of increased intracranial pressure.25 Hypernatremia is also increasingly recognized in hypoalbuminemic hospitalized patients with kidney failure who are edematous and unable to concentrate their urine.

Euvolemia: Hypernatremia Associated With Normal Body Sodium

Most patients with hypernatremia secondary to water loss appear euvolemic with normal total body Na+ because loss of water without Na+ does not lead to overt volume contraction unless severe. Water loss need not result in hypernatremia unless unaccompanied by water intake. Because hypodipsia is uncommon, hypernatremia usually develops only in those who have no access to water and in very young children and old persons, who may have an altered perception of thirst. Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states and is associated with a high urine osmolality because the osmoreceptor-AVP renal response is intact. The urine Na+ concentration varies with intake. Renal water loss leading to euvolemic hypernatremia results either from a defect in AVP production or release (central diabetes insipidus) or from a failure of the collecting duct to respond to the hormone (nephrogenic diabetes insipidus). Defense against the development of hyperosmolality requires the appropriate stimulation of thirst and the patient’s ability to respond by drinking water.

Polyuric disorders can result from either an increase in Cosm or an increase in Cwater. An increase in Cosm occurs with loop diuretic use, renal salt wasting, excess salt ingestion, vomiting (bicarbonaturia), alkali administration, and administration of mannitol (as a diuretic,

Mechanisms of Urine Concentration
Na+/Cl
Diminished by
age, renal disease

Na+/Cl

Glomerular
filtration

Distal convoluted tubule
Proximal
tubule

Na+/Cl

Decreased vasopressin
release/action: nephrogenic
or central diabetes insipidus

H_2O
Thick
ascending
limb
Na+/Cl
H_2O

Na+/Cl
Na+/Cl

Vasopressin
H_2O

H_2O

H_2O

H_2O

Collecting duct

Na+/Cl
Generation of
medullary
hypertonicity by
normal functioning
of thick ascending
limb, urea delivery,
normal medullary
blood flow

H_2O
Delivery of H_2O determined by
glomerular filtration rate,
proximal tubule water, and solute
reabsorption
H_2O

Membranes
permeable
to urea

Urea

Loop of
Henle
Na+/Cl reabsorption reduced
by loop diuretics, osmotic diuretics,
interstitial renal disease

Decreased medullary
urea movement
into the medulla (water
diuresis, decreased
dietary protein intake)
reduces urea
accumulation and
interstitial osmolality

Fig. 9.9 Urine-Concentrating Mechanisms. Determinants of normal urine concentration and disorders causing hypernatremia. (Modified from Cogan MC. Normal water homeostasis. In: Cogan MC, ed. Fluid and Electrolytes. Lange; 1991:98–106.)

Diagnostic Approach in Hypernatremia
Hypernatremia
Assess volume
status

Hypovolemia
Total body water ↓↓
Total body Na+ ↓
Urinary (Na+)
≥20 mmol/L
Renal losses
Osmotic or loop diuretic
Postobstruction
Intrinsic kidney disease

Urinary (Na+)
<20 mmol/L
Extrarenal losses
Excess sweating
Burns
Diarrhea
Fistulas

Euvolemia (no edema)
Total body water ↓
No change in total body Na+
Urinary (Na+)
variable
Kidney losses
Diabetes insipidus
Hypodipsia

Extrarenal losses
Insensible losses:
respiratory, dermal

Hypervolemia
Total body water ↑
Total body Na+ ↑↑
Urinary (Na+)
>20 mmol/L
Sodium gains
Primary

hyperaldosteronism
Cushing syndrome
Hypertonic dialysis
Hypertonic $NaHCO_3$
NaCl tablets

Fig. 9.10 Algorithm for diagnostic assessment of the patient with hypernatremia. (Modified from Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady HR, Wilcox CS, eds. Therapy in Nephrology and Hypertension. Saunders; 1999:257–269.)

TABLE 9.6

Interpretation of Water Deprivation Test

Condition	Urinary Osmolality With Water Deprivation (mOsm/kg H2O)	Serum Vasopressin After Dehydration (pg/mL)	Increase in Urinary Osmolality With Exogenous Vasopressin or Desmopressin
Normal	>800	>2	Little or no increase
Complete central diabetes insipidus	<300	Undetectable	Substantially increased
Partial central diabetes insipidus	300–800	<1.5	Increase of >10% of urinary osmolality after water deprivation
Nephrogenic diabetes insipidus	<300–500	>5	Little or no increase
Primary polydipsia	>500	<5	Little or no increase

From Lanese D, Teitelbaum I. Hypernatremia. In: Jacobson HR, Striker GE, Klahr S, eds. The Principals and Practice of Nephrology. 2nd ed. Mosby; 1995:893–898.

for bladder lavage, or for the treatment of cerebral edema). An increase in Cwater occurs with excess ingestion of water (psychogenic polydipsia) or in abnormalities of the renal concentrating mechanism (DI).

Diabetes Insipidus

DI is characterized by polyuria and polydipsia and is caused by defects in AVP action. Patients with central and nephrogenic DI and primary polydipsia present with polyuria and polydipsia. These entities can be differentiated by clinical evaluation, with measurements of AVP levels and response to a water deprivation test, followed by AVP administration (Table 9.6).36

WATER DEPRIVATION TEST

Test procedure: Water intake is restricted until the patient loses 3% to 5% of body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure patient does not become excessively dehydrated.) Aqueous vasopressin is given as 5 units subcutaneously, and urinary osmolality is measured after 60 minutes. Expected responses are outlined in Table 9.6

Central diabetes insipidus

Clinical features. Central DI usually has an abrupt onset. Patients have a constant need to drink, have a predilection for cold water, and typically have nocturia. By contrast, the compulsive water drinker may give a vague history of the onset and has large variations in water intake and urine output. Nocturia is unusual in compulsive water drinkers. A serum osmolality of more than 295 mOsm/kg H2O suggests central DI, and less than 270 mOsm/kg H2O suggests compulsive water drinking.

Causes. Central DI is caused by infection, tumors, granuloma, and trauma affecting the CNS in 50% of patients; in the other 50% it is idiopathic (Box 9.2). In a survey of 79 children and young adults, central DI was idiopathic in half the patients. The other half had tumors or Langerhans cell histiocytosis; these patients had an 80% risk for development of anterior pituitary hormone deficiency compared with the patients with idiopathic disease.5

Autosomal dominant DI is caused by point mutations in a precursor gene for vasopressin that cause “misfolding” of the provasopressin peptide, preventing its release from the hypothalamic and posterior pituitary neurons.5 Patients present with a mild polyuria and polydipsia in the first year of life. These children have normal physical and mental development. There is a rare autosomal recessive central DI associated with diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome).37 DI is usually partial with gradual onset in Wolfram syndrome. The defect resulting in Wolfram syndrome is linked to the WFS1 gene, which encodes an endoplasmic reticulum membrane-embedded protein called wolframin that is expressed in pancreatic beta cells and neurons.

BOX 9.2

Insipidus

Causes of Central Diabetes

Congenital Causes
- Autosomal dominant
- Autosomal recessive

Acquired Causes
- Posttraumatic
- Iatrogenic (postsurgical)
- Tumors (metastatic from breast, craniopharyngioma, pinealoma)
- Histiocytosis
- Granuloma (tuberculosis, sarcoid)
- Aneurysm
- Meningitis
- Encephalitis
- Guillain-Barré syndrome
- Drugs
- Idiopathic

Entries in italics are the most common causes.

A rare clinical entity involving the combination of central DI and deficient thirst has been reported in approximately 100 patients. When vasopressin secretion and thirst are both impaired, affected patients are vulnerable to recurrent episodes of hypernatremia. Formerly called essential hypernatremia, the disorder is now called central DI with deficient thirst, or adipsic DI.38

Differential diagnosis. Under basal conditions, AVP levels are unhelpful because there is a significant overlap among the polyuric disorders. Measurement of circulating AVP or copeptin levels after a water deprivation test is more useful (see Table 9.6).

Treatment. Central DI is treated with hormone replacement or pharmacologic agents (Table 9.7). In acute settings, when renal water losses are extensive, DDAVP is the treatment of choice. For chronic central DI, desmopressin acetate is the agent of choice. It has a long half-life and none of the significant vasoconstrictive effects of aqueous AVP. DDAVP is administered at the dose of 10 to 20 μg intranasally every 12 to 24 hours. It is tolerated well, safe to use in pregnancy, and resistant to degradation by circulating vasopressinase. Oral DDAVP (0.1–0.8 mg every 12 hours) is available as second-line therapy. In patients with partial DI, in addition to DDAVP itself, agents that potentiate the release of AVP may be used, including chlorpropamide, clofibrate, and carbamazepine.

Congenital nephrogenic diabetes insipidus. Inherited forms of DI are caused by mutations in genes for V2-receptors or AQP2.[5] These entities are discussed further in Chapter 49. Urine volumes are typically very high, and there is a risk for severe hypernatremia if patients do not have free access to water. Thus, patients must drink enough water to match urine output and prevent dehydration.

Therapy for congenital nephrogenic DI is only partially effective and includes a thiazide diuretic, a very low salt diet, and indomethacin. Sildenafil improved urine concentration in a patient with congenital nephrogenic DI.[39] Simvastatin induces an increase in urine AQP2 and osmolality in hypercholesterolemic patients, suggesting that it may be useful in congenital nephrogenic DI.[39] Metformin results in a sustained increase in urine osmolality in rodent models of nephrogenic diabetes insipidus, but it has not been tested in patients.[39]

Acquired nephrogenic diabetes insipidus. Acquired nephrogenic DI is more common than congenital nephrogenic DI but rarely as severe. In patients with acquired nephrogenic DI, the ability to elaborate a maximal concentration of urine is impaired, but urine-concentrating mechanisms are partially preserved. For this reason, urine volumes are less than 3 to 4 L/day, which contrasts with the much higher volumes seen in patients with congenital or central DI or compulsive water drinking. Table 9.8 outlines the causes and mechanisms of acquired nephrogenic DI.

Chronic kidney disease. A defect in urine-concentrating ability may develop in patients with CKD of any etiology, but this defect is most prominent in tubulointerstitial diseases, particularly medullary cystic disease. (A complete discussion on the mechanisms of abnormalities in urine concentration and dilution in CKD can be

TABLE 9.7

Insipidus

Treatment of Central Diabetes

Disease

Drug

Dose

Interval (hr)

Complete central diabetes insipidus

Partial central diabetes insipidus

Desmopressin (DDAVP)

Desmopressin (DDAVP)

Desmopressin (DDAVP)

Aqueous vasopressin

Chlorpropamide
Clofibrate
Carbamazepine

10–20 μg intranasally

12–24

0.1–0.8 mg orally

Every 12

10–20 μg intranasally

12–24

5–10 U
subcutaneously
250–500 mg
500 mg
400–600 mg

4–6

TABLE 9.8

24
6 or 8
24

found in Berl and Combs[13]). Disruption of inner medullary structures and diminished medullary concentration are thought to play a role; alterations in V2 receptor and AQP2 expression also contribute (see Fig. 9.6). To achieve daily osmolar clearance, patients should be advised to maintain a fluid intake that matches their urine volume.

Electrolyte disorders. Hypokalemia causes a reversible abnormality in urine-concentrating ability. Hypokalemia stimulates water intake and reduces interstitial tonicity, which relates to the decreased Na^+-Cl reabsorption in the TAL. Hypokalemia resulting from diarrhea, chronic diuretic use, and primary aldosteronism also decreases intracellular cyclic adenosine monophosphate accumulation and causes a reduction in AVP-sensitive AQP2 expression (see Fig. 9.6). Hypercalcemia also impairs urine-concentrating ability, resulting in mild polydipsia. The pathophysiologic mechanism is multifactorial and includes a reduction in medullary interstitial tonicity caused by decreased vasopressin-stimulated adenylyl cyclase in the TAL and a defect in adenylyl cyclase activity with decreased AQP2 expression in the collecting duct, mediated by the calcium-sensing receptor.[7]

Pharmacologic agents. Lithium is the most common cause of nephrogenic DI, occurring in up to 50% of patients receiving longterm lithium therapy. Lithium causes downregulation of AQP2 in the collecting duct; experimentally, it also increases cyclooxygenase-2 (COX-2) expression and urinary prostaglandins, which may contribute to the polyuria.[7] The concentrating defect of lithium may persist even when the drug is discontinued. The epithelial sodium channel (ENaC) is the entrance pathway for lithium into collecting duct principal cells. Amiloride inhibits lithium uptake through ENaC and has been used clinically to treat nephrogenic DI caused by lithium. Aldosterone administration dramatically increased urine production in experimental nephrogenic DI caused by lithium (an effect associated with decreased expression of AQP2 on luminal membranes of collecting duct), whereas administration of the mineralocorticoid receptor blocker spironolactone decreased urine output and increased AQP2 expression.[7] Clopidogrel, P2Y12-R purinergic receptor antagonist, ameliorates lithium-induced NDI in mice by increasing water and sodium reabsorption in the collecting duct.39 It is not yet known if spironolactone or clopidogrel will be a useful treatment for lithium-induced nephrogenic DI in patients.

Other drugs impairing urine-concentrating ability include amphotericin, foscarnet, and demeclocycline, which reduce renal medullary adenylyl cyclase activity, thereby decreasing the effect of AVP on the collecting ducts.

Sickle cell anemia. Patients with sickle cell disease and trait often have a urine-concentrating defect. In the hypertonic medullary interstitium, the “sickled” red cells cause occlusion of the vasa recta and papillary damage. Although initially reversible, medullary infarcts

Acquired Nephrogenic Diabetes Insipidus: Causes and Mechanisms

Disease State	Defect in Medullary Interstitial Tonicity	Defect in cAMP Generation	Downregulation of Aquaporin 2
Chronic kidney disease	Yes	Yes	Yes
Hypokalemia	Yes	Yes	Yes
Hypercalcemia	Yes	Yes	—
Sickle cell disease	Yes	—	—
Protein malnutrition	Yes	—	Yes
Demeclocycline therapy	—	Yes	—
Lithium therapy	—	Yes	Yes
Pregnancy	—	—	

—

cAMP, Cyclic adenosine monophosphate.

Other
Downregulation of V2 receptor
message
—
—
—
—
—
—
Placental secretion of vasopressinase

Management of Hypernatremia

Hypernatremia

Assess volume status

Hypovolemia

Euvolemia

Hypervolemia

Correction of volume deficit
- Administer isotonic saline until hypovolemia improves
- Treatment of the cause of losses (insulin, relief of obstruction, removal of osmotic diuretics, etc.)

Correction of water deficit
- Calculate water deficit
- Administer 0.45% saline, 5% dextrose, or oral water to replace the deficit and ongoing losses
- In central diabetes insipidus (DI) with severe losses, aqueous vasopressin (pitressin) 5 units subcutaneously q6h
- Follow serum (Na^+) carefully to avoid water intoxication

Removal of Na^+
- Discontinue offending agents
- Furosemide
- Hemodialysis as needed for kidney failure

Correction of water deficit
- Calculate water deficit
- Administer 0.45% saline, 5% dextrose, or oral water to replace the deficit and ongoing losses

Long-term therapy
- Central DI (see Table 9.7)
- Nephrogenic DI: Remove offending drugs, low Na^+ diet, thiazide diuretics, amiloride for lithium-induced DI, correction of K^+ and Ca^{2+}

Fig. 9.11 Algorithm for management of the patient with hypernatremia. (Modified from Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Saunders; 2008:337–352.)

occur with sickle cell disease in the second to third decade of life, and even with sickle cell trait by the fourth to fifth decade, and the concentrating defects become irreversible.

Dietary abnormalities. Extensive water intake or a marked decrease in salt and protein intake leads to impairment of maximal urine-concentrating ability through a reduction in medullary interstitial tonicity. On a low-protein diet with excessive water intake, there is a decrease in vasopressin-stimulated osmotic water permeability that is reversed with feeding.

Gestational diabetes insipidus. In gestational DI, there is an increase in circulating vasopressinase, which is produced by the placenta. Patients are typically unresponsive to AVP but respond to desmopressin, which is resistant to vasopressinase.

Clinical Manifestations of Hypernatremia

Certain patients are at increased risk for development of severe hypernatremia (Box 9.3). Signs and symptoms mostly relate to the CNS and include altered mental status, lethargy, irritability, restlessness, seizures (usually in children), muscle twitching, hyperreflexia, and spasticity. Fever, nausea or vomiting, labored breathing, and intense thirst can also occur. In children, mortality of acute hypernatremia ranges from 10% to 70%; as many as two-thirds of survivors have neurologic sequelae. In contrast, mortality in patients with chronic hypernatremia is 10%. In adults, serum [Na+] greater than 160 mmol/L is associated with 75% mortality, although this may reflect associated comorbidities rather than hypernatremia. Chronic hypernatremia is independently associated with higher mortality in patients with CKD.[40] Patients presenting to the intensive care unit with a serum [Na+] greater than 155 mmol/L have a significantly increased risk of mortality, with an odds ratio of 3.64.[41] Thus, both acute and chronic hypernatremia are associated with an increased risk of mortality.

Patient Groups at Risk for Development of Severe Hypernatremia

BOX 9.3

- Elderly patients
- Infants
- Hospitalized patients
- Hypertonic infusions
- Tube feedings
- Osmotic diuretics
- Lactulose
- Mechanical ventilation
- High-risk patient groups
- Altered mental status
- Uncontrolled diabetes mellitus
- Underlying polyuric disorders

From Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Philadelphia: Elsevier; 2008:337–352.

Treatment of Hypernatremia

Hypernatremia occurs in predictable clinical settings, allowing opportunities for prevention. Elderly and hospitalized patients are at high risk because of impaired thirst and inability to access free water independently.42 Certain clinical situations, such as recovery from AKI, catabolic states, therapy with hypertonic solutions, uncontrolled diabetes, and burns, should prompt close attention to serum sodium concentration and increased administration of free water.

Hypernatremia always reflects a hyperosmolar state. The primary goal in the treatment of these patients is the restoration of serum tonicity. Fig. 9.11 outlines specific management options.12 Because restoration of volume takes precedence over restoration of tonicity, in hypovolemic hypernatremic patients, sodium-containing solutions should be used until euvolemia is achieved. Thereafter, dextrose in water or oral water intake should be given to decrease serum sodium concentration.

The rapidity with which hypernatremia should be corrected is controversial. Some animal studies and case series in pediatric patients suggest that a correction rate of more than 0.5 mmol/L/hr in [Na^+] can cause seizures. Cerebral edema also can be caused by rapid correction of hypernatremia by the net movement of water into the brain. Most clinicians believe that even in adults, correction should be achieved during 48 hours at a rate no greater than 2 mmol/L/hr, but the current maximum rate for correction in adults has not been definitively established because there are no reports of cerebral edema with rapid correction in this population. One study in a population of chronically hypernatremic patients showed that there was no difference in 30-day mortality between rapid correction (>12 mmol/L/day) versus less than 12 mmol/L/day, so a more rapid correction could potentially be a safe option.43

SELF-ASSESSMENT QUESTIONS

1. A 78-year-old woman sustained a stroke and is receiving enteral nutrition by nasoduodenal tube at a nursing home. She is transferred to the hospital with altered mental status. Nursing home staff reported that she had plentiful urine output 2 days before transfer. Laboratory data on hospital arrival reveal serum sodium of 165 mmol/L, blood urea nitrogen (BUN) 60 mg/dL, and creatinine 1.6 mg/dL; all were normal 6 weeks earlier. Additional laboratory data include serum osmolality of 341 mOsm/kg and urine osmolality 690 mOsm/kg, urine sodium 7 mmol/L, and urine potassium 32 mmol/L. The most likely explanation for this patient’s polyuria and hypernatremia and the most appropriate confirmatory test are:

A. Nephrogenic diabetes insipidus and measurement of ADH.
B. Central diabetes insipidus and measurement of ADH.
C. Lithium toxicity and measurement of serum lithium level.
D. Increased solute load and measurement of electrolyte-free water clearance.

2. A 71-year-old woman with a history of coronary artery disease and mild hypertension is seen in the clinic. She is free of symptoms. Her medications include lisinopril (20 mg/day), occasional zolpidem tartrate (Ambien), and multivitamins. Her blood pressure is 140/95 mm Hg, weight 62 kg, and skin turgor normal. Examination reveals no evidence of edema or ascites. Laboratory results are as follows:

- Serum creatinine: 0.9 mg/dL.
- Sodium: 120 mmol/L.
- Potassium: 3.9 mmol/L.
- Chloride: 95 mmol/L.
- HCO_3 : 22 mmol/L.
- Uosm: 686 mOsm/kg.
- UNa: 127 mmol/L.
- Normal thyroid and adrenal function.
- Chest radiograph unremarkable.

Which of the following statements explains this patient’s status?

A. Patient is unlikely to have improved water excretion because she is not taking a thiazide diuretic.
B. Patient probably has idiopathic SIADH.
C. The hyponatremia is probably a consequence of poor solute intake.
D. Patient’s hyponatremia is caused by age-related decrements in vasopressin metabolism.
3. A 74-year-old man with a history of heart failure is admitted with increasing shortness of breath. He is treated with lisinopril 20 mg/day, hydrochlorothiazide (HCTZ) 50 mg/day, and digoxin 0.25 mg/day. Examination reveals blood pressure of 145/90 mm Hg, pulse rate 88/min, respiratory rate 24/min, and O_2 saturation 90% on 2 L. His electrolytes are normal. The patient is prescribed a low-sodium restricted diet, furosemide 40 mg twice daily, and fluid restriction. In the next 24 hours, he excretes 2.5 L of urine. Laboratory results are as follows:
✓ •✓ Serum creatinine: 1.8 mg/dL.
✓ •✓ BUN: 25 mg/dL.
✓ •✓ Sodium: 147 mmol/L.
✓ •✓ Potassium: 3.7 mmol/L.
✓ •✓ HCO_3 : 26 mmol/L.
✓ •✓ Chloride: 120 mmol/L.
✓ •✓ Uosm: 392 mOsm/kg.
✓ •✓ UNa: 59 mmol/L.
✓ •✓ UK: 32 mmol/L.
Which of the following treatment regimens is most likely to prevent worsening of this patient’s hypernatremia?
A. 1 mL of half-normal per milliliter of urine.
B. 0.5 mL of 5% dextrose in water per milliliter of urine.
C. 0.5 mL of normal saline per milliliter of urine.
D. 0.5 mL of normal saline per milliliter of urine.

REFERENCES

1. Verbalis J. The syndrome of inappropriate antidiuretic hormone secretion and other hypo-osmolar disorders. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:2012–2054.
2. Narins RG, Krishna GC. Disorders of water balance. In: Stein JH, ed. Internal Medicine. Boston: Little, Brown; 1987:794.
3. Nielsen S, Knepper MA, Kwon TH. Regulation of water balance. Urine concentration and dilution. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:96–123.
4. Cohen DM. The transient receptor potential vanilloid-responsive 1 and 4 cation channels: role in neuronal osmosensing and renal physiology. Curr Opin Nephrol Hypertens. 2007;16:451–458.
5. Bichet D. Nephrogenic and central diabetes insipidus. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:2055–2081.
6. Andres-Hernando A, Jensen T, Kuwabara M, et al. Vasopressin mediates fructose-induced metabolic syndrome by activating the V1b receptor. JCI Insight. 2021;6.
7. Brown D, Fenton RA. The cell biology of vasopressin action. In: Skorecki KL, Chertow GM, Marsden PA, Taal MW, Yu AP, eds. The Kidney. 10th ed. Philadelphia: Elsevier; 2016:281–302.
8. Klein JD, Sands JM. Urea transport and clinical potential of urearetics. Curr Opin Nephrol Hypertens. 2016;25:444–451.
9. Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady HR, Wilcox CS, eds. Therapy in Nephrology and Hypertension. Philadelphia: Saunders; 1999:257–269.
10. Nguyen MK, Ornekian V, Butch AW, Kurtz I. A new method for determining plasma water content: application in pseudohyponatremia. Am J Physiol Renal Physiol. 2007;292:F1652--F1656.
11. Cogan MC. Normal water homeostasis. In: Cogan MC, ed. Fluid and Electrolytes. Norwalk, CT: Lange; 1991:98–106.
12. Thurman JM, Berl T. Therapy of dysnatremic disorders. In: Wilcox CS, ed. Therapy in Nephrology and Hypertension. 3rd ed. Philadelphia: Saunders; 2008:337–352.
13. Berl T, Combs C. Water metabolism in chronic kidney disease. In: Kimmel P, Rosenberg M, eds. Chronic Renal Disease. San Diego: Elsevier; 2015:367–374.
14. Liamis G, Elisaf M. Hyponatremia induced by drugs. In: Simon E, ed. Hyponatremia. Springer; 2013:111–126.
15. Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. Ann Int Med. 1997;126:20–25.
16. Almond CS, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the boston marathon. N Engl J Med. 2005;352:1550–1556.
17. Daphnis E, Stylianou K, Alexandrakis M, et al. Acute renal failure, translocational hyponatremia and hyperkalemia following intravenous immunoglobulin therapy. Nephron Clin Pract. 2007;106:c143–c148.
18. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Int Med J. 2010;40:574–580.
19. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007;356:2064–2072.
20. Fenske WK, Christ-Crain M, Horning A, et al. A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. J Am Soc Nephrol. 2014;25:2376–2383.
21. Verkman AS, Anderson MO, Papadopoulos MC. Aquaporins: important but elusive drug targets. Nat Rev Drug Disc. 2014;13:259–277.

22. Franchi-Gazzola R, Dall’Asta V, Sala R, et al. The role of the neutral amino acid transporter SNAT2 in cell volume regulation. Acta Physiol (Oxford, England). 2006;187:273–283.
23. Gankam Kengne F, Nicaise C, Soupart A, et al. Astrocytes are an

early target in osmotic demyelination syndrome. J Am Soc Nephrol. 2011;22:1834–1845.
24. Vexler ZS, Ayus JC, Roberts TP, Fraser CL, Kucharczyk J, Arieff AI. Hypoxic and ischemic hypoxia exacerbate brain injury associated with metabolic encephalopathy in laboratory animals. J Clin Invest. 1994;93:256–264.
25. Koenig MA, Bryan M, Lewin 3rd JL, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70:1023–1029.
26. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342:1581–1589.
27. Perianayagam A, Sterns RH, Silver SM, et al. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. CJASN. 2008;3:331–336.
28. Rondon-Berrios H, Berl T. Mild chronic hyponatremia in the ambulatory setting: significance and management. CJASN. 2015;10:2268–2278.
29. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM Monthly J Assoc Phys. 2008;101:583–588.
30. Furst H, Hallows KR, Post J, et al. The urine/plasma electrolyte ratio: a predictive guide to water restriction. Am J Med Sci. 2000;319:240–244.
31. Greenberg A, Verbalis JG, Amin AN, et al. Current treatment practice and outcomes. Report of the hyponatremia registry. Kidney Int. 2015;88:167–177.
32. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099–2112.
33. Jovanovich AJ, Berl T. Where vaptans do and do not fit in the treatment of hyponatremia. Kidney Int. 2013;83:563–567.
34. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol. 2007;27:447–457.
35. Berl T. Vasopressin antagonists. N Engl J Med. 2015;372:2207–2216.
36. Lanese D, Teitelbaum I. Hypernatremia. In: Jacobson HR, Striker GE, Klahr S, eds. The Principals and Practice of Nephrology. 2nd ed. St. Louis: Mosby; 1995:893–898.
37. Smith CJ, Crock PA, King BR, Meldrum CJ, Scott RJ. Phenotype-genotype correlations in a series of wolfram syndrome families. Diabet Care. 2004;27:2003–2009.
38. Eisenberg Y, Frohman LA. Adipsic diabetes insipidus: a review. Endocr Pract. 2016;22:76–83.
39. Sands JM, Klein JD. Physiological insights into novel therapies for nephrogenic diabetes insipidus. Am J Physiol Renal Physiol. 2016;311. F1149–F52.
40. Kovesdy CP, Lott EH, Lu JL, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation. 2012;125:677–684.
41. Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. Inten Care Med. 2010;36:304–311.
42. Polderman KH, Schreuder WO, Strack van Schijndel RJ, Thijs LG. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med. 1999;27:1105–1108.
43. Chauhan K, Pattharanitima P, Patel N, et al. Rate of correction of hypernatremia and health outcomes in critically ill patients. CJASN. 2019;14:656–663.

10

Disorders of Potassium Metabolism

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INTRODUCTION

Potassium disorders are some of the most frequently encountered fluid and electrolyte abnormalities in clinical medicine. Patients with disorders of potassium metabolism may be asymptomatic, or they may have symptoms ranging from mild weakness to sudden death. An abnormal serum potassium level, once verified, should be promptly addressed, but inappropriate treatment can worsen symptoms and even lead to death.

NORMAL PHYSIOLOGY OF POTASSIUM METABOLISM

Potassium Intake

Potassium is necessary for essentially all cellular functions, is present in most foods, and is excreted primarily by the kidney. The typical Western diet provides about 70 mmol of potassium daily, even though the recommended intake for people with normal renal function is closer to 120 mmol per day.1 The gastrointestinal (GI) tract efficiently absorbs potassium, and total dietary potassium intake depends on the composition of the diet. Table 10.1 shows the potassium content of several foods high in potassium.

Potassium Distribution

After absorption from the GI tract, potassium distributes rapidly into the extracellular fluid (ECF) and intracellular fluid (ICF) compartments. Cellular potassium uptake is rapid and limits the magnitude of changes in serum potassium concentration. During potassium deficiency, shift of potassium from intracellular to extracellular compartments limits the change in extracellular potassium concentration.

Most body potassium is intracellular, with only 1% to 2% in the ECF. Potassium is the major intracellular cation, with cytosolic K^+ concentrations about 100 to 120 mmol/L. Total intracellular K^+ content is 3000 to 3500 mmol in healthy adults and is found primarily in muscle (70%), with a lesser amount in bone, red blood cells, liver, and skin (Table 10.2). The electrogenic sodium pump, Na^+,K^+-ATPase, is the primary effector of this asymmetric potassium distribution: It transports two potassium ions into cells and extrudes three sodium ions, which results in high intracellular potassium concentration (high $[K^+_i]$) and low intracellular sodium concentration (low $[Na^+_i]$). Potassium-selective ion channels are the predominant determinant of the resting membrane potential. Therefore, the intracellular/extracellular $[K^+]$ ratio largely determines the resting cell membrane potential and the intracellular electronegativity. Maintenance of this ratio and membrane potential is critical for normal nerve conduction and muscular contraction.

Under some conditions, the normal distribution of potassium between the extracellular and intracellular pools is altered (Fig. 10.1).

Plasma osmolality, several hormones, and exercise are frequent causes of potassium shifts. Because the amount of extracellular K^+ relative to intracellular K^+ is low, modest net movement of K^+ into or out of the extracellular pool can result in substantial changes in extracellular K^+ concentration.

Several hormones, most prominently catecholamines, insulin, and aldosterone, have important roles in regulating serum K^+. The effect of catecholamines differs depending on which adrenergic receptor subtype they activate. Activation of β_2-adrenergic receptors stimulates Na^+,K^+-ATPase, inducing cellular potassium uptake and decreasing serum K^+, whereas α_1-adrenergic receptor activation has the opposite effect. Thus, drugs that block the β_2-adrenoreceptor tend to increase serum K^+, and those that block the α_1-adrenoreceptor tend to lower serum K+.

Insulin has important effects on serum K+. It activates Na+,K+ATPase, directly increasing cellular K+ uptake and decreasing serum K+. This effect is rapid and enables insulin administration to be a component of the acute therapy of hyperkalemia. Importantly, insulin stimulates Na+,K+-ATPase through a mechanism that is distinct from its stimulation of glucose entry and does not involve effects on either α- or β-adrenoreceptors. Thus, the effects of insulin and β2adrenoceptor activation are additive. In people with diabetes, hyperglycemia resulting from either the lack of adequate insulin release or responsiveness leads to hyperosmolality, which can also induce cellular potassium shifts (see later).

Aldosterone regulates serum potassium in part by altering the distribution of potassium between ECF and ICF by enhancing cellular potassium uptake through stimulation of Na+,K+-ATPase.2 Indeed, aldosterone administration can cause hypokalemia in the absence of altered potassium balance through mechanisms involving altered cellular K+ distribution.2,3 Pharmacologic inhibition of aldosterone action with mineralocorticoid receptor blockers (MRBs) can cause hyperkalemia.

Serum osmolality is another important factor that alters cellular potassium distribution. Hyperosmolality can cause hyperkalemia when it is the result of “effective osmoles,” such as mannitol or persistent hyperglycemia in the absence of adequate insulin and/or insulin responsiveness. The likely mechanism is that the increased serum osmolality induces water movement out of the cells, decreasing cell volume and increasing intracellular [K+], which stimulates K+permeable channels and increases K+ movement out of cells. Urea in patients with high blood urea nitrogen (BUN) levels is an “ineffective osmole” because it rapidly crosses plasma membranes and thus does not alter cell volume. Administering glucose to a nondiabetic patient, because it stimulates insulin secretion, can actually stimulate insulininduced cellular potassium uptake and decrease serum K+.

Exercise has multiple effects on K+. Cellular K+ release is required for repolarization of contracting skeletal muscle cells and can result in mild

TABLE 10.1 Select Foods With High Potassium Content

Food	Portion Size	K+ (mmol)
Artichoke, boiled	1, medium	27
Avocado	1, medium	38
Banana	Medium	12
Cantaloupe, cut up	1 cup	13
Grapefruit juice	8 oz	10
Hamburger, lean	8 oz	18
Milk	8 oz	10

Cellular Potassium Shifts
Plasma/extracellular space
Cell
Fall in
serum K+

Increase in
serum K+

Increased by

Insulin
β2-Adrenoceptor
agonists
Alkalosis
α-Adrenoceptor
antagonists

Orange juice

8 oz

12

Potato, baked

7 oz

22

Prunes

10

16

Raisins

19

Sirloin steak

^{2} cup
8 oz

Squash

1 cup

15–20

Tomato juice

6 oz

10

Tomato paste

½ cup

31

Increased by
Acidosis
Hyperglycemia
β2-Adrenoceptor
antagonists
(β-blockers)
α-Adrenoceptor
agonists
Increase in
osmolality
Exercise

Fig. 10.1 Regulation of extracellular/intracellular potassium shifts.

Renal Handling of Potassium

TABLE 10.2 Distribution of Total Body Potassium in Organs and Body Compartments

Organ/Fluid	Total K^+ Amount	Body Compartment	K^+ Concentration
Muscle	2650 mmol	Intracellular fluid	100–120 mmol/L
Liver	250 mmol	Extracellular fluid	~4 mmol/L
Interstitial fluid	35 mmol		
Red blood cells	350 mmol		
Plasma	15 mmol		

hyperkalemia during strenuous physical exercise. Catecholamines released during exercise can contribute to this hyperkalemia because α_1-adrenergic receptor activation shifts potassium out of cells. The local increase in extracellular potassium induces arterial dilation in normal blood vessels, which increases skeletal muscle blood flow and acts as an adaptive mechanism during exercise. The skeletal muscle interstitial acidosis associated with intense exercise may also contribute to K^+ release.[4] Catecholamines released during exercise, however, also activate β_2-adrenoceptors, which stimulates skeletal muscle cellular potassium uptake and minimizes the severity of exercise-induced hyperkalemia and can also lead to hypokalemia after cessation of exercise. With preexisting potassium depletion, postexercise hypokalemia may be severe and can cause rhabdomyolysis.[5]

Metabolic acidosis is often associated with abnormal serum potassium. Although hyperkalemia may be seen with lactic acidosis, this may be because of tissue ischemia leading to cellular death and cytoplasmic K^+ release. In diabetic ketoacidosis, the hyperglycemia and insulin deficiency are likely the primary mechanisms of the associated hyperkalemia. In type 4 renal tubular acidosis (RTA), hyperkalemia contributes to the metabolic acidosis by inhibiting net acid excretion in the form of ammonium.6

Renal Potassium Handling With Normal Kidney Function

Long-term potassium homeostasis occurs primarily through changes in renal potassium excretion. Serum potassium is almost completely

Distal convoluted
tubule
10%–15%

Proximal
convoluted 100%
tubule
65%–70%

Cortical
collecting
duct

35%

Thick
ascending
limb
50%

140%

120%

25%

K+

Outer
medullary
collecting
duct
Inner
medullary
collecting
duct

50%

Fractional excretion of K+:
(K+) (Cr)s × 100
FEK+ = + u
(K)s(Cr)u
where Cr is creatinine,
s is serum, and u is urine

Fig. 10.2 Renal handling of potassium.

ionized, is not bound to plasma proteins, and is filtered efficiently by the glomerulus (Fig. 10.2). The proximal tubule reabsorbs the majority (~65%–70%) of filtered potassium, but there is relatively little variation in proximal tubule potassium reabsorption in response to hypokalemia or hyperkalemia. In the loop of Henle, potassium is secreted in the descending loop, at least in deep nephrons, particularly with adaptation to a large K+ intake, and is reabsorbed in the ascending loop through the action of the Na+-K+-2Cl cotransporter (Fig. 10.3A). However, most K+ transported by this protein is recycled back into the tubular lumen through an apical K+ channel, and thus there is little net

Collecting Duct Principal Cell: K+ Secretion

Thick Ascending Limb
Lumen

Blood

NKCC2
Na+

3 Na+

Na+,K+-ATPase

~

2 Cl
K+
Cl
K+
ROMK

Lumen

Blood

Na+ channel
(ENaC)

3 Na+

Na
2 K+

Cl channel
K+ channel

Na+,K+-ATPase

~

2 K+

K+
K+ channel

K+

K+
K channel

MR
Aldosterone

A

B

Collecting Duct Intercalated Cell:
K+ Reabsorption

Lumen

Blood

3 Na+
K+

~

H+
Antiporter

K+

Na+,K+-ATPase

~

2 K+

K channel

C

Fig. 10.3 Mechanisms of Potassium Reabsorption and Secretion. Potassium transport in the thick ascending limb of Henle loop (TAL) and in the collecting tubule principal and intercalated cells. (A) In the TAL, the majority of K^+ reabsorbed by the apical Na^+,K^+-2Cl^- cotransporter (NKCC2) recycles across the apical membrane through apical renal outer medulla K^+ (ROMK) channel. (B) In the cortical collecting duct principal cell, K^+ secretion involves integrated functions of the basolateral Na^+, K^+-ATPase, apical Na^+ channel (ENaC), and apical K^+ channel. Aldosterone stimulates this process through interaction with the mineralocorticoid receptor (MR), resulting in increased expression and activity of each of these processes. Although cortisol can also activate MR, the enzyme 11β-hydroxysteroid dehydrogenase type 2, which is present in the principal cell, converts cortisol to cortisone, a steroid hormone that does not activate MR. (C) Collecting duct intercalated cells can reabsorb K^+ through the actions of an apical H^+-K^+-ATPase.

potassium reabsorption. This absorption can be reversed to secretion by administration of a loop diuretic or by substantial potassium loading. Nonetheless, the magnitude of the change in loop of Henle potassium transport in various physiologic conditions is relatively small.

The collecting duct and its proximal extension, the initial collecting tubule, are the primary sites where the kidney regulates K^+ excretion. These segments have the ability both to secrete K^+, enabling adaptation to K^+ excess states, and to reabsorb K^+, enabling adaptation to K^+ depletion states. The principal cell of the cortical collecting duct secretes potassium, whereas intercalated cells throughout the entire collecting duct reabsorb potassium. In the principal cell, sodium is reabsorbed through the apical epithelial sodium channel (ENaC), which stimulates basolateral Na^+,K^+-ATPase (see Fig. 10.3B); active potassium uptake by this protein maintains a high intracellular K^+.

After basolateral potassium uptake, K^+ is secreted into the luminal fluid by two types of potassium channels and by KCl cotransporters. Intercalated cells actively reabsorb potassium through an apical H^+ K^+-ATPase[7] (Fig. 10.3C); this protein actively secretes H^+ into the luminal fluid in exchange for reabsorption of luminal potassium. The presence of two separate potassium transport processes, secretion by principal cells and reabsorption by intercalated cells, contributes to rapid and effective regulation of renal potassium excretion.

Several factors influence principal cell potassium secretion. These include luminal flow rate, distal sodium delivery, aldosterone, extracellular potassium intake, and extracellular pH. Luminal flow rate and distal sodium delivery frequently vary together, but changes in luminal flow rate appear more important by activating flow-induced K^+ secretion through large conductance (BK) potassium channels.[8,9] Reduced luminal flow, such as occurs in prerenal azotemia and in obstructive uropathy, may contribute to the hyperkalemia that is often seen in these conditions. Decreased sodium reabsorption, whether from reduced luminal sodium delivery or treatment with ENaC inhibitors (i.e., potassium-sparing diuretics), decreases K^+ secretion by altering electrochemical forces for K^+ secretion. Conversely, increased sodium delivery to the collecting duct, as may occur with a high salt diet or with administration of either loop or thiazide diuretics, increases principal cell sodium reabsorption and causes a secondary increase in potassium secretion. Aldosterone has many effects that increase principal cell potassium secretion, including increased Na^+,K^+-ATPase, increased apical expression of ENaC, and increased apical K^+ channels. The net effect is increased principal cell-mediated K^+ secretion. Changes in extracellular potassium directly alter Na^+,K^+-ATPase activity, thereby altering K^+ secretion. Metabolic acidosis decreases K^+ secretion, both through direct effects on potassium channels and through changes in interstitial ammonia concentration, which decreases K^+ secretion.[10]

Intercalated cell-mediated potassium reabsorption occurs in parallel with principal cell-mediated potassium secretion. Active potassium reabsorption occurs through the action of the potassium-reabsorbing protein, H^+-K^+-ATPase. The major factors regulating H^+-K^+-ATPase expression and activity include potassium balance, aldosterone, and acid-base status. Potassium depletion increases H^+-K^+-ATPase expression, resulting in increased active potassium reabsorption and decreased net potassium excretion. Aldosterone increases H^+-K^+ ATPase expression and activity and, by decreasing net potassium excretion, may minimize changes in urinary potassium excretion during aldosterone excess that otherwise would lead to more severe hypokalemia. Metabolic acidosis has both direct and indirect effects, mediated through alterations in ammonia metabolism, that increase H^+-K^+-ATPase potassium reabsorption.[6]

Regulators of renal K^+ transport in the distal nephron include the “with no lysine” (WNK) kinases.[11,12] Under basal conditions, WNK kinases activate Na^+ reabsorption in the distal convoluted tubule and inhibit the renal outer medulla potassium (ROMK) channel. This combination of effects—increased DCT Na^+ reabsorption, which decreases collecting duct Na^+ delivery, in conjunction with decreased ROMK expression—promotes decreased K^+ secretion. The specific mechanisms through which WNK regulates K^+ secretion are under active investigation, and medications targeting WNK inhibition are in development and may in the future enable entirely new treatments of hypertension and K^+ disorders.[13]

The intestinal tract also contributes to renal potassium homeostasis. Potassium sensors, present in either the intestinal tract or the portal venous system, elicit a rapid increase in renal potassium excretion through mechanisms independent of serum potassium and aldosterone.[2,14] This reflex system, which is still not understood fully, supplies a mechanism to "sense" dietary potassium intake and alter renal

potassium excretion without involving aldosterone concentration and prior to changes in serum potassium. This mechanism contributes to the greater safety of oral compared with intravenous (IV) potassium administration.

The contribution of the intestinal tract to K+ excretion in fecal contents is unclear. An early study suggested stool potassium averaged 12% of dietary intake in normal subjects and 34% in patients with severe renal insufficiency.15 In contrast, a study examining anephric patients showed fecal K+ excretion averaged approximately 3 mEq/day, which did not differ from that observed in control patients with intact renal function.16 In this latter study, fecal K+ excretion was not altered by either MRB therapy or mineralocorticoid agonists.16

Renal Potassium Handling in Chronic Kidney Disease

Because the kidneys are the major route for elimination of potassium, as kidney function declines, the balance between dietary potassium intake, renal potassium excretion, and baseline serum potassium changes. In general, most patients with chronic kidney disease (CKD) maintain their serum potassium in the normal range, although there is a graded increase in mean serum K+ as the glomerular filtration rate (GFR) declines. The risk of developing hyperkalemia is increased in patients with stage 4 and 5 CKD; patients with stage 3 CKD who have diabetes mellitus, tubulointerstitial disease, or receive certain drugs also are at increased risk.

Many of the medications used in the treatment of patients with CKD alter potassium homeostasis. Common medications that predispose to hyperkalemia (Table 10.3) include agents that inhibit the epithelial Na channel (ENaC) or the renin-angiotensin-aldosterone system (RAAS), nonsteroidal antiinflammatory drugs (NSAIDs), and calcineurin inhibitors. Medications that can directly inhibit ENaC, such as amiloride, triamterene, trimethoprim, and pentamidine, acutely reduce the rate of renal K+ excretion and can cause hyperkalemia. Drugs that inhibit the RAAS, such as mineralocorticoid receptor blockers (MRBs), angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme (ACE) inhibitors, direct renin inhibitors, and heparin can inhibit aldosterone's action or generation, which reduces renal K+ excretion. Mineralocorticoid blockers are increasingly used in patients with CHF and with refractory hypertension and may slow the progression of CKD. NSAIDs that inhibit prostaglandin synthesis and β-blockers that inhibit renin release and catecholamine action can also increase the risk of hyperkalemia. In contrast, both loop and thiazide diuretics increase renal K+ excretion and predispose to hypokalemia.

Patients with CKD generally tolerate hyperkalemia with fewer cardiac and electrocardiographic (ECG) abnormalities than do patients with normal kidney function, although the mechanism is incompletely understood. In particular, patients with CKD appear to tolerate serum [K+] of 5.0 to 5.5 mmol/L with no significant adverse effect, and levels of 5.5 to 6.0 mmol/L are associated with lower mortality than [K+] of 3.5 to 3.9 mmol/L.17 Nevertheless, severe hyperkalemia (>6.0 mmol/L or presence of ECG changes) can be lethal and should be treated aggressively.

HYPOKALEMIA

Epidemiology

The incidence of potassium disorders depends greatly on the patient population. Less than 1% of adults with normal kidney function who are not receiving medications develop frank hypokalemia or hyperkalemia. However, diets with high sodium and low potassium content may lead to potassium depletion. Thus, hypokalemia or hyperkalemia suggests that either an underlying disease is present or that the

TABLE 10.3

Drugs Classes Associated With Hyperkalemia

Class

Mechanism

Examples

Potassium-containing drugs

Increased potassium intake

KCl, penicillin G, Na citrate, K citrate

β-Adrenergic receptor blockers
(β-blockers)

Inhibit renin release

Propranolol, metoprolol, atenolol

ACE inhibitors

Inhibit conversion of angiotensin I to angiotensin II

Captopril, lisinopril

ARBs

Inhibit activation of AT1 receptor by angiotensin II

Losartan, valsartan, irbesartan

Direct renin inhibitors

Inhibit renin activity, leading to decreased angiotensin II production

Aliskiren

Heparin

Inhibit aldosterone synthase, rate-limiting enzyme for aldosterone synthesis

Heparin sodium

Aldosterone receptor antagonists

Block aldosterone receptor activation

Spironolactone, eplerenone, finerenone
K+

Amiloride, triamterene; certain antibiotics,
specifically trimethoprim and pentamidine

Potassium-sparing diuretics

Block collecting duct apical ENaC Na channel, decreasing gradient for secretion

NSAIDs and COX-2 inhibitors

Inhibit prostaglandin stimulation of collecting duct K+ secretion; inhibit renin release

Ibuprofen, diclofenac

Digitalis glycosides

Inhibit Na+, K+-ATPase necessary for collecting duct K+ secretion and regulation of K+ distribution into cells

Digoxin

Calcineurin inhibitors

Inhibit Na+, K+-ATPase necessary for collecting duct K+ secretion

Cyclosporine, tacrolimus

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COX, cyclooxygenase; ENaC, epithelial sodium channel; NSAIDs, nonsteroidal antiinflammatory drugs.

individual is taking drugs that alter potassium handling. For example, hypokalemia may be present in as many as half of patients taking diuretics18 and is present in many patients with primary or secondary hyperaldosteronism.

Clinical Manifestations

Potassium deficiency, because it alters the ratio of extracellular to intracellular potassium, alters the resting membrane potential, which can impair normal functioning of almost every cell in the body. Several studies have shown that hypokalemia, even when mild, is associated with increased long-term mortality. Overall, children and young adults tolerate hypokalemia better than elderly persons. Prompt correction is warranted in patients with coronary heart disease or in patients receiving digitalis glycosides because hypokalemia increases the risk of lethal cardiac arrhythmias.

Hypokalemia also predisposes to arrhythmia, including ventricular tachycardia and ventricular fibrillation26 and the risk of sudden cardiac death. Diuretic-induced hypokalemia is of particular concern because sudden cardiac death may occur more frequently in those treated with thiazide diuretics.26 Ventricular arrhythmias are also more common in patients receiving digoxin who develop hypokalemia.

Hormonal

Hypokalemia impairs insulin release and induces insulin resistance, resulting in worsened glucose control in diabetic patients.27 The insulin resistance that usually occurs with thiazide diuretic therapy is caused by endothelial dysfunction mediated by thiazide-induced hypokalemia and hyperuricemia.28

Muscular

Several clinical studies have shown chronic hypokalemia is associated with increased mortality.19–23 This association persists after extensive statistical analysis of confounding and associated factors. At present, whether correction of the abnormal K+ alters the associated mortality is unknown. However, because treatment is generally well tolerated, targeting a serum/plasma K+ of 4.0 mEq/L or greater is a reasonable goal.

Hypokalemia can lead to skeletal muscle weakness and to an increased risk of exertion-related rhabdomyolysis. Hypokalemia hyperpolarizes skeletal muscle cells, thereby impairing the ability to generate the action potential needed for muscle contraction. Hypokalemia also reduces skeletal muscle blood flow, possibly by impairing local nitric oxide release; this effect can predispose patients to rhabdomyolysis during vigorous exercise.29 Severe hypokalemia can also lead to respiratory muscle weakness and, if severe, respiratory failure.

Cardiovascular

Kidney Related

Potassium deficiency increases blood pressure, salt-sensitive changes in BP, and the cardiac sensitivity to arrhythmias. Epidemiologic studies link hypokalemia and a low-potassium diet with an increased prevalence of hypertension, and experimental studies show hypokalemia increases blood pressure by 5 to 10 mm Hg and that potassium supplementation can lower blood pressure by a similar amount.24 Potassium deficiency also increases the effect of dietary NaCl on blood pressure. This effect involves multiple mechanisms, including stimulating sodium retention and increasing intravascular volume and sensitizing the vasculature to endogenous vasoconstrictors.24 In part, sodium retention is related to increased NCC- and ENaC-mediated sodium reabsorption in the distal convoluted tubule and cortical collecting duct, respectively.25

Hypokalemia leads to several important disturbances of kidney function. Reduced medullary blood flow and increased renal vascular resistance may predispose to hypertension, tubulointerstitial and cystic changes, alterations in acid-base balance, and impairment of urinary concentrating mechanisms.
Potassium depletion causes tubulointerstitial fibrosis that is generally greatest in the outer medulla. The degree of reversibility is related to the duration of hypokalemia, and if prolonged, hypokalemia may result in kidney failure. Experimental studies suggest an increased risk for irreversible kidney injury when hypokalemia is present during the neonatal period.30 Longstanding potassium depletion also causes kidney hypertrophy and predisposes to kidney cyst formation, particularly when there is increased mineralocorticoid activity.

Mortality

Metabolic alkalosis is a common acid-base consequence of severe potassium depletion. It results primarily from increased net acid excretion caused by increased potassium reabsorption and proton excretion in the collecting tubule as well as enhanced ammonia excretion, in combination in stimulation of proximal tubule bicarbonate reabsorption.31

Severe hypokalemia can cause mild polyuria, typically 2 to 3 L/day. Both increased thirst and mild nephrogenic diabetes insipidus contribute to the polyuria.32 The nephrogenic diabetes insipidus is caused by decreased expression of several proteins, such as the water transporter aquaporin 2 (AQP2), and the urea transporters (UT)-A1, UTA3, and UT-B, which are involved in urine concentration and water reabsorption.

Hypokalemia increases both ammonia production and expression of collecting duct proteins involved in ammonia secretion. This leads to increased ammonia excretion in the urine, increasing net acid excretion and leading to development of metabolic alkalosis. In addition, there is increased ammonia to the renal veins, from where it is added to the systemic circulation. In patients with acute or chronic liver disease, this increased ammonia delivery may exceed hepatic ammonia clearance, increase plasma ammonia levels and either precipitate or worsen hepatic encephalopathy.6

Etiology

Hypokalemia results typically from one of four etiologies: pseudohypokalemia, redistribution, extrarenal potassium loss, or urinary potassium loss; multiple etiologies may coexist in a specific patient.

Pseudohypokalemia

Pseudohypokalemia refers to the condition in which serum potassium decreases, artifactually, after phlebotomy. The most common cause is acute leukemia; the large numbers of abnormal leukocytes take up potassium when the blood is stored in a collection vial for prolonged periods at room temperature. Rapid separation of plasma and storage at 4°C is used to confirm this diagnosis. If confirmed, only plasma potassium measurements, and not serum levels, should be used for subsequent clinical decision making to avoid this artifact leading to inappropriate treatment.

Redistribution

Because less than 2% of total body potassium is in the ECF compartment, quantitatively small potassium shifts from the ECF to the ICF compartment can cause substantial hypokalemia. A chronic increase in aldosterone secretion increases the pump-leak kinetics and reduces plasma K^+ in the absence of perceptible increases in urinary K^+ excretion if intake is constant.

A clinically rare, but dramatic, cause of redistribution-induced hypokalemia is hypokalemic periodic paralysis. In this condition, acute and severe hypokalemia resulting from redistribution leads to flaccid paralysis or severe muscular weakness. It occurs typically during the night or the early morning, or after a carbohydrate-rich meal, and can persist for 6 to 24 hours. A genetic defect in a dihydropyridinesensitive calcium channel has been identified in some patients, whereas other cases are associated with hyperthyroidism. Aggressive potassium administration during the attack is necessary to speed recovery and avoid the risk of respiratory failure.

Nonrenal Potassium Loss

The skin and the GI tract excrete small amounts of potassium under normal circumstances. Occasionally, excessive sweating or chronic diarrhea results in substantial potassium loss and leads to hypokalemia.33 Vomiting or nasogastric suction may also result in loss of potassium, although gastric fluids typically contain only 5 to 8 mmol/L of potassium. The concomitant metabolic alkalosis, however, can increase urinary potassium loss and contribute to development of hypokalemia.34

Renal Potassium Loss

The most common cause of hypokalemia is urinary potassium loss, which typically results from drugs, endogenous hormone production, or, more rarely, intrinsic kidney defects.

Drugs. Both thiazide and loop diuretics increase urinary potassium excretion, and the incidence of diuretic-induced hypokalemia is related to both dose and treatment duration. When loop and thiazide diuretics are dosed to produce similar effects on sodium excretion, thiazide diuretics have greater effects on urinary potassium and are more likely to lead to hypokalemia. Some penicillin analogs, such as piperacillin/tazobactam, increase distal tubular delivery of a nonreabsorbable anion, which obligates the presence of a cation such as potassium and thereby increases urinary potassium excretion.35 The antifungal agent amphotericin B directly increases collecting duct potassium secretion. Aminoglycosides may cause hypokalemia either with or without simultaneous nephrotoxicity. The mechanism is incompletely understood but may relate to magnesium depletion (see later discussion). Cisplatin is an antineoplastic agent that can induce hypokalemia from renal potassium wasting; the increased potassium excretion may persist after discontinuation of the medication. Toluene exposure, from sniffing certain glues, can cause potassium wasting, leading to hypokalemia.36 In addition, certain herbal products, including herbal cough mixtures, licorice tea, licorice root, and gan cao, contain glycyrrhizic and glycyrrhetinic acids, which have mineralocorticoid-like effects.37

Endogenous hormones. Aldosterone is an important hormone regulating total body potassium homeostasis. Aldosterone predominantly causes hypokalemia by stimulating cellular potassium uptake,2 but it can also lead to inappropriately high urinary potassium excretion during, and likely contributing to, hypokalemia.

Genetic causes. Genetic defects leading to excessive aldosterone production and resulting in hypokalemia is occasionally seen (see Chapter 49). These conditions include glucocorticoid-remediable aldosteronism, congenital adrenal hyperplasia, and apparent mineralocorticoid excess. These conditions are discussed in detail in Chapter 49.

Magnesium depletion. Magnesium deficiency can cause inappropriately high potassium excretion despite hypokalemia.38 This appears to occur because intracellular magnesium inhibits the apical ROMK channels that are critical for distal nephron K+ secretion. In magnesium deficiency, decreased intracellular magnesium reduces the magnesium-mediated inhibition of ROMK channels, leading to increased ROMK-mediated K+ secretion and thereby to increased net K+ secretion.39 Magnesium deficiency occurs most often as a complication of prolonged diuretic use or from proton pump inhibitor (PPI) therapy. It may also result from ethanol abuse, uncontrolled diabetes mellitus, and after solid organ transplant. Magnesium deficiency should be suspected when potassium replacement does not correct hypokalemia; treatment of the underlying cause of hypomagnesemia, such as discontinuation of PPI agents, generally reverses the potassium wasting.

Primary renal defect. Intrinsic renal potassium transport defects leading to hypokalemia are rare. They include Bartter syndrome and Gitelman syndrome, which have clinical phenotypes similar to those that follow use of loop and thiazide diuretics, respectively, and Liddle syndrome. These are discussed in Chapter 49.

Evaluation of Hypokalemia
Hypokalemia

Pseudohypokalemia
Confirm by rapid separation of
plasma or storing sample at 4°C

Yes

Are abnormal
leukocytes present?
No

Yes Evidence of elevated aldosterone,
recent insulin, theophylline, or
adrenergic agent use

Redistribution

No
Nonrenal K+ loss

Yes

Evidence of fluid loss from skin
(excessive sweating)
or GI tract (gastric or stool fluid loss)?

Drugs, such as diuretics,
aminoglycosides, and
amphotericin

Renal K+ loss?
>20 mmol/24 h
in urine

No

No

Yes

Bicarbonaturia
(e.g., RTA,
metabolic alkalosis)
Hypomagnesemia

Aldosterone
low, cortisol
normal

Evaluate BP

Poor dietary intake,
recent diuretic use, or
recent K+ loss from
GI tract

High
Evaluate plasma,

aldosterone, and cortisol

Aldosterone
low or normal,
cortisol high

Aldosterone
high, cortisol
normal
Low

Liddle
syndrome

Cushing
syndrome

Hyperaldosteronism
(primary, secondary,
or GRA)

Bartter or Gitelman
syndrome or
surreptitious
diuretic abuse

Fig. 10.4 Diagnostic evaluation of hypokalemia. BP, Blood pressure; GI, gastrointestinal; GRA, glucocorticoidremediable aldosteronism; RTA, renal tubular acidosis.

Bicarbonaturia. Bicarbonaturia can result from metabolic alkalosis, distal renal tubular acidosis, or treatment of proximal renal tubular acidosis. In each case, the increased distal tubular bicarbonate delivery increases potassium secretion.

Diagnostic Evaluation

The evaluation of hypokalemia is summarized in Fig. 10.4. The clinician should first exclude pseudohypokalemia or potassium redistribution from the extracellular to the intracellular space. Insulin, aldosterone, fludrocortisone, and sympathomimetic agents, such as theophylline and β2-adrenoceptor agonists, are common causes of potassium redistribution. In the hypertensive patient, hypokalemia in the absence of diuretic use suggests primary aldosteronism diuretic use suggests primary aldosteronis, for which specific testing is appropriate (see Chapter 49).

If neither pseudohypokalemia nor potassium redistribution is present, hypokalemia indicates that total body potassium depletion caused by either renal, GI, or skin losses is present. Urinary potassium loss is caused most often by diuretics. Hypomagnesemia can also cause potassium wasting and frequently results from loop or thiazide diuretic use. Less common causes of renal potassium loss include proximal and distal RTA, diabetic ketoacidosis, and ureterosigmoidostomy.

Primary aldosteronism should be considered in the patient who also has hypertension. Less commonly, surreptitious diuretic use or vomiting, laxative abuse, and genetic causes such as Bartter or Gitelman syndrome should be considered when the cause of the hypokalemia is not obvious. Excessive potassium loss may also result from skin losses from excessive sweating or from the GI tract from diarrhea, vomiting, nasogastric suction, or GI fistula. Occasionally, patients are reluctant to admit to self-induced diarrhea, and the diagnosis may need to be confirmed by direct testing of the stool for cathartic agents.

Treatment

Primary short-term risks of hypokalemia are cardiovascular arrhythmias and neuromuscular weakness. Overly rapid therapy can cause acute hyperkalemia, which can cause ventricular fibrillation and sudden death. The rate of K replacement should balance these risks.

In the great majority of hypokalemic patients, emergency therapy is not necessary. The body responds to potassium losses by shifting potassium from ICF to ECF, thereby minimizing the change in extracellular

ECG Changes in Hyperkalemia

Total Body Potassium Deficit in
Chronic Hypokalemia

QRS Complex

1400
P wave

Total body K+ deficit

1200

Approximate Serum
Potassium (mmol/L)

ECG Change

4-5

Normal

6-7

Peaked T waves

7-8

Flattened P wave,
prolonged PR interval,
depressed ST segment,
peaked T wave

8-9

Atrial standstill,
prolonged QRS duration,
further peaking T waves

>9

Sinusoid wave pattern

T wave

1000
800
600
400
200
0
1.5

2

2.5

3

3.5

4

Serum K+ (mmol/L)

Fig. 10.5 Total Body Potassium Deficit in Hypokalemia. Because of shift of potassium from the intracellular fluid to the extracellular fluid compartment during chronic potassium depletion, the magnitude of deficiency can be masked and is generally much larger than would be calculated solely from the extracellular fluid volume volume and the change in serum potassium.

[K+]. During potassium replacement, there is shift of potassium back into ICF. Consequently, the amount of potassium replacement needed is much greater than predicted by the change in extracellular [K+] and the ECF volume (Fig. 10.5).

Oral or enteral potassium administration is preferred if the patient can take oral medication and has normal GI tract function. Acute hyperkalemia is highly unusual when potassium is given orally. This reflects several factors, most prominently gut sensors that minimize changes in serum potassium levels. When potassium is given intravenously, acute hyperkalemia can occur if the administration rate is too rapid and, if it occurs, can cause sudden cardiac death. Thus, unless immediate life-threatening conditions are present, the maximum rate of IV KCl administration should not exceed 10 mmol/h. In life-threatening conditions, such as hypokalemia leading to respiratory compromise, severe hypokalemia in a patient requiring urgent surgery, and the patient with an acute myocardial infarction and life-threatening ventricular ectopy, more rapid administration may be needed. In these patients, potassium chloride (KCl) can be administered intravenously at a dose of 5 to 10 mmol over 15 to 20 minutes. Continuous ECG monitoring should be used under these circumstances. This dose can be repeated as needed.

The choice of the parenteral fluid used to administer the potassium can affect the response. In patients without diabetes mellitus, dextrosecontaining fluids lead to a reflex increase in serum insulin levels, which can cause redistribution of potassium from ECF to ICF. As a result, administering KCl in dextrose-containing solutions, such as dextrose 5% in water (D5W), can stimulate cellular potassium uptake to an extent that results in paradoxical worsening of the hypokalemia.40 Consequently, parenteral KCl should be administered in dextrose-free solutions.

The underlying condition should be treated whenever possible. If patients with diuretic-induced hypokalemia require ongoing diuretic administration, the addition of potassium-sparing diuretics may be considered. When oral replacement therapy is required, KCl is the preferred drug in most patients, except those with metabolic acidosis, in whom potassium citrate may be considered as a concomitant alkali source. Hypomagnesemia, if present, should be treated; otherwise, there may be ongoing urinary potassium losses that delay or preclude

Fig. 10.6 Electrocardiographic (ECG) Changes in Hyperkalemia. Progressive hyperkalemia results in identifiable changes in the electrocardiogram. These include peaking of the T wave, flattening of the P wave, prolongation of the PR interval, depression of the ST segment, prolongation of the QRS complex, and, eventually, progression to a sine wave pattern. Ventricular fibrillation may occur at any time during this ECG progression.

correction of the hypokalemia. If clinically indicated for other reasons, the use of β-blockers, ACE inhibitors, or ARBs can assist in maintaining serum potassium levels.

HYPERKALEMIA

Epidemiology

Hyperkalemia is distinctly unusual in healthy individuals with normal kidney function not being treated with drugs that alter K+ handling, with less than 1% of normal healthy adults developing hyperkalemia. This low frequency is a testament to potent renal mechanisms for potassium excretion. Because of this, chronic hyperkalemia, if not caused by pseudohyperkalemia or redistribution, should strongly suggest impaired renal potassium excretion, whether from decreased nephron/collecting duct number, from medications that decrease renal potassium excretion, or from adrenal insufficiency.

Clinical Manifestations

Hyperkalemia can be asymptomatic, can cause mild symptoms, or can be life threatening. Importantly, the mortality risk of hyperkalemia is independent of the patient’s clinical symptoms and reflects acute effects of hyperkalemia on cardiac conduction and repolarization. This is demonstrable on the ECG (Fig. 10.6). The initial effect of hyperkalemia is a generalized increase in the height of the T waves, most evident in the precordial leads, but typically present in all leads, which is known as “tenting.” More severe hyperkalemia is associated with delayed electrical conduction, resulting in an increased PR interval and a widened QRS complex. This is followed by progressive flattening and eventual absence of the P waves. Under extreme conditions, the QRS

Evaluation of Hyperkalemia
Are ECG changes present
(see Fig. 10.5)?
Is pseudohyperkalemia
present?

No further
evaluation needed

History of
dietary K+
excess?

Dietary
counseling

Yes

No

Emergently treat K+
(see Table 10.5)

Yes

Further evaluation based on
history and laboratory

No

Is CKD present?
Is obstructive
uropathy present on
ultrasound?

Treat
obstruction

Is metabolic
acidosis
present?

Is hyperosmolarity
(non-urea
osmolyte) present?

Treat metabolic
acidosis

Treat
hyperosmolarity

Are K-raising medications
being administered
(see Table 10.3)?

Are these medications
associated with
mortality improvement?
Consider dietary

counseling to decrease
K intake or addition of
diuretic to increase
K excretion

Yes
No

Discontinue or change to
alternative medication, if
possible

No

Clinically meaningful
reduction in K

Yes

Continue to
monitor K+

Fig. 10.7 Workup of hyperkalemia. CKD, Chronic kidney disease; ECG, electrocardiography.

complex widens sufficiently that it merges with the T wave, resulting in a junctional rhythm that degenerates to a sine wave pattern. Finally, ventricular fibrillation develops. Although the ECG findings correlate generally with the degree of hyperkalemia, the rate of progression from mild to severe cardiac effects can be unpredictable and may not correlate well with changes in the serum potassium concentration.

Hyperkalemia also has effects on noncardiac tissues. Skeletal muscle cells are particularly sensitive to hyperkalemia, causing generalized weakness. In patients with severe hyperkalemia, diaphragmatic muscle weakness may lead to respiratory failure.

Mortality

Several clinical studies have shown that chronic hyperkalemia is independently associated with increased mortality.19–22 41–44 Whether correction of the abnormal K+ alters the associated mortality is unknown.

However, the relatively recent availability of generally well-tolerated enteric K+-binding resins enables pharmacologic therapy of hyperkalemia without having to discontinue medications that have beneficial effects on mortality, such as ACE inhibitors/ARB, β-blockers, and MRBs, in specific clinical conditions but that can also increase potassium levels.

Future studies are needed to determine whether correction of hyperkalemia with enteric K+-binding medications will improve mortality.

Etiology

Hyperkalemia can result from pseudohyperkalemia, potassium redistribution from intracellular to extracellular space, or imbalances between potassium intake and renal potassium excretion. A diagnostic approach is shown in Fig. 10.7

Pseudohyperkalemia

Pseudohyperkalemia refers to the condition where potassium release from blood cells occurs after the phlebotomy procedure. This most commonly results from damaged erythrocytes and is identified clinically by the presence of free hemoglobin in the plasma, reported as “hemolysis” by most clinical laboratories. If hemolysis is present, the reported serum [K+] measurement does not accurately reflect the actual serum [K+]. Treatment should not be prescribed based on this value, and repeat measurement is necessary. Ischemia from prolonged tourniquet time or from exercise of the limb in the presence of a tourniquet can also lead to abnormally increased potassium values. Potassium can also be released from the other cellular elements present in blood during clotting. This can occur in patients with severe leukocytosis (>70,000/cm3) or thrombocytosis. About one-third of patients with platelet counts of 500 to 1000 × 109/L exhibit pseudohyperkalemia. Pseudohyperkalemia is diagnosed by showing that the serum [K+] is more than 0.3 mmol/L higher than in a simultaneous plasma sample. If not caused by hemolysis, future potassium levels may need to be measured in plasma samples to allow for accurate measurement of extracellular [K+].

Redistribution

Redistribution of potassium from ICF to ECF may occur with severe hyperglycemia (from development of hyperosmolarity), during insulin deficiency, and with administration of drugs that alter cellular K+ uptake, such as β2-adrenoceptor blockers, ACE inhibitors, ARB, and MR blockers. During diabetic ketoacidosis, both the hyperosmolarity that results from the hyperglycemia and the insulin deficiency contribute to transcellular K+ shifts that are the primary cause of the often-observed hyperkalemia. During treatment with insulin, resolution both of the hyperglycemia, and its resultant hyperosmolarity, and of the insulin deficiency leads to increased cellular potassium uptake and a decrease in the serum potassium. In the patient with diabetic ketoacidosis who presents with a normal serum potassium, potassium redistribution from the insulin deficiency and hyperglycemia-induced hyperosmolarity may be masking substantial total body potassium deficiency resulting from hyperglycemia-induced polyuria. In this case, severe hypokalemia may develop during insulin treatment. Close and careful management of serum potassium may be needed. Patients who have received mannitol may also develop hyperosmolarity-induced hyperkalemia. Digoxin overdose can block cellular potassium uptake and lead to hyperkalemia that requires rapid treatment.

Excess Intake

Excessive potassium ingestion generally does not lead to chronic hyperkalemia unless other contributing factors are present. Under normal conditions, the kidney has the capacity to excrete several multiples of the mean daily potassium intake. However, if renal potassium excretion is impaired, as from drugs, acute kidney injury (AKI), or CKD, excessive potassium intake can contribute to the development of hyperkalemia.

Common sources of excess potassium intake are potassium supplements, salt substitutes, enteral nutrition products, and several common foods. As many as 4% of patients receiving potassium supplements develop hyperkalemia. “Salt substitutes” have an average of 10 to 13 mmol K/g. Many enteral nutrition products contain at least 40 mmol/L KCl; administration of 100 mL/h of such products can result in a potassium intake of about 100 mmol/day. Also, many food products are particularly high in potassium (see Table 10.1).

Impaired Renal Potassium Excretion

Chronic hyperkalemia typically involves a component of impaired renal potassium excretion. As previously discussed, renal potassium excretion is determined primarily by collecting duct potassium secretion. The number of collecting duct segments parallels GFR, and therefore impaired GFR, whether from CKD or AKI, results in impaired capacity to excrete potassium. In CKD, adaptive increases in the ability of each collecting duct segment to secrete potassium may allow renal potassium excretion to remain moderately well preserved until GFR is reduced to 10 to 20 mL/min. Multiple drugs affect renal potassium secretion (see Table 10.3); these drugs are sometimes used in combination, which further exacerbates the risk of hyperkalemia.

Obstructive uropathy leads frequently to hyperkalemia, at least in part from decreased collecting duct ENaC and Na^+,K^+-ATPase expression and activity. Hyperkalemia may persist after relief of the obstruction.[45] This impairment appears to be related to a persistent defect in collecting duct K^+ secretion and not to aldosterone deficiency.[45]

Mineralocorticoid hormones are necessary for the normal response to hyperkalemia. Lack of these hormones both causes potassium redistribution from ICF to ECF and reduces the maximal ability of the kidneys to secrete potassium. Primary adrenal insufficiency should be strongly considered in the patient with chronic hyperkalemia and other findings suggestive of adrenal insufficiency, such as spontaneous hypotension and hyponatremia.

The colon can excrete potassium, but adaptive changes in enteric potassium excretion are quantitatively small and generally are not sufficient to maintain normal potassium homeostasis.

A rare genetic disorder, pseudohypoaldosteronism type 2 (PHA2; also known as Gordon syndrome) is characterized by hypertension, hyperkalemia, non–anion gap metabolic acidosis, and normal GFR[46] and is discussed in Chapter 49.

Determining the Role of Excessive Potassium Intake in Chronic Hyperkalemia

In most patients, a careful history and measurement of K^+ in a 24-hour urine collection will identify the role of excessive dietary potassium intake in the development of chronic hyperkalemia. In selected patients, specifically those not using diuretics and either unable to be compliant with or preferring not to perform a 24-hour urine collection, assessment of the urine potassium/creatinine ratio in a random urine specimen may be used, with urinary potassium greater than 60 mmol K^+/g creatinine suggesting excessive dietary K^+ intake is present. If there is a clinical concern about possible hypoaldosteronism as a primary cause of the hyperkalemia, such as in a patient with concomitant normal or low blood pressure and hyponatremia, the transtubular K^+ gradient (TTKG), when considered in context with assessment of K^+ intake, can be helpful (Table 10.4).

Treatment

Acute Therapy

Acute therapies for hyperkalemia are divided into those that minimize the cardiac effects of hyperkalemia, those that induce potassium uptake by cells resulting in a decrease in serum potassium, and those that remove potassium from the body (Table 10.5). Sodium bicarbonate ($NaHCO_3$) therapy should not be used unless the patient is frankly acidotic ($pH < 7.2$) or there is substantial endogenous renal function. Hypertonic $NaHCO_3$ therapy (e.g., 50 mmol in 50 mL of sterile water) can worsen intravascular volume overload, as frequently seen in the patient with oliguric AKI; can cause acute hypernatremia; and can acutely increase serum potassium in the anephric patient, likely as a result of the acute increase in plasma osmolality.[47]

Blocking cardiac effects. IV calcium administration rapidly antagonizes the effects of hyperkalemia on the myocardial conduction system and on myocardial repolarization and does so without changing plasma K^+. Calcium should be given intravenously as the initial therapy if unambiguous ECG changes of hyperkalemia are present. If the ECG is ambiguous, comparison with a previous ECG may be helpful. Patients with a prolonged PR interval, a widened QRS complex, or the absence of P waves should receive IV calcium in the form of either calcium chloride or calcium gluconate without delay. Responses typically occur within 1 to 3 minutes but generally last for only 20 to 60 minutes. Doses may be repeated as needed if ECG changes persist or they recur. If a delay in more definitive therapy, such as institution of dialysis, is anticipated, a continuous calcium infusion can be used.

IV calcium is relatively safe if certain precautions are taken.
IV calcium should not be administered in NaHCO3-containing

solutions because calcium carbonate ($CaCO_3$) precipitation can occur. Hypercalcemia, which occurs during rapid calcium infusion, can potentiate the myocardial toxicity of digoxin. Thus, patients taking digoxin, particularly if they have evidence of digoxin toxicity as a contributing cause of hyperkalemia, should be given calcium as a slow infusion over 20 to 30 minutes.

Cellular potassium uptake. The second most rapid way to treat hyperkalemia is to stimulate cellular potassium uptake using either insulin or β_2-adrenergic agonist administration. Insulin rapidly stimulates cellular potassium uptake and should be administered intravenously to ensure rapid and predictable bioavailability. The effect of insulin on serum $[K^+]$ is seen generally within 10 to 20 minutes and can last for 4 to 6 hours. Glucose is generally coadministered to

TABLE 10.4

Gradient

Transtubular Potassium

The transtubular potassium gradient (TTKG) is a measurement of net K^+ secretion by the collecting duct after correcting for changes in urinary osmolality and is often used to determine whether hyperkalemia is caused by aldosterone deficiency/resistance or whether the hyperkalemia is secondary to nonrenal causes. As with all diagnostic aids, clinical correlation is indicated, and potassium intake should be assessed.

TTKG =

K^+

U

K^+

S

$Osmo_U / Osmo_S$

where $[K^+]_U$ and $[K^+]_S$ are the concentration of K^+ in urine and serum, respectively, and $Osmo_U$ and $Osmo_S$ are the osmolality of urine and serum, respectively.

TTKG Value	Indication
6–12	Normal
>10	Suggests normal aldosterone action and extrarenal cause of hyperkalemia
<5–7	Suggests aldosterone deficiency or resistance

After 0.05 mg 9α-Fludrocortisone:
>10
Hypoaldosteronism is likely.
No change

Suggests a renal tubule defect from either K+-sparing diuretics (amiloride, triamterene, spironolactone), aldosterone resistance (interstitial renal disease, sickle cell disease, urinary tract obstruction, PHA1), or increased distal K+ reabsorption (PHA2, urinary tract obstruction)

TABLE 10.5

avoid hypoglycemia but may not be needed if hyperglycemia coexists. This is particularly important because extracellular glucose in patients with diabetes mellitus can function as an “ineffective osmole” and can increase the serum potassium concentration. It is important to recognize that decreased kidney function can lead to delayed insulin clearance, and hypoglycemia can result from IV insulin administration, even if glucose is coadministered, because glucose uptake may occur more rapidly than insulin clearance. Accordingly, patients given IV insulin for treatment of hyperkalemia should be closely monitored for the development of hypoglycemia. If dialysis is indicated and a delay in its initiation is anticipated, administering a continuous infusion of insulin, 4 to 10 U/h (with 10% dextrose in water, D10W), may be beneficial; periodic monitoring of serum glucose and potassium is required.

β2-Adrenoceptor agonists directly stimulate cellular potassium uptake and can be administered via IV, subcutaneously (SC), or by inhalation. However, β2-agonist therapy frequently causes tachycardia, and as many as 25% of patients do not respond to β2-agonist therapy given by nebulizer.[48] A common mistake when administering nebulized β2-adrenoceptor agonists is underdosage; the dose required is two to eight times that usually given for bronchodilation and is 50 to 100 times greater than the dose administered by metered dose inhalers.

Potassium removal. Most patients with persistent, severe hyperkalemia benefit from K+ removal from the ECF. Definitive treatment of these patients requires potassium elimination through the kidneys, GI tract, or dialysis. Patients with chronic hyperkalemia may also benefit from drugs that stimulate renal or stool K+ excretion.

With chronic or mild hyperkalemia, loop or thiazide diuretics increase renal potassium excretion; this is particularly important for patients with hyperkalemic renal tubular acidosis (Type 4 RTA), in whom the hyperkalemia is an important causative factor in the development of the metabolic acidosis.[49,50] With life-threatening hyperkalemia, diuretics should generally not be used because the rate of renal potassium excretion is not adequate. If a rapidly reversible cause of kidney failure is identified (e.g., obstructive uropathy or prerenal azotemia and kidney failure from volume depletion), treating the underlying condition may be sufficient, as long as there is close observation of serum potassium and continuous ECG monitoring.

A second mode of potassium elimination is with enteric K+-binding medications. Cation exchange resins, such as sodium polystyrene sulfonate or calcium polystyrene sulfonate (calcium resonium), have been used for decades. These resins exchange sodium or calcium, respectively, for potassium in the GI tract, enabling potassium elimination. They can be administered orally or as a retention enema. The rate of potassium removal is relatively slow, requiring about 4 hours for onset, although

Acute Treatment of Hyperkalemia

Mechanism

Therapy

Dose

Onset

Duration

Antagonize
membrane effects

Calcium

Calcium gluconate, 10% solution, 10 mL IV over
10 min

1–3 min

30–60 min

Cellular potassium
uptake

Insulin

Regular insulin, 10 U IV, with dextrose 50%, 50
mL, if plasma glucose <250 mg/dL

30 min

4–h

Potassium removal

135

β2-Adrenergic agonist

Nebulized albuterol, 10 mg

30 min

2–h

Sodium polystyrene sulfonate or
calcium polystyrene sulfonate
(calcium resonium)

30–60 g PO in 20% sorbitol or 30–60 g in water,
per retention enema

4–6 h

6–12 h

Patiromer

16.8–25.2 g

4–6 h

6–12 h

Sodium zirconium cyclosilicate

10 g

4–6 h

6–12 h

Hemodialysis

—

Immediate

Until dialysis completed

administering the resin as a retention enema results in more rapid onset of action. When given orally, cation exchange resins are generally administered with 20% sorbitol to avoid constipation. If given as an enema, sorbitol should be avoided because rectal administration of cation exchange resins with sorbitol may increase the risk of colonic perforation.51 Questions have been raised recently as to the efficacy of these compounds and whether the risk of colonic perforation exceeds their benefits.52 Two new enteric potassium-binding medications, patiromer and sodium zirconium cyclosilicate,53 54 have been developed. They have a better subjective side effect profile than the K+-binding resins, which leads to better long-term tolerability. Although all enteric K+-binding medications appear to lower K+ levels within 6 to 24 hours, none should be relied on for the treatment of life-threatening hyperkalemia.

Acute hemodialysis is the primary method of potassium removal in AKI or advanced CKD when hyperkalemia is life-threatening. Serum potassium can decrease as much as 1.2 to 1.5 mmol/h with a low potassium (2 mmol/L) dialysate. In general, the more severe the hyperkalemia, the more rapid should be the reduction in serum potassium until K+ is less than 6.0 mEq/L. However, care should be taken to avoid reducing the serum potassium too rapidly in patients with coronary heart disease or severe cardiac arrhythmias. In these patients, longer dialysis with dialysate potassium of 3 mmol/L allows serum potassium to equilibrate to that level. However, rigorous data supporting which patients should be treated with higher K^+ dialysate are not available. Our policy is to use 3 mmol/L K+ dialysate in patients with a history of sudden cardiac death. We also recommend rechecking serum potassium after completion of the dialysis procedure to verify effective correction of the hyperkalemia, waiting 1 to 2 hours to allow transcellular reequilibration. Continuous dialysis modalities, such as peritoneal dialysis and continuous venovenous hemodialysis, generally do not remove potassium sufficiently quickly for use in patients with life-threatening hyperkalemia but may be justified under unusual circumstances where hemodialysis is not available.

If dialysis is delayed, as when access to equipment or nursing support is not immediate, or while vascular access is being established, other therapies should be instituted and continued until hemodialysis is begun.

Specific therapies are available for certain causes of hyperkalemia. For example, digoxin-specific Fab fragments are beneficial in patients with severe digitalis glycoside toxicity.55 Hyperkalemia in patients with acute urinary tract obstruction may be treated by relieving the obstruction, but the rate of potassium excretion afterward is variable, and frequent measurement of serum potassium is necessary.

Chronic Treatment

Management of chronic hyperkalemia is a common and often challenging problem, particularly in the CKD patient. Patients with CKD have impaired capacity to excrete a potassium load rapidly and are often treated with medications, such as ACE inhibitors, ARB, β blockers, and MRBs, that can cause hyperkalemia.

Although most patients with chronic hyperkalemia are receiving medicines associated with the development of hyperkalemia, discontinuing all drugs that can cause hyperkalemia may not be the correct approach. Many medicines, such as ACE inhibitors, ARBs, β-blockers, and MRBs, have significant cardiovascular, renoprotective, and mortality benefits. Discontinuing these drugs simply because of mild hyperkalemia is therefore not recommended in the first-line management.

However, if the patient is receiving combined therapy with ACE inhibitor and ARB, discontinuing one of these drugs may decrease the risk of further hyperkalemia, and this does not appear to be associated with adverse renal effects. Similarly, if a patient is receiving combination therapy of either an ACE inhibitor or an ARB with a direct renin inhibitor, such as aliskiren, the direct renin inhibitor may be discontinued.

Instead of immediately discontinuing such beneficial drugs without review, a careful assessment should be made for medicines that cause hyperkalemia but are not necessary for renoprotective or cardioprotective benefits and therefore can be discontinued, such as NSAIDs, cyclooxygenase (COX)-2 inhibitors, potassium-sparing diuretics (e.g., amiloride, triamterene), and oral KCl or potassium citrate supplementation. If hyperkalemia persists, addition of diuretics to increase potassium excretion can be considered. Thiazide diuretics may be preferred because, when adjusted for their effect on sodium excretion, thiazide diuretics are associated with a greater increase in renal potassium excretion than loop diuretics. In the patient with CKD, the thiazide diuretic metolazone may be effective.56 Combination of thiazide and loop diuretics is more effective than either alone. Finally, screening for and treating metabolic acidosis may facilitate correction of the hyperkalemia. Alkali therapy may also increase K+ clearance.

A dietary history should be obtained, and if the patient is ingesting a diet with potassium-rich foods, instruction on avoidance of these foods should be provided. However, routine instruction in a lowpotassium diet for CKD patients is not recommended. Recent studies have suggested that a diet higher in potassium-rich foods may be associated with slower progression of CKD.57

Finally, chronic therapy with drugs that increase enteric K+ excretion can be considered, such as patiromer or sodium zirconium cyclosilicate.53 54 These drugs may allow for greater use of drugs that improve mortality in selected patient populations but whose use is otherwise limited because of development of hyperkalemia (e.g., ACE inhibitors and ARBs).

Synthetic mineralocorticoid therapy, such as fludrocortisone, has also been used for the treatment of chronic hyperkalemia. This approach may be helpful in patients with chronic hypotension caused by adrenal insufficiency who have normal kidney function. In CKD patients, the accompanying renal sodium retention, intravascular volume expansion, and increased blood pressure are relative contraindications to synthetic mineralocorticoids. Furthermore, selective blockade of the mineralocorticoid receptor appears to decrease kidney injury in several experimental models of renal injury, suggesting that administration of synthetic mineralocorticoids may be injurious. As a result, their adverse effects may exceed their benefits in patients with CKD.

SELF-ASSESSMENT QUESTIONS

1. Deficiency of which of the following ions can result in renal potassium wasting?
A. Phosphate
B. Calcium
C. Sulfate
D. Magnesium

2. Which of the following drugs is not associated with development of hyperkalemia?
A. Terazosin
B. Propranolol
C. Spironolactone
D. Cyclosporine

3. Hypokalemia is associated with which of the following conditions?
A. Decreased insulin sensitivity
B. Increased renal interstitial fibrosis
C. Increased risk of hepatic encephalopathy
D. Polyuria
E. All of the above

REFERENCES

1. Bailey RL, Parker EA, Rhodes DG, et al. Estimating sodium and potassium intakes and their ratio in the American diet: data from the 2011-2012 NHANES. J Nutr. 2015;146:745–750.
2. Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. N Engl J Med. 2015;373:60–72.
3. Young DB, Jackson TE. Effects of aldosterone on potassium distribution. Am J Physiol. 1982;243:R526–R530.
4. Street D, Nielsen JJ, Bangsbo J, Juel C. Metabolic alkalosis reduces exercise-induced acidosis and potassium accumulation in human skeletal muscle interstitium. J Physiol. 2005;566:481–489.
5. Aizawa H, Morita K, Minami H, Sasaki N, Tobise K. Exertional rhabdomyolysis as a result of strenuous military training. J Neurol Sci. 1995;132:239–240.
6. Weiner ID. Roles of renal ammonia metabolism other than in acid-base homeostasis. Pediatr Nephrol. 2017;32:933–942.
7. Milton AE, Weiner ID. Intracellular pH regulation in the rabbit cortical collecting duct A-type intercalated cell. Am J Physiol. 1997;273:F340–7.
8. Woda CB, Bragin A, Kleyman TR, Satlin LM. Flow-dependent K+ secretion in the cortical collecting duct is mediated by a maxi-K channel. Am J Physiol Renal. 2001;280:F786–F793.
9. Good DW, Wright FS. Luminal influences on potassium secretion: sodium concentration and fluid flow rate. Am J Physiol. 1979;236: F192–F205.
10. Hamm LL, Gillespie C, Klahr S. NH4Cl inhibition of transport in the rabbit cortical collecting tubule. Am J Physiol. 1985;248:F631–7.
11. Hadchouel J, Ellison DH, Gamba G. Regulation of renal electrolyte transport by WNK and SPAK-OSR1 kinases. Annu Rev Physiol. 2016;78:367–389.
12. Bazua-Valenti S, Gamba G. Revisiting the NaCl cotransporter regulation by with-no-lysine kinases. Am J Physiol Cell Physiol. 2015;308:C779–C791.
13. Yamada K, Park HM, Rigel DF, et al. Small-molecule WNK inhibition regulates cardiovascular and renal function. Nat Chem Biol. 2016;12:896–898.
14. Youn JH, McDonough AA. Recent advances in understanding integrative control of potassium homeostasis. Ann Rev Physiol. 2008;71:381–401.
15. Hayes Jr CP, McLeod ME, Robinson RR. An extravenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Am Physicians. 1967;80:207–216.
16. Sugarman A, Brown RS. The role of aldosterone in potassium tolerance: studies in anephric humans. Kidney Int. 1988;34:397–403.
17. Korgaonkar S, Tilea A, Gillespie BW, et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. Clin J Am Soc Nephrol. 2010;5:762–769.
18. Bloomfield RL, Wilson DJ, Buckalew Jr VM. The incidence of diureticinduced hypokalemia in two distinct clinic settings. J Clin Hypertens. 1986;2:331–338.
19. Chen Y, Sang Y, Ballew SH, et al. Race, serum potassium, and associations with ESRD and mortality. Am J Kidney Dis. 2017;70:244–251.
20. Patel RB, Tannenbaum S, Viana-Tejedor A, et al. Serum potassium levels, cardiac arrhythmias, and mortality following non-ST-elevation myocardial infarction or unstable angina: insights from MERLIN-TIMI 36. Eur Heart J Acute Cardiovasc Care. 2017;6:18–25.
21. Nakhoul GN, Huang H, Arrigain S, et al. Serum potassium, end-stage renal disease and mortality in chronic kidney disease. Am J Nephrol. 2015;41:456–463.
22. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. JAMA. 2012;307:157–164.
23. Ahmed A, Zannad F, Love TE, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. Eur Heart J. 2007;28:1334–1343.
24. Barri YM, Wingo CS. The effects of potassium depletion and supplementation on blood pressure: a clinical review. Am J Med Sci. 1997;314:37–40.

25. Huang CL, Kuo E. Mechanisms of disease: WNK-ing at the mechanism of salt-sensitive hypertension. Nat Clin Pract Nephrol. 2007;3:623–630.

26. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med. 1994;330:1852–1857.
27. Knochel JP. Diuretic-induced hypokalemia. AJM. 1984;77:18–27.
28. Reungjui S, Pratipanawatr T, Johnson RJ, Nakagawa T. Do thiazides worsen metabolic syndrome and renal disease? The pivotal roles for hyperuricemia and hypokalemia. Curr Opin Nephrol Hypertens. 2008;17:470–476.
29. Singhal PC, Abramovici M, Venkatesan J, Mattana J. Hypokalemia and rhabdomyolysis. Miner Electrolyte Metab. 1991;17:335–339.
30. Ray PE, Suga S, Liu XH, Huang X, Johnson RJ. Chronic potassium depletion induces renal injury, salt sensitivity, and hypertension in young rats. Kidney Int. 2001;59:1850–1858.
31. Tizianello A, Garibotto G, Robaudo C, et al. Renal ammoniagenesis in humans with chronic potassium depletion. Kidney Int. 1991;40:772–778.
32. Berl T, Linas SL, Aisenbrey GA, Anderson RJ. On the mechanism of polyuria in potassium depletion. The role of polydipsia. J Clin Invest. 1977;60:620–625.
33. Knochel JP, Dotin LN, Hamburger RJ. Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. J Clin Invest. 1972;51:242–255.
34. Schwartz WB, Cohen JJ. The nature of the renal response to chronic disorders of acid-base equilibrium. AJM. 1978;64:417–428.
35. Gill MA, DuBe JE, Young WW. Hypokalemic, metabolic alkalosis induced by high-dose ampicillin sodium. Am J Hosp Pharm. 1977;34:528–531.
36. Taher SM, Anderson RJ, McCartney R, Popovtzer MM, Schrier RW. Renal tubular acidosis associated with toluene “sniffing.” N Engl J Med. 1974;290:765–768.
37. Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney. Am J Kidney Dis. 2004;44:1–11.
38. Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implications. AJM. 1987;82:24–29.
39. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18:2649–2652.
40. Kunin AS, Surawicz B, Sims EA. Decrease in serum potassium concentrations and appearance of cardiac arrhythmias during infusion of potassium with glucose in potassium-depleted patients. N Engl J Med. 1962;266:228–233.
41. Falk RS, Robsahm TE, Paulsen JE, Stocks T, Drake I, Heir T. Fasting serum potassium and long-term mortality in healthy men. BMC Publ Health. 2021;21:711.
42. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. Clin J Am Soc Nephrol. 2017;12:245–252.
43. Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. Am J Nephrol. 2016;44:179–186.
44. Faxen J, Xu H, Evans M, Jernberg T, Szummer K, Carrero JJ. Potassium levels and risk of in-hospital arrhythmias and mortality in patients admitted with suspected acute coronary syndrome. Int J Cardiol. 2019;274:52–58.
45. Batlle DC, Arruda JA, Kurtzman NA. Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. N Engl J Med. 1981;304:373–380.
46. Gordon RD. Syndrome of hypertension and hyperkalemia with normal glomerular filtration rate. Hypertension. 1986;8:93–102.
47. Allon M. Hyperkalemia in end-stage renal disease: mechanisms and management. J Am Soc Nephrol. 1995;6:1134–1142.
48. Allon M, Dunlay R, Copkney C. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. Ann Intern Med. 1989;110:426–429.

49. Sebastian A, Schambelan M, Sutton JM. Amelioration of hyperchloremic acidosis with furosemide therapy in patients with chronic renal insufficiency and type 4 renal tubular acidosis. Am J Nephrol. 1984;4:287–300.
50. Harris AN, Grimm PR, Lee HW, et al. Mechanism of hyperkalemiainduced metabolic acidosis. J Am Soc Nephrol. 2018;29:1411–1425.

References

51. Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. Am J Kidney Dis. 1992;20:159–161.
52. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol. 2010;21:733–735.
53. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–221.
54. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372:222–231.

55. Smith TW, Butler Jr VP, Haber E, et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. N Engl J Med. 1982;307:1357–1362.
56. Paton RR, Kane RE. Long-term diuretic therapy with metolazone of renal failure and the nephrotic syndrome. J Clin Pharmacol. 1977;17:243–251.
57. Veiras LC, Han J, Ralph DL, McDonough AA. Potassium supplementation prevents sodium chloride cotransporter stimulation during angiotensin II hypertension. Hypertension. 2016;68:904–912.

11

Disorders of Calcium, Phosphate, and Magnesium Metabolism

Bryan Kestenbaum, Pascal Houillier

CALCIUM HOMEOSTASIS AND DISORDERS OF CALCIUM METABOLISM

Distribution of Calcium in the Organism

Most (>99%) calcium in the body is bound and associated with bony structures. Free calcium, in diffusible nonionized or ionized forms, is found in the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. Similar to potassium, there is a steep concentration gradient between calcium (Ca^{2+}) inside cells and the extracellular compartment (Fig. 11.1).

The serum calcium concentration is tightly regulated within a narrow range by parathyroid hormone (PTH) and calcitriol (1,25dihydroxycholecalciferol). Fig. 11.2 demonstrates physiologic defense mechanisms used to counter changes in the serum Ca^{2+} concentration.1 Acute alkalosis causes a decrease in serum Ca^{2+}, and acute acidosis causes an increase in Ca^{2+}. The long-term maintenance of calcium homeostasis depends on intestinal Ca^{2+} absorption, bone accretion and resorption, and urinary excretion (Fig. 11.3).

The extracellular ionized Ca^{2+} concentration is sensed by principal cells in the parathyroid glands via the calcium-sensing receptor (CaSR), which is the primary determinant of PTH synthesis and release. PTH secretion increases or decreases within seconds in response to changes in extracellular ionized Ca^{2+}. The CaSR is present in numerous tissues, including the kidneys.2 Mutations of the CASR gene cause clinical syndromes characterized by hypercalcemia or hypocalcemia (see later).

Intestinal, Skeletal, and Kidney Handling of Calcium

Only about 25% of dietary calcium is absorbed in the gastrointestinal (GI) tract under normal conditions. Intestinal calcium absorption falls precipitously in chronic kidney disease (CKD) because of decreased kidney synthesis of calcitriol. Calcium absorption can be subdivided into transcellular and paracellular flow (Fig. 11.4). Transcellular flux takes place through the apical transient receptor potential channel vanilloid subtype 6 (TRPV6) calcium channel.3 Calcitriol stimulates active calcium transport by binding to and activating the vitamin D receptor (VDR), which induces expression of TRPV6, calbindin-D9k, and Ca^{2+}-ATPase (PMCA1b).4 Other hormones, including estrogens, prolactin, growth hormone, and parathyroid hormone (PTH), as well as the amount of dietary calcium intake, also stimulate intestinal calcium absorption, either directly or indirectly (Fig. 11.5).5

The primary source of vitamin D derives from exposure to ultraviolet light, which converts 7-dehydrocholesterol to cholecalciferol (vitamin D_3) in the skin. Cholecalciferol can also be obtained through supplementation and dietary sources; however, the cholecalciferol content of most foods is low. Ergocalciferol (vitamin D_2) is an alternative vitamin D supplement that does not occur naturally in humans. Cholecalciferol and ergocalciferol (which contains an additional methyl group) have minimal inherent biologic function and require two hydroxylation steps for full hormonal activity. The first step, 25-hydroxylation, occurs in the liver by vitamin D 25-hydroxylase encoded by the CYP2R1 gene. This step is believed to be nonrate limiting; however, polymorphisms in CYP2R1 are associated with differences in circulating 25-hydroxyvitamin D concentrations in the general population. The serum 25-hydroxyvitamin D concentration is widely accepted as the measure of vitamin D stores. Further hydroxylation to 1,25-dihydroxyvitamin D (calcitriol) is performed by 25-hydroxyvitamin D-1 alpha hydroxylase encoded by the CYP27B1 gene. This step occurs predominantly in the kidneys but can also occur in macrophages, parathyroid glands, and other tissues. The activated, 1-hydoxy forms of vitamin D are subsequently catabolized by the CYP24A1 enzyme (cytochrome P450 family 24 subfamily A member 1) to prevent toxicity. Serum 1,25-dihydroxyvitamin D concentrations are approximately 1000-times lower than 25-hydroxyvitamin D, highlighting the tight hormonal control of the final hydroxylation step.

An increase in intestinal calcium absorption is required in puberty and pregnancy, whereas in lactation, calcium is mostly obtained from maternal bone.[6] In puberty and pregnancy, calcitriol synthesis is increased to enhance calcium absorption. Intestinal calcium absorption is also increased in states of vitamin D excess and acromegaly.

Rarely, the ingestion of calcium and alkali in large quantities can overwhelm checks on calcium absorption, resulting in hypercalcemia (milkalkali syndrome).

A decrease in intestinal calcium transport occurs in advanced age, kidney disease (because of reduced calcitriol synthesis), gastrectomy, intestinal malabsorption syndromes, diabetes mellitus, corticosteroid treatment, and estrogen deficiency and with dietary factors such as high vegetable fiber and fat content, low calcium-tophosphate ratio in food, and fructose ingestion. The decrease in calcium absorption in older adults probably results from multiple factors in addition to lower serum calcitriol and intestinal VDR.[7]

The net balance between calcium entry and exit is positive during skeletal growth in children, zero in young adults, and negative in older persons. Exchangeable skeletal calcium contributes to the maintenance of extracellular calcium homeostasis. Several growth factors, hormones, and genetic factors participate in the differentiation from mesenchymal precursor cell to osteoblast and maturation of the osteoclast from its granulocyte-macrophage precursor cell (Fig. 11.6). Bone formation and resorption is also regulated by many hormones, growth factors, and mechanical factors[8,9] (Fig. 11.7).

The kidneys regulate minute-by-minute calcium balance, and the intestine, kidney, and skeleton ensure homeostasis in the mid and long term (Fig. 11.8).[10] The synthesis of calcitriol from substrate 25-hydroxyvitamin D is increased by PTH and reduced by fibroblast growth factor 23 (FGF-23) and perhaps hyperphosphatemia. The adjustment of blood calcium is mainly achieved by modulation of tubular calcium reabsorption, perfectly compensating minor increases or decreases in the filtered calcium load (normally about 220 mmol

[8800 mg] per day; see Fig. 11.3). The bulk of calcium reabsorption in the kidneys occurs in the proximal tubules following the convective flow of salt and water, with relatively smaller contributions from the thick ascending limb and distal tubular segments.

Excess volume delivery to the kidneys, such as with a high-sodium diet, may diminish the concentration gradient between the proximal tubule and peritubular capillary, reducing the driving force for calcium absorption and increasing urinary calcium excretion. This mechanism is suspected to contribute to the pathogenesis of calcium-based kidney stones and provides a rationale for recommending a low-sodium diet in this setting. On the other hand, volume depletion increases the reabsorption of salt, water, and, by convection, calcium in the proximal tubules, exacerbating states of calcium excess. For this reason, intravascular volume repletion is an essential first step in the treatment of hypercalcemia.

In the thick ascending limb (TAL), calcium transport is paracellular, functionally linked with activity of the Na+-K+-2Cl transporter and the attendant lumen-positive transepithelial voltage. Stimulation of the basolateral CaSR decreases the paracellular pathway permeability to calcium.11 The result is decreased calcium reabsorption through the Claudin-16 and 19 complex in tight junctions (Fig. 11.9). In contrast, understimulation of the CaSR by low serum calcium levels increases tubular calcium reabsorption. In the distal tubules, active calcium transport occurs via the transcellular route through the transient receptor potential channel vanilloid subtype 5 (TRPV5). This channel is located in the apical membrane and coupled with a specific basolateral calcium-ATPase (PMCa1b) and Na+-Ca2+ exchanger (NCX1). Both PTH and calcitriol increase distal tubular Ca2+ transport. Several classes of diuretics alter kidney calcium handling. Loop diuretics increase urinary calcium excretion by inhibiting the Na+-K+ 2Cl cotransporter, whereas thiazide diuretics and amiloride increase distal tubular calcium absorption.

Distribution of Calcium in
Extracellular and Intracellular Spaces
Calcium

Intracellular
(cytoplasmic free)
50–100 nmol/L

Extracellular
Total: 2.25–2.65 mmol/L
(9–10.6 mg/dL)

Protein bound 45%

HYPERCALCEMIA

Diffusible
(ultrafilterable) 55%

Free ionized 45%

Complexed 10%

Fig. 11.1 Calcium distribution in extracellular and intracellular spaces.

Routine measurement of the serum calcium concentration [Ca2+] reports the total concentration in the tube, including bound and unbound fractions.

Increased serum [Ca2+] can therefore result from an increase in serum proteins (false hypercalcemia) or reflect a real increase in ionized [Ca2+] (true hypercalcemia). If laboratory assays for ionized calcium are not available, serum [Ca2+] can be corrected using serum albumin: each

Defense Against Hypercalcemia

Defense Against Hypocalcemia

Increased
serum Ca2+

Decreased
plasma Ca2+

Activation of
Ca2+-sensing receptor

Inactivation of
Ca2+-sensing receptor

↓ Parathyroid hormone
and ↑ calcitonin release

↑ Parathyroid
hormone release

↓ Renal 25hydroxyvitamin D 3
1α-hydroxylase

↑ Fractional renal
Ca2+ excretion

↓ Mobilization of Ca 2+
from skeleton and
soft tissues

↑ Renal 25hydroxyvitamin D 3
1α-hydroxylase

↓ Fractional renal
Ca2+ excretion

↑ Mobilization of Ca 2+
from skeleton and
soft tissues

↓ Calcitriol synthesis

↑ Active intestinal
Ca2+ absorption

↓ Active intestinal
Ca2+ absorption

A

Normal serum Ca 2+

↑ Calcitriol synthesis

B

Normal serum Ca 2+

Fig. 11.2 Calcium Regulation. Physiologic defense mechanisms against increases or decreases in serum calcium levels. (A) Hypercalcemia. (B) Hypocalcemia. (Modified from Kumar R. Vitamin D and calcium transport. Kidney Int. 1991;40:1177–1189.)

Ingested Calcium and
Its Intestinal Net Absorption

Calcium Homeostasis in the Healthy Adult
Intracellular (non-bone)
compartment
100 mmol

15
10

?
7.5 mmol
Extracellular
compartment
5 mmol 20–25 mmol 7.5 mmol

8–11 mmol

Intestine

220 mmol

Bone
compartment

5
0

–5
0

25 mol
10–25 mmol

Net calcium absorption
(mg/kg per day)

15–30 mmol

139

Kidney

3–5 mmol
Fig. 11.3 Calcium Homeostasis in Healthy Adults. Net zero Ca2+ balance is the result of net intestinal absorption (absorption minus secretion) and urinary excretion, which by definition are the same. After its passage into the extracellular fluid, Ca2+ enters the extracellular space, is deposited in bone, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude under steady-state conditions.

5

10
15
20
25
30
35

Daily calcium intake (mg/kg)
Fig. 11.5 Calcium Ingestion and Absorption. Relationship between ingested calcium and its absorption in the intestinal tract (net) in healthy young adults. (From Wilkinson R. Absorption of calcium, phosphate, and magnesium. In: Nordin BEC, ed. Calcium and Magnesium Metabolism. Churchill Livingstone; 1976:36–112.)

Mechanisms of Osteoblast Differentiation
Adipocyte

Chondroblast

?

PPARℴ2
Precursor
cell

Transepithelial Calcium Transport

Mesenchymal
stromal stem cell
Cbfa 1

Blood

Intestinal
lumen
Calbindin D9k

Ca2+ (10

Ca2+
sensing
receptor

3 M)

Ca2+ (10 7M)

Mitochondrion

Endoplasmic
reticulum

Ca2+
Na+– Ca2+
exchanger
(NCX1)aa

Nucleus

TRPV6

VDR

A

Mechanisms of Osteoclast Differentiation

Ca2+– ATPase
(PMCA1b)
Calcitriol
Ca2+ (10

Osteoclast
progenitor

3 M)

M-CSF receptor
(c-Fms)

Paracellular
transport
Electrical
potential 0
difference

M-CSF

Transcellular
transport
55 mV

1,25 (OH)2D3
Activated osteoblasts
PGE1,PGE2, IGF-1...
TGF-n

Osteoblast

RANK
RANK-L

Osteoclast
Differentiation
and fusion
OPG
RANK-L

5 mV

Fig. 11.4 Transepithelial Calcium Transport in the Small Intestine. Calcium penetrates into the enterocyte channels via a transient receptor potential calcium channel (TRPV6) through the brush border membrane along a favorable electrochemical gradient. Under physiologic conditions, the cation is pumped out of the cell at the basolateral side against a steep electrochemical gradient by the adenosine triphosphate–consuming pump Ca^{2+}-ATPase. When there is a major elevation of intracytoplasmic Ca^{2+}, the cation leaves the cell using the Na^{+}-Ca^{2+} exchanger. Passive Ca^{2+} influx and efflux are sensitive to calcitriol, which binds the vitamin D receptor (VDR).

B

1,25 (OH)2D3
PGE2, PTH, IL-1
TGF-n

Osteoblast/stroma cell

Fig. 11.6 Mechanisms of Osteoblast Differentiation. (A) Major growth factors and hormones controlling the differentiation from the mesenchymal precursor cell to the osteoblast. (B) The major growth factors, cytokines, and hormones controlling osteoblast and osteoclast activity. IGF, Insulin-like growth factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; PGE2, prostaglandin E2; PPAR,

peroxisome proliferator–activated receptor; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-κβ ligand; TGF, transforming growth factor.

Determinants of Skeletal Homeostasis and Bone Mass
BMP

SOST

Mechanical
load

o-blockers

LRP5/
Wnt

Intermittent
PTH

Androgens

o-adrenergic receptors

Aging
Bone resorption

Immobilization
Leptin

Bone
mass

Bone formation

Estrogen
deficiency

Estrogen

Immobilization

Low Ca
(PTH)

Bisphosphonates

Calcium
Vitamin D
Calcitonin

SERMs

Fig. 11.7 Determinants of Skeletal Homeostasis and Bone Mass. Physiologic (black) and pharmacologic (red) stimulators and inhibitors of bone formation and resorption are listed with the relative impact (represented by thickness of arrows). BMP, Bone morphogenetic protein; LRP5, low-density lipoprotein receptor–related protein 5; PTH, parathyroid protein; SERMs, selective estrogen receptor modulators; SOST, sclerostin. (From Kinyamu HK. Association between intestinal vitamin D receptor, calcium absorption, and serum 1,25 dihydroxyvitamin D in normal young and elderly women. J Bone Miner Res. 1997;12:922–928.)

Calcium Reabsorption in the Kidney

Glomerulus

Distal convoluted tubule
5%–10%

Cortex
Proximal
convoluted
tubule
50%–60%

External
medulla

Inner
medulla

Proximal
pars recta
(3%–10%)

Thick
ascending
limb
(20%–25%)

Collecting
tubule
2%

Henle’s
loop

1%–3%

Fig. 11.8 Sites of Calcium Reabsorption. Percentage of Ca^{2+} absorbed in various segments of the renal tubule after glomerular ultrafiltration. (Modified from Martin T, Gooi JH, Sims NA. Molecular mechanisms in coupling of bone formation to resorption. Crit Rev Eukaryot Gene Expr. 2009[19]:73–88.)

1.0 g/dL higher serum albumin concentration is associated with a concomitant 0.20 to 0.25 mmol/L (0.8–1.0 1.0 mg/dL) greater serum [Ca2+].
However, simple correction for serum albumin may not be valid in patients with CKD stages 3 to 5.12

Causes of Hypercalcemia

Hypercalcemia may be caused by an increase in intestinal calcium absorption, excess bone resorption, enhanced kidney tubular reabsorption, or a combination of these processes. The most common clinical causes of hypercalcemia are malignancy and primary hyperparathyroidism, which can be distinguished by measurement of PTH.
Regardless of the primary cause, secondary volume depletion prolongs hypercalcemia by interfering with urinary calcium excretion (Fig. 11.10).

Reabsorption in the Loop of Henle
Na+
K+
Urine

NKCC2
+
K+ K
K+

2CI
K+

ROMK

CI

CICKb

Blood
Inhibit

Ca++
CASR

Ca++
Mg++

Claudin 16 - Claudin 19
Claudin 14

Stimulate
Inhibit

Paracellular
CI

CI
CI

Fig. 11.9 Reabsorption in the Loop of Henle. Transport of Na+, K+, $2Cl^-$ into the cell via NKCC2 drives paracellular reabsorption of calcium and magnesium through a claudin 16-claudin 19 complex. Stimulation of the calcium-sensing receptor on the basolateral cell surface, such as by hypercalcemia, inhibits calcium and magnesium reabsorption.

Malignant Neoplasia

An important cause of hypercalcemia is excessive bone resorption induced by neoplastic processes, usually solid tumors.13 Tumors of the neck, breast, lung, and kidney are the most common, followed by hematopoietic neoplasias, particularly myeloma. Tumors causing hypercalcemia act on the skeleton by direct invasion (metastases) or by producing factors that stimulate osteoclastic activity (paraneoplastic processes). The most common tumor-derived factor is PTH-related protein (PTHrP). Only 8 of the 13 first amino acids of PTHrP are homologous to the N-terminal fragment of PTH, but the effects of both hormones on target cells are similar because they share a common receptor (the PTH/PTHrP receptor, PTH1R). In multiple myeloma and lymphomas, osteoclast-activating factors secreted by clonal cells include interleukins (IL-1α, IL-1β, IL-6) and tumor necrosis factor (TNF)-α. Certain tumors, especially kidney masses, may secrete other osteoclast-activating factors, such as PGE1 and PGE2. Some lymphoid tumors, including Hodgkin disease, T-cell lymphoma, and leiomyoblastoma, can synthesize excess quantities of calcitriol, which promote hypercalcemia.

Primary Hyperparathyroidism

In more than 80% of patients, hyperparathyroidism is caused by an adenoma of a single parathyroid gland; 10% to 15% have diffuse hyperplasia of all glands, and less than 1% have parathyroid carcinoma.

Causes of Hypercalcemia

Solid tumors
Breast cancer
Bronchial cancer
Renal cancer
Thyroid cancer

Primary hyperparathyroidism
Primary adenoma
Primary diffuse hyperplasia
Primary adenocarcinoma
Multiple endocrine
neoplasias (MEN-1, MEN-2A)

Neoplastic
diseases

Other endocrinopathies
Hyperthyroidism
Acromegaly
Pheochromocytoma
Acute adrenal insufficiency
Tertiary hyperparathyroidism
(chronic renal failure)

Familial
hypocalciuric
hypercalcemia

Pseudohyperparathyroidism
(Jansen disease)

Hypercalcemia

Neoplasias of
hematopoietic
system
Myeloma
Lymphoma

Leukemia

Vitamin intoxication
Hypervitaminosis D
Hypervitaminosis A

141

Other
Immobilization
Treatment with
certain medications
(thiazides, lithium,
theophylline)
Milk-alkali syndrome
Recovery phase of
acute renal failure
(rhabdomyolysis)
False hypercalcemia
(by hemoconcentration)

Granulomatous
diseases
Sarcoidosis
Tuberculosis (?)
Berylliosis
Coccidioidomycosis
Histoplasmosis
Leprosy
Silicon-induced
granulomas

Fig. 11.10 Causes of Hypercalcemia. Neoplastic diseases and primary hyperparathyroidism are the most common causes of hypercalcemia. (From Harada S, et al. Control of osteoblast function and regulation of bone mass. Nature. 2003;12:922–928.)

Primary hyperparathyroidism typically presents in middle age with asymptomatic mild hypercalcemia and a high or high normal serum PTH concentration. Under normal conditions, even a mild increase in serum [Ca2+] should potently suppress PTH secretion. Consequently, primary hyperparathyroidism should be suspected when both serum [Ca2+] and PTH are at the higher end of the normal range. Urinary calcium excretion is increased in primary hyperparathyroidism, which may assist in the diagnosis.

Primary hyperparathyroidism is usually idiopathic but can be inherited either as diffuse hyperplasia of the parathyroid glands alone or as a component in multiple glandular hereditary endocrine disorders. Patients with multiple endocrine neoplasia type 1 (MEN-1) have various combinations of parathyroid, anterior pituitary, enteropancreatic, and other endocrine tumors, resulting in hypersecretion of prolactin, gastrin, and PTH. MEN-1 is caused by inactivating germ-line mutations of a tumor suppressor gene (MEN-1) that is inherited as an autosomal dominant trait. In MEN-2A, the thyroid medulla and the adrenal medulla are involved, resulting in hypersecretion of calcitonin and catecholamines. MEN-2A is caused by activating mutations of the RET proto-oncogene. It is also inherited as an autosomal dominant trait. MEN-4 is characterized by the occurrence of parathyroid and anterior pituitary tumors possibly associated with tumors of the adrenals, kidneys, and reproductive organs; it is because of cyclindependent kinase inhibitor (CDNK1B) mutations.14

Granulomatous Diseases

The formation of macrophage-laden granulomas in specific infectious and inflammatory diseases can promote unchecked activity of macrophage-associated 1 alpha hydroxylase activity, leading to excess calcitriol synthesis and hypercalcemia. Common granulomatous diseases associated with hypercalcemia are sarcoidosis and tuberculosis; other conditions include histoplasmosis, coccidioidomycosis, berylliosis, and leprosy. Laboratory measurement of the serum 1,25-dihydroxyvitamin D concentration can help identify these conditions.

Other Endocrine Causes

Other endocrine disorders associated with moderate hypercalcemia include hyperthyroidism, acromegaly, pheochromocytoma, and acute adrenal insufficiency.

Inherited Causes

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare hereditary disease, most often caused by inactivating mutations in the CASR gene with autosomal dominant transmission,15 more rarely in the gene for G-protein subunit α11 (GNA11), or adaptor-related protein complex 2, sigma 1 subunit (AP2S1).16 The key clinical finding in FHH is an inappropriately low urinary calcium excretion in the setting of highnormal serum [Ca2+]. Serum PTH levels are often normal or moderately increased, potentially mimicking the diagnosis of primary hyperparathyroidism. The key distinction is low urine calcium excretion in FHH, assessed by calculating the fractional excretion of calcium (FECa) from a 24-hour urine collection:

$$\text{Fraction excretion of calcium (FECa)} = \frac{(\text{Urine calcium}) \times (\text{Serum creatinine})}{(\text{Serum calcium}) \times (\text{Urine creatinine})}$$

In FHH, the FECa is usually less than 0.01; however, some overlap may still be seen with primary hyperparathyroidism.17 FHH rarely leads to severe hypercalcemia except in the neonatal period.

Jansen Disease

Jansen disease is a rare hereditary form of short-limbed dwarfism characterized by severe hypercalcemia, hypophosphatemia, and metaphyseal chondrodysplasia. The condition is caused by activating mutations of the gene coding for the PTH1R receptor, a particular form of pseudohyperparathyroidism.

Other Causes

Hypercalcemia is seen with protracted bedrest, especially in the setting of prolonged hospitalization. Hypercalcemia is rarely observed with intoxication from vitamin A or D supplements and thiazide diuretics. Large doses of oral calcium (5–10 g/day), when ingested with alkali (antacids), can lead to hypercalcemia and nephrocalcinosis (milkalkali syndrome).

Hypercalcemia in Chronic Kidney Disease

The natural history of CKD includes a gradual reduction in serum [Ca2+] because of reduced calcitriol synthesis. The presence of hypercalcemia in patients with advanced CKD or end-stage kidney disease (ESKD) should alert the clinician to a potential iatrogenic cause, specifically the overadministration of calcium-containing phosphate binders and vitamin D receptor agonists (calcitriol, paricalcitol). A second potential cause of hypercalcemia in ESKD is tertiary hyperparathyroidism, in which the parathyroid glands lose responsiveness to therapy with severe elevation of serum PTH.

Clinical Manifestations

The severity of symptoms and signs caused by hypercalcemia depends not only on the degree but also the rapidity of development. Common symptoms are fatigue, muscle weakness, inability to concentrate, nervousness, increased sleepiness, and depression. GI symptoms include constipation, nausea and vomiting, and, rarely, peptic ulcer disease or pancreatitis. Kidney-related signs include hypertension, polyuria (secondary to nephrogenic diabetes insipidus), salt wasting, kidney stones and their complications, and, occasionally, tubulointerstitial disease with medullary and, to a lesser extent, cortical nephrocalcinosis. Patients with chronic hypercalcemia often present with a modest elevation in the serum creatinine concentration, indicating reduced GFR. Neuropsychiatric manifestations are common and include headache, loss of memory, somnolence, stupor, and, rarely, coma. Ocular symptoms include conjunctivitis from crystal deposition and, rarely, band keratopathy. The electrocardiogram (ECG) may show shortening of the QT interval and coving of the ST wave. Hypercalcemia may increase cardiac contractility and can amplify digitalis toxicity.

Diagnosis

In addition to the clinical history, examination, and review of medications, measurement of ionized [Ca2+] and serum PTH are the first steps in investigating the cause of hypercalcemia. Primary hyperparathyroidism should be suspected if the PTH concentration is high or high-normal in the presence of a high or high-normal serum [Ca2+], although FHH is not excluded by this laboratory pattern. If PTH is appropriately suppressed with hypercalcemia, then the possibility of a neoplastic disorder should be considered. Subsequent laboratory steps to determine the cause of hypercalcemia include serum protein electrophoresis and measurement of PTHrP, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D.

Treatment

The treatment of hypercalcemia is aimed at the underlying cause, although severe (>3.25 mmol/L) and symptomatic hypercalcemia always requires rapid correction. Initially, the patient should be volume expanded with isotonic saline or balanced crystalloids to inhibit tubular calcium reabsorption and enhance urinary calcium excretion.

Only when euvolemia is established can loop diuretics be considered to further augment urinary calcium excretion; however, intravenous (IV) fluids should be continued to prevent hypovolemia. Volume expansion must be carefully managed in patients with heart failure or advanced kidney disease. Oral intake, IV administration of fluids and electrolytes, and acid-base balance should be carefully monitored.

Bisphosphonates are the treatment of choice, especially in patients with hypercalcemia associated with cancer.[13] These agents inhibit bone resorption and calcitriol synthesis. Bisphosphonates can be administered orally in less severe disease or by IV in severe hypercalcemia.

Common bisphosphonates include pamidronate 15 to 90 mg IV over 1 to 3 days and zoledronate 4 mg IV once; IV doses should be infused in 500 mL of isotonic saline or dextrose over at least 2 hours (pamidronate) or 15 minutes (zoledronate). Although package warnings state that bisphosphonates should be used with caution in patients with CKD, this warning pertains to the theoretical possibility of inducing hypocalcemia. Bisphosphonates have been safely used in patients with CKD for the correction of hypercalcemia. Calcitonin acts within hours, especially after IV administration. Human, porcine, or salmon calcitonin can be given. However, calcitonin often has no effect, or only a short-term effect, because of the rapid development of tachyphylaxis.

Denosumab, a monoclonal antibody to the receptor activator of nuclear factor κ-B ligand (RANKL), is a potent inhibitor of bone resorption that can be useful in bisphosphonate-refractory hypercalcemia. Denosumab is not removed by the kidneys. The typical dose is 120 mg subcutaneously and can be repeated no earlier than 1 week after the first administration.[18]

Corticosteroids such as prednisone (or prednisolone), 0.5 to 1.0 mg/kg daily, are mainly indicated in patients with sarcoidosis or tuberculosis, to decrease macrophage synthesis of calcitriol. Corticosteroids also can be used in patients with hypercalcemia associated with some hematopoietic tumors (e.g., myeloma, lymphoma) and even for some solid tumors such as breast cancer. Ketoconazole, an antifungal agent that can inhibit renal and extrarenal calcitriol synthesis, can also be used to treat hypervitaminosis D.

In rare cases of malignant hypercalcemia, treatment with prostaglandin antagonists such as indomethacin or aspirin can be successful. Hyperkalemia and impaired kidney function may occur with indomethacin. Hypercalcemia caused by thyrotoxicosis can rapidly resolve with IV administration of propranolol or less rapidly with oral administration.

In patients with primary hyperparathyroidism, consideration for parathyroidectomy is based on the severity of hypercalcemia and the accompanying complications of the disease, including loss of bone mineral density, nephrolithiasis, and kidney dysfunction. For nonsurgical, asymptomatic candidates, potential medical therapies include bisphosphonates and the CaSR agonist cinacalcet (a calcimimetic).[19] Cinacalcet is also effective in patients with parathyroid carcinoma. Surgical parathyroidectomy remains an important therapeutic option in patients with ESKD who are unresponsive to vitamin D analogs and calcimimetics.[20]

HYPOCALCEMIA

A decrease in total serum [Ca^{2+}] may occur as a result of reduced serum albumin (false hypocalcemia) or can reflect a real change in ionized [Ca^{2+}] (true hypocalcemia). False hypocalcemia is best excluded by direct measurement of ionized [Ca^{2+}]. Alternatively, total serum [Ca^{2+}] can be corrected for serum albumin as described previously.

Causes of true hypocalcemia can be divided into conditions that are

Causes of Hypocalcemia
Associated with normal/low plasma phosphate
Vitamin D deficiency: decreased intake or decreased absorption
(postgastrectomy, primary biliary cirrhosis, intestinal Ca malabsorption)
Decreased 25-hydroxyvitamin D generation (liver disease, anticonvulsants)
Decreased calcitriol formation (renal failure, type 1
vitamin D–dependent rickets)
Resistance to calcitriol (type 2 vitamin D–dependent rickets)
Acute pancreatitis
Magnesium deficiency
Hungry bone syndrome (postsurgical treatment of hyperparathyroidism
or vitamin D deficiency)

Hypocalcemia

Associated with high plasma phosphate
Idiopathic or sporadic hypoparathyroidism
Postoperative hypoparathyroidism
Acquired hypoparathyroidism
(postirradiation, amyloidosis)
Pseudohypoparathyroidism: type 1 or 2
Chronic renal failure, advanced stage
Acute renal failure, oligoanuric stage

Associated with
hypoalbuminemia
Hemodilution
Nephrotic syndrome
Exudative enteropathy
Cirrhosis

Fig. 11.11 Causes of hypocalcemia.

associated with high or low serum phosphate concentrations (Fig. 11.11).

Hypocalcemia Associated With Hyperphosphatemia

Chronic and Acute Kidney Disease

A gradual loss of functioning nephrons leads to reduced calcitriol production and a subsequent decrease in intestinal calcium absorption.
In parallel, serum phosphate concentrations progressively rise once the glomerular filtration rate (GFR) falls below approximately 35 mL/min/1.73 m2. Kidney disease and hyperphosphatemia stimulate the release of fibroblast growth factor 23 (FGF-23), a bone-derived hormone that further suppresses calcitriol synthesis by inhibiting 1-alpha hydroxylase activity. However, hypocalcemia and hyperphosphatemia arising from CKD may be masked by treatments, including calciumcontaining phosphate binders and vitamin D receptor agonists.
Hypocalcemia may also be observed in the setting of acute kidney injury (AKI). Several mechanisms may contribute to hypocalcemia in AKI, including an abrupt decline in calcitriol synthesis, an increase in FGF-23, and incomplete PTH response to the fall in serum [Ca2+].
Hypocalcemia may also be observed in the polyureic recovery phase of AKI, especially after rhabdomyolysis.

Hypoparathyroidism

Under normal conditions, PTH increases serum [Ca2+] and enhances urinary excretion of phosphate. Loss of PTH (hypoparathyroidism) therefore leads to hypocalcemia and hyperphosphatemia.
Hypoparathyroidism may occur after intentional (parathyroidectomy) or nonintentional (thyroidectomy) removal of the parathyroid glands.
Hypoparathyroidism can also be caused by autoimmune destruction

of parathyroid tissue, radiation, infiltrative diseases, or genetic conditions affecting development and/or function of the parathyroid glands.

Sporadic cases are occasionally seen in patients with pernicious anemia or adrenal insufficiency. Pseudohypoparathyroidism (iPPSD;

Inactivating PTH/PTHrP Signaling Disorders, including former pseudohypoparathyroidism type 1a and 1b) is a group of rare genetic diseases characterized by isolated or syndromic end organ resistance to PTH.21 Magnesium deficiency impairs the PTH response to hypocalcemia, producing a state of relative hypoparathyroidism. In addition, massive oral phosphate administration, such as used in bowel preparations, can also cause hypocalcemia with hyperphosphatemia, often in association with AKI.22

Distribution of Phosphate in Extracellular
and Intracellular Spaces

Hypocalcemia Associated With Hypophosphatemia

Extracellular phosphate
(1% of total phosphate)
0.8–1.5 mmol/L
(2.5–4.6 mg/dL)

Hypocalcemia with hypophosphatemia may occur in vitamin D–deficient states because of insufficient daylight exposure, dietary deficiency of vitamin D, decreased absorption after GI surgery, intestinal malabsorption syndromes (steatorrhea), or hepatobiliary disease (primary biliary cirrhosis). However, overt hypocalcemia caused by substrate 25-hydroxyvitamin D deficiency is uncommon because 1,25-dihydroxyvitamin D is tightly maintained at much lower concentrations.

Vitamin D–dependent rickets are a rare group of inherited disorders caused by defects in vitamin D metabolic enzymes (discussed in the section on hypophosphatemia).

Hypocalcemia is observed in the majority of critically ill adults and children. No singular mechanism has been identified; defects in calcitriol synthesis, PTH release, and target organ sensitivity to these hormones have been described. Hypocalcemia is also seen with hypomagnesemia in patients with acute pancreatitis caused by saponification in necrotic fat.

An acute decrease in ionized [Ca^{2+}] occurs during acute hyperventilation and the respiratory alkalosis that follows, regardless of the cause of hyperventilation.

Clinical Manifestations

As with hypercalcemia, the symptoms of hypocalcemia depend on the rate of development and severity. The most common manifestations, in addition to fatigue and muscular weakness, are increased irritability, loss of memory, a state of confusion, hallucination, paranoia, and depression. The best-known clinical signs are the Chvostek sign (tapping of facial nerve branches leading to twitching of facial muscle) and the Trousseau sign (carpal spasm in response to forearm ischemia caused by inflation of a sphygmomanometer cuff).

Patients with acute hypocalcemia may have paresthesias of the lips and the extremities, muscle cramps, and occasionally frank tetany, laryngeal stridor, or seizures. Chronic hypocalcemia may be associated with cataracts, brittle nails with transverse grooves, dry skin, and decreased or even absent axillary and pubic hair, especially in idiopathic hypoparathyroidism.

On the electrocardiogram (ECG), the corrected QT interval is frequently prolonged, and arrhythmias may occur. The electroencephalogram shows nonspecific signs such as an increase in slow, high-voltage waves. Intracranial calcifications, notably of the basal ganglia, are observed radiographically in 20% of patients with early-onset hypoparathyroidism but much less frequently in patients with postsurgical hypoparathyroidism or pseudohypoparathyroidism.

Treatment

Therapy of hypocalcemia is directed toward the underlying cause.

Severe and symptomatic (tetany) hypocalcemia requires rapid treatment with calcium gluconate as an IV bolus (e.g., 10 mL 10% weight/volume [2.2 mmol of calcium], diluted in 50 mL of 5% dextrose in water or isotonic saline), followed by 12 to 24 g over 24 hours. Calcium gluconate is preferred to calcium chloride, which can lead to extensive skin necrosis in accidental extravasation. Acute respiratory alkalosis, if present, should be corrected if possible.

Phosphate

Monosodium
phosphate

Disodium
phosphate

Intracellular free phosphate
approximately
1.4 mmol/L (4.3 mg/dL)

Phosphoric
esters

Fig. 11.12 Phosphate distribution in extracellular and intracellular spaces.

Treatment of chronic hypocalcemia includes oral administration of calcium salts, thiazide diuretics, and vitamin D. The amount of elemental calcium of the various salts differs greatly: the calcium content is 40% in carbonate, 36% in chloride, 12% in lactate, and only 8% in gluconate salts. The daily amount prescribed can be 1 to 4 g elemental calcium in adults. Concurrent magnesium deficiency (serum [Mg^{2+}] <0.70 mmol/L) should be treated with oral magnesium oxide or carbonate 100 to 300 mg elemental magnesium/day or with magnesium sulfate 4 to 8 mmol/day intramuscularly or 20 to 40 mmol/day in D5W IV.

Treatment of hypocalcemia secondary to hypoparathyroidism is difficult because urinary calcium excretion increases markedly with calcium and active vitamin D supplementation, potentially leading to nephrocalcinosis/nephrolithiasis and loss of kidney function. To reduce urinary calcium, thiazide diuretics can be used in association with restricted salt intake.

Therapy with vitamin D receptor agonists is the conventional treatment for idiopathic or acquired hypoparathyroidism because these compounds are better tolerated than massive doses of calcium salts. Large amounts of active vitamin D and calcium are often required for extended periods after surgical parathyroidectomy because of massive redistribution of calcium into the bone (hungry bone syndrome). Such patients require regular monitoring to avoid hypercalcemia, hyperphosphatemia, and hypercalciuria.

PHOSPHATE HOMEOSTASIS

Distribution of Phosphate in the Organism

Phosphorus is distributed in the body as 85% within bone and teeth; 15% inside cells; and less than 1% in the extracellular fluid, which includes the circulation. Fig. 11.12 shows the distribution of phosphate in extracellular and intracellular compartments. Within cells, phosphate regulates key enzymatic processes and serves as an essential structural component of nucleic acids and phospholipid membranes.

In the bloodstream, phosphate circulates as HPO_4^{2-} and H_2PO_4 in an approximate 4 to 1 ratio at physiologic pH. Normal serum phosphate concentrations range from 2.8 to 4.5 mg/dL (0.9–1.5 mmol/L) with known circadian fluctuation.[23] The lowest concentrations are observed in the morning between 8 am and 10 am, and relatively higher concentrations are seen in late afternoon.[24] Dietary phosphate intake has only a minimal impact on the serum phosphate concentration in normal individuals and nondialyzed persons with mild to moderate CKD.

Phosphate Homeostasis in the Healthy Adult
Intracellular (non-bone)
compartment 3–5 mmol

15–50 mmol
?
Intestine

15–20 mmol

40 mmol
Extracellular
compartment
15 mmol 40 mmol

120–200
mmol

100–170
mmol

Bone
compartment

Intestinal
lumen

Blood

Phosphate
(variable
concentration)

Phosphate
(10^{-3} mol/L)

Phosphate
Na^+-Pi
cotransport
(NPT2b)

15–25 mol

Na^+

Phosphate
[10 3 mol/L]

Phosphate

Nucleus
Anion

Kidney

20–50 mmol
Fig. 11.13 Phosphate Homeostasis in Healthy Adults. At net zero balance, identical net intestinal uptake (absorption minus secretion) and urinary loss occur. After its passage into the extracellular fluid, phosphate enters the intracellular space, is deposited in bone or soft tissue, or is

eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also the same under steady-state conditions.

Fig. 11.13 shows the balance of ingestion, body distribution, and excretion of phosphate in a healthy person. Phosphate needs are highest in children during growth. Phosphates are widely found in milk products, meat, eggs, and cereals, and are used extensively as food additives.
Phosphate enters epithelial cells via cotransport with sodium. Three different Na+-Pi cotransporter families have been identified and characterized. Members of the type 1 Na+-Pi family participate in kidney uric acid transport but do not directly impact phosphate homeostasis.25 The members of the type 2 family of Na-Pi cotransporters are the key players in phosphate regulation and are NPT2a, NPT2b, and NPT2c (encoded by SLC34A1, SLC34A2, and SLC34A3). NPT2a and NPT2c are expressed in the apical brush border of the proximal tubules, whereas NPT2b is expressed in the small intestine.26–29 The type 3 family of Na+-Pi cotransporters (encoded by SLC20A1 and SLC20A2) is ubiquitously expressed. Type 3 transporters do not participate directly in phosphate homeostasis; however, they mediate phosphate entry into vascular smooth muscle cells, which is hypothesized to be an important step in the pathogenesis of kidney-related vascular calcification.30 Mutations in SLC20A2 are the cause of primary familial brain calcification syndrome, a rare condition characterized by progressive bilateral calcification of the basal ganglia, thalami, and cerebellum.31

Intestinal, Renal, and Skeletal Handling of Phosphate

Intestinal phosphate absorption occurs via transepithelial and paracellular routes (Fig. 11.14). In contrast to the relatively restricted absorption of calcium, intestinal phosphate absorption is permissive, with 60% to 75% of dietary phosphate absorbed (15–50 mmol/day) in a linear, nonsaturable fashion (Fig. 11.15). The amount of intestinal phosphate absorption depends on the source of dietary phosphate: Absorption is highest for phosphate-containing food additives and lowest for plant-based phosphate sources.32 Cations, such as calcium, magnesium, and aluminum, bind to phosphate in the intestinal tract, limiting its absorption.

Paracellular
transport
Transcellular
transport

Electrical
55 mV
+5 mV
potential 0
difference

Fig. 11.14 Transepithelial Phosphate Transport in the Small Intestine. Phosphate enters the enterocyte (influx) through the brush border membrane using the Na+/Pi cotransport system, with a stoichiometry of 2:1, operating against an electrochemical gradient. Phosphate exit at the basolateral side possibly occurs by passive diffusion or more probably by anion exchange.

Ingested Phosphate and
Its Intestinal Net Absorption
Net daily phosphorus
absorption (mg/kg)

25–65 mmol

Transepithelial Phosphate Transport

30
20
10

r = 0.946
P < .001

0
0

10
20
30
40
Daily phosphate intake (mg/kg)

Fig. 11.15 Phosphate Ingestion and Absorption. Relationship between ingested phosphate and phosphorus absorbed in the digestive tract (net absorption) in healthy young adults. (From Wilkinson R. Absorption of calcium, phosphate, and magnesium. In: Nordin BEC, ed. Calcium and Magnesium Metabolism. Churchill Livingstone; 1976:36–112.)

Calcitriol is the primary hormonal determinant of intestinal phosphate absorption. Calcitriol upregulates NPT2b cotransporters in the small intestine, increasing phosphate entry via transcellular transport.33 34 Vitamin D receptor agonists, including calcitriol and its analogs, enhance phosphate and calcium absorption, whereas nonactivated vitamin D supplements, such as cholecalciferol and ergocalciferol, have only a minimal impact on intestinal uptake. In experimental models, nicotinamide, a form of vitamin B3, inhibits NPT2b expression, suggesting a role in the treatment of hyperphosphatemia. However, nicotinamide had no effect on serum phosphate concentrations in patients with moderate to advanced CKD in a randomized trial.35

Nomogram for Estimation of the Renal Threshold Phosphate Concentration

1.0

00
0.
0.0

2.0

0.2

1.8

0.4

1.6

0.6
0.8
mmol/l

2.0

1

0
0.

05

4.0

1.4

9

9
0.

5.0

95

0.

1.2

0

3.0

9
0.

Renal threshold phosphate concentration (TmP/GFR)

Actual plasma phosphate concentration
mg/dL

0.0
00
0.

0

1
0.

P

0.

TR

1.0
80
0. .70
0 60
0. 50
0.8
3.0
2.0
1.2
20
0. .30
0.
0
0 40
4
.
0
0.6
0. 50
1.4
30
0. 0
0.
6
.
20
0
4.0
1.6
1.0
0. 0.4
70
.
0
0
1
0
.
8
0
1.8
0.
00
0
9
0.
0. 0.0
5.0

0.0
2.0
00
1.

Fig. 11.16 Nomogram for Estimation of Kidney Threshold Phosphate Concentration. A straight line through the appropriate values of phosphate concentration and TRP (amount of phosphate reabsorbed, or CP/Ccr, where C is clearance for phosphate or creatinine) passes through the corresponding value of TmP/GFR. GFR, Glomerular filtration rate. (From Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: Molecular mechanisms. Physiol Rev. 2000;80[4]:1373–1409.)

1.0

/C
Cp

cr

The kidneys play a major role in phosphate homeostasis by controlling its excretion. In both animals and humans, ingestion of a phosphate-containing meal leads to rapid excretion of phosphate in the urine without detectable changes in serum concentrations.36 Phosphate is minimally protein bound, freely filtered in the glomerulus, and reabsorbed to a variable extent by the proximal tubules to match the body's needs. Under steady-state conditions, urinary phosphate excretion equals phosphate absorption through the gut. This balance is typically achieved by excretion of 5% to 20% of the filtered phosphate load; however, higher fractional excretions are usually needed to maintain balance in advanced CKD because of the progressive loss of filtering nephrons. The proportion of phosphate reabsorption can be estimated by the urinary fractional excretion of phosphate (FEPO4).

Fraction excretion of phosphate (FEPO4)

$$= \frac{(\text{Urine phosphate}) \times (\text{Serum creatinine}) \times 100\%}{(\text{Serum phosphate}) \times (\text{Urine creatinine})}$$

FEPO4 values are typically less than 20% in people without kidney disease and can reach values of 50% or higher in advanced CKD to compensate for the loss of functional nephrons.37 An alternative method for assessing kidney phosphate reabsorption is the maximal tubular reabsorption of phosphate (TmP) factored for GFR (TmP/GFR, Bijvoet index). This value represents the concentration above which most phosphate is excreted in the urine and below which most is reabsorbed. TmP/GFR is calculated from the serum phosphate concentration and the tubular reabsorption of phosphate (Fig. 11.16).

After passage through the glomerulus, phosphate is reabsorbed via NPT2a and NPT2c cotransporters in the proximal tubule. The expression of these transporters, and thus total kidney phosphate reabsorption, is primarily regulated by PTH, FGF-23, and the serum phosphate concentration itself. PTH and FGF-23 downregulate NPT2a and NPTc on the apical brush border, thereby increasing urinary phosphate excretion.38 39 PTH is believed to act by modulating the sodium-hydrogen exchanger regulator factor-1 (NHERF-1), a scaffolding protein that links membrane bound NPTa to the cytoskeleton.40 FGF-23 is a hormone that is produced in bone and binds to target receptors in the kidneys. The transmembrane coreceptor α-klotho stabilizes the FGF-23-receptor interaction to promote downregulation of NPT2a and NPT2c on the apical cell surface.41 Genetic disruption of FGF-23 or klotho in animal models results in an identical phenotype of hyperphosphatemia, calcitriol toxicity, vascular calcification, and premature death.42 Although PTH and FGF-23 act synergistically to enhance kidney phosphate excretion, these hormones have opposing actions on vitamin

D metabolism. PTH promotes the synthesis of calcitriol by stimulating 1-alpha hydroxylase, which converts substrate 25-hydroxyvitamin D into its active form.43 In contrast, FGF-23 inhibits calcitriol synthesis by suppressing 1-alpha hydroxylase and by catalyzing its conversion to an inactive 24-hydroxylated compound.44

Bone permanently exchanges phosphate with the surrounding milieu. Entry and exit of phosphate from bone amount to approximately 10 mmol/day (slowly exchangeable phosphate) for a total skeleton content of approximately 20,000 mmol. The net balance is positive during growth, zero in the young adult, and negative in older persons.

HYPERPHOSPHATEMIA

Causes of Hyperphosphatemia

Hyperphosphatemia is commonly caused by impaired phosphate excretion in acute or chronic kidney disease.45 Hyperphosphatemia may also be caused by increased exogenous or endogenous phosphate supply (Fig. 11.17).

Acute Kidney Injury

An acute reduction in GFR leads to phosphate retention and a subsequent increase in serum phosphate. Serum concentrations may reach extremely high values if there is concomitant release from tissues, such as in rhabdomyolysis. Serum FGF-23 concentrations increase rapidly in the setting of AKI, demonstrating a unique sensitivity of this hormonal system to changes in kidney function, phosphate metabolism, or both signals in combination.46

Chronic Kidney Disease

Serum phosphate concentrations generally remain within the normal range in CKD until the GFR falls below about 35 mL/min per 1.73m2 47 The preservation of serum phosphate concentrations in CKD highlights the complex regulatory mechanisms involved in phosphate homeostasis. The gradual loss of filtering nephrons leads to phosphate retention, which stimulates the phosphaturic hormones PTH and FGF-23. These hormones defend the serum phosphate concentration by enhancing kidney phosphate excretion. However, the price paid for maintaining phosphate balance in CKD is chronic elevation of both PTH and FGF-23, which are associated with adverse clinical consequences, including bone and cardiovascular disease (see Chapters 85 and 88).48 49 Moreover, FGF-23 potently suppresses calcitriol synthesis, possibly to limit further intestinal phosphate absorption, leading to reduced calcium absorption and ongoing stimulation of PTH. Eventually, the remaining filtering nephrons can no longer support further phosphate excretion, and serum concentrations begin to rise.

Causes of Hyperphosphatemia
Enhanced catabolism
Hemolysis
Rhabdomyolysis
Malignant hyperthermia

Lactic
acidosis

Increased endogenous
supply: movement from
intracellular compartment

Chronic respiratory
alkalosis

Other causes
Acromegaly
Pseudotumoral
calcinosis

Neoplastic diseases
Leukemia
Lymphoma

Reduced renal
phosphate
excretion

Hyperphosphatemia

Increased exogenous supply
Excessive intake of
phosphate salts (oral, intravenous,
or rectal)
Treatment with pharmacologic
doses of vitamin D or its derivatives

Other causes
Cortical
hyperostosis
Intermittent
hyperphosphatemia

Renal failure
Acute
Chronic
(GFR < 25 mL/min)

Parathyroid
dysfunction

Abnormal
plasma
PTH

Pseudohypoparathyroidism
types 1 and 2

Drug treatment

Bisphosphonate

Hypoparathyroidism
Reduced secretion
of parathyroid
hormone (PTH)
Idiopathic
Postsurgical
Peripheral
resistance to PTH

Fig. 11.17 Causes of hyperphosphatemia. GFR, Glomerular filtration rate; PTH, parathyroid hormone.

By this time, secondary hyperparathyroidism is typically evident, along with elevated FGF-23, calcitriol deficiency, and hypocalcemia.

Lytic States

Excess phosphate loss from tissues can be observed in states of extreme cell lysis, particularly rhabdomyolysis (crush injury) or malignant neoplasms and their treatment (especially lymphomas and leukemias). Hyperphosphatemia in rhabdomyolysis is typically accompanied by hypocalcemia, myoglobinuria, and AKI. Severe hypercatabolic states, such as sepsis or diabetic ketoacidosis, can also cause hyperphosphatemia by increasing phosphate release from cells (which is usually accompanied by an acute reduction in GFR).

Treatment-Induced Hyperphosphatemia

A massive supply of exogenous phosphate, as may occur with phosphatebased laxatives or enemas, can cause hyperphosphatemia. Oral sodium phosphate solutions for colonoscopy contain large quantities of phosphate that can cause precipitation of calcium phosphate crystals within the kidney tubules and AKI.50 Recovery from this condition is slow and often incomplete, with some cases resulting in permanent dialysis. For these reasons, bowel preparations other than those based on sodium phosphate salts should be used in patients with CKD. Bisphosphonates, in particular etidronate in Paget disease, can sometimes increase serum phosphate concentrations, possibly through increased liberation of tissue phosphate or an increase in tubular reabsorption.

Familial Tumoral Calcinosis

This rare autosomal recessive disorder is caused by mutations in either GALNT3 or FGF23 genes and seen primarily in people of Middle Eastern or African ancestry. GALNT3 encodes a glycosyl transferase that catalyzes the O-glycosylation of FGF-23 to protect the molecule from enzymatic cleavage. Disruption GALNT3 yields a less stable form of FGF-23 that is proteolytically degraded within the cell.52
Direct mutations in FGF-23 in tumoral calcinosis also yield a less stable form of the molecule, resulting in a shared phenotype.53 The lack of functional FGF-23 leads to unopposed phosphate reabsorption by the proximal tubules and calcitriol excess, resulting in hyperphosphatemia, hypercalcemia, and soft tissue calcifications. Serum PTH concentrations may be normal or mildly suppressed.

Respiratory Alkalosis by Prolonged Hyperventilation

Respiratory alkalosis caused by prolonged hyperventilation is characterized by kidney resistance to the actions of PTH, hyperphosphatemia, and hypocalcemia. There may also be functional pseudohypoparathyroidism because kidney phosphate clearance is diminished, whereas serum PTH is normal, despite hypocalcemia. There is no decrease in urinary calcium excretion.

Clinical Manifestations

States of reduced PTH secretion (idiopathic or postsurgical hypoparathyroidism) or resistance to its peripheral action (pseudohypoparathyroidism) lead to diminished tubular excretion of phosphate. The resulting hyperphosphatemia increases the ultrafiltered load, leading to regulation of serum phosphate concentrations at a new steady state.

Acute and severe hyperphosphatemia can cause hypocalcemia by blocking calcitriol synthesis via inhibition of 1-alpha hydroxylase. Chronic hyperphosphatemia is suspected to play a causal role in the pathogenesis of kidney-related soft tissue calcification and CKDmineral bone disorder (see Chapter 88). In extreme cases, hyperphosphatemia can induce tumor-like deposits of calcium phosphate in soft tissue (Teutschlander disease; Fig. 11.18), crystals within the kidney tubules, and vascular calcification within the arteries of the skin (calciphylaxis or calcific uremic arteriolopathy; see Chapter 91).

Acromegaly

Treatment

Hypoparathyroidism

Insulin-like growth factor 1 (IGF-1) and growth hormone (GH) enhance phosphate reabsorption in the proximal tubules by increasing tubular Npt2a expression. Acromegaly, a hormonal disorder characterized by excess GH and stimulation of IGF-1, is frequently associated with hyperphosphatemia.[51]

The treatment of acute hyperphosphatemia is aimed at increasing phosphate excretion by the kidneys, either by IV fluids or by kidney replacement therapies in severe AKI. IV dextrose and insulin promote a shift of phosphate into cells, similar to effects on potassium. The treatment of chronic hyperphosphatemia in patients with advanced

Prevention of Hypophosphatemia on a Low-Phosphate Diet

Prolonged intake of a low-phosphate diet

↓ Plasma phosphate

↑ Fractional intestinal phosphate absorption

↑ Tubular 25-hydroxyvitamin D3 1α-hydroxylase

↑ Fractional tubular phosphate reabsorption

↑ Plasma calcitriol

↓ Plasma parathyroid hormone

Normal plasma phosphate concentration

Fig. 11.19 Prevention of Hypophosphatemia. Compensatory mechanisms during prolonged intake of a phosphate-poor diet help prevent hypophosphatemia.

Fig. 11.18 Tumor-like extraskeletal calcification in the shoulder.

CKD and ESKD may require an oral phosphate binder, which complexes with phosphate in the GI tract to limit absorption (see Chapter 88). Phosphate is removed by dialysis; however, the rate of phosphate elimination during intermittent hemodialysis sessions declines over the course of a single treatment. More frequent sessions may be needed for efficient phosphate clearance.

HYPOPHOSPHATEMIA

Decreased serum phosphate concentrations may occur because of prolonged periods of reduced phosphate intake or malabsorption. However, as shown in Fig. 11.19, several defense mechanisms counter a reduction in serum phosphate that may result from reduced intake.

Causes of Hypophosphatemia

Hypophosphatemia may be caused by genetic diseases or acquired conditions (Fig. 11.20). These conditions may be mechanistically classified into those caused by kidney phosphate wasting, a shift of phosphate into cells, or protracted states of reduced phosphate intake. The urinary phosphate excretion can be used to distinguish among these mechanistic processes. Severe hypophosphatemia (<0.3 mmol/L) is almost always caused by acquired rather than inherited disorders.

Inherited Forms of Hypophosphatemia

Inherited diseases causing hypophosphatemia are usually diagnosed in childhood, when they present with rickets, osteomalacia, dental abscesses, and enthesopathy. These conditions include genetic mutations that culminate in an excess of circulating FGF-23 (hypophosphatemic rickets), disorders of proximal tubular reabsorption (Fanconi syndrome), or defects secondary to another genetically transmitted disease, mainly metabolic disorders or disturbances in the actions of vitamin D.

X-Linked hypophosphatemic rickets. Hypophosphatemic rickets are a group of genetic disorders characterized by a shared phenotype of excess circulating FGF-23, which leads to kidney phosphate wasting, suppressed calcitriol synthesis, and impaired bone mineralization.

X-linked hypophosphatemic rickets typically presents in childhood with chronic hypophosphatemia, skeletal deformities, osteomalacia, and short stature; however, the short stature may not be recognized until later in the disease process.54 The condition is caused by mutations in PHEX (phosphate-regulating endopeptidase on the X chromosome), which is believed to play a role in the proteolysis of FGF-23.55 PHEX mutations cause release of excess intact FGF-23 into the circulation with consequent kidney phosphate wasting. PTH levels are typically normal or slightly elevated in response to secondary calcitriol deficiency and hypocalcemia. The alkaline phosphatase level is elevated.

Autosomal-dominant hypophosphatemic rickets. Children with this phosphate-wasting disorder present with skeletal defects, including bowing of the long bones, widening of costochondral joints, and dental abscesses. The condition is caused by activating mutations in FGF-23. In contrast to familial tumoral calcinosis, in which FGF-23 mutations yield an unstable form of the molecule that is prone to proteolysis, mutations in autosomal-dominant hypophosphatemic rickets yield an aberrant form of FGF-23 that is resistant to proteolytic cleavage.56

Autosomal-recessive hypophosphatemic rickets. This disorder is caused by mutations in either DMP1, ENPP1, or FAM20C, which result in increased production of intact FGF-23.57 ENPP1 and FAM20C mutations are also associated with pathologic calcification of the medium and large arteries.

Fanconi syndrome and proximal renal tubular acidosis. Fanconi syndrome (see Chapter 50) is characterized by complex transport defects in the proximal tubules that lead to impaired reabsorption of glucose, amino acids, bicarbonate, and phosphate. Because more than 70% of the filtered phosphate load is typically reabsorbed in the proximal tubules, Fanconi syndrome is associated with kidney phosphate wasting and hypophosphatemia. Inherited causes of

Causes of Hypophosphatemia
Increased losses: enhanced urinary phosphate excretion
Hyperparathyroidism
Vitamin D deficiency
Renal tubular diseases
Phosphate wasting by mesenchymal tumor
Extracellular volume expansion
Diuretics
Administration of bicarbonate or its precursors
Corticosteroid treatment
Renal transplantation

Hypophosphatemia

Decreased input: intestinal malabsorption
Vitamin D deficiency
Malabsorption (resection of small intestine, diseases of intestinal mucosa)
Starvation (chronic alcoholism)

Acquired forms

Hereditary causes

Defects of renal tubular phosphate reabsorption

Primary defects
Isolated defects (vitamin D–resistant rickets: X-linked dominant, autosomal dominant, or recessive defect)
Fanconi syndrome: primary (idiopathic; Lowe syndrome) or secondary, associated with other metabolic diseases

Associated with other genetically transmitted disorders
Anomaly of vitamin D metabolism or action (resistance to calcitriol actions; deficient

1α-hydroxylase)
Distal tubular acidoses

Enhanced endogenous production: intracellular transfer
Increase in a specific pathway of cellular synthesis (administration of glucose, fructose, insulin, or catecholamines)
Hyperventilation (e.g., associated with sepsis, salicylate intoxication, alcoholism, hepatic coma, sensation of panic)
Increase in cellular metabolism (androgen or corticosteroid administration, malignant tumor, recovery from hypothermia)
“Hungry bone” (skeletal metastases of the prostate, initial treatment phase of rickets or osteomalacia, period after parathyroidectomy)

Fig. 11.20 Causes of hypophosphatemia.

Fanconi syndrome include primary disorders (Lowe syndrome, Dent disease) and other metabolic conditions (cystinosis, Wilson disease). In Dent disease and Lowe syndrome, defective recycling of megalin to the apical cell surface of the proximal tubule has been found, implicating a role in abnormal endocytic function.58

Fanconi syndrome with kidney phosphate wasting may also occur in adults as an acquired disorder. Common causes are multiple myeloma59 and specific drugs, such as tenofovir, ifosfamide, and carbonic anhydrase inhibitors. In acquired Fanconi syndromes, kidney 1α-hydroxylase activity may be impaired, leading to reduced calcitriol synthesis and impaired bone mineralization.

Hypophosphatemia linked to other inherited diseases. Several rare inherited disorders of vitamin D metabolism may be associated with hypophosphatemia.60 These include mutations in CYP27B1, which encodes 1α-hydroxylase, and CYP2R1. Inactivating mutations in CYP27B1 (vitamin D–dependent rickets type I) typically present with severe hypocalcemia in the first year of life. The treatment is calcitriol replacement. Mutations in VDR (vitamin D–dependent rickets type II) also present early in life. In addition to hypocalcemia, hypophosphatemia, and bone disease, alopecia is a defining feature.

VDR mutations may respond to extremely high doses of calcitriol depending on the severity of the mutation.

Distal renal tubular acidosis (type 1). Distal renal tubular acidosis type 1 (see Chapter 13) is associated with hypercalciuria and nephrocalcinosis because chronic metabolic acidosis enhances citrate reabsorption in the proximal tubules, preventing formation of soluble calcium-citrate complexes in the urine. Chronic acidosis also increases release of calcium and phosphate from bone. Hypophosphatemia is inconsistently found in this disorder.

Acquired Forms of Hypophosphatemia

The number of acquired diseases that are associated with hypophosphatemia is even greater than the inherited diseases (see Fig. 11.19).

True phosphate deficiency associated with total body depletion must be distinguished from shifts of phosphate into cells or increased skeletal mineralization.

Alcoholism. Alcoholism is the most common cause of severe hypophosphatemia in Western countries. The mechanisms are multiple, including prolonged insufficient food intake, GI malabsorption, and, among hospitalized patents, glucose infusion, which stimulates insulin release driving phosphate from the extracellular to intracellular compartment.

Hyperparathyroidism. Primary hyperparathyroidism typically presents in middle age with asymptomatic hypercalcemia.[61] PTH downregulates NPT2a cotransporters in the proximal tubule causing kidney phosphate wasting and hypophosphatemia.

Posttransplantation hypophosphatemia. Kidney phosphate wasting is common in kidney transplant recipients, whether the organ is from a living or deceased donor. The primary cause is residual elevations of PTH, FGF-23, or both phosphaturic hormones in combination as a consequence of previous longstanding kidney disease.[62]

Acute respiratory alkalosis. In acute respiratory alkalosis, serum phosphate concentrations can sometimes decrease considerably to values as low as 0.1 mmol/L (0.3 mg/dL). Such a decrease is never observed in acute metabolic alkalosis. Hypophosphatemia that follows acute and intense hyperventilation is probably the result of muscle sequestration of extracellular phosphate. In contrast, prolonged chronic hyperventilation is associated with hyperphosphatemia (see previous discussion).

Diabetic ketoacidosis. During decompensated diabetes with acidosis provoked by the accumulation of ketone bodies, serum phosphate concentrations may initially be normal or high, even in the presence of hyperphosphaturia. Correction of ketoacidosis by insulin and refilling of the extracellular compartment leads to massive transfer of phosphate into the intracellular compartment, hypophosphatemia, and, subsequently, a reduction in urinary phosphate excretion. Serum phosphate concentrations typically do not decrease to less than 0.3 mmol/L (0.9 mg/dL) unless there is preexisting phosphate deficiency.

Total parenteral nutrition. Hyperalimentation can also be associated with severe hypophosphatemia because of insulin-mediated shift of phosphate into cells, particularly if phosphate is omitted from the parenteral nutrition solution. Severe hypophosphatemia is also a recognized complication of acute refeeding after starvation.

Tumor-induced osteomalacia. Certain mesenchymal tumors (hemangiopericytomas, fibromas, angiosarcomas) may express FGF23 and other phosphatonins (sFRP-4, matrix extracellular phosphoglycoprotein [MEPE], or FGF-7). These tumors may present with a paraneoplastic syndrome of marked FGF-23 excess (tumor-induced osteomalacia) with clinical features of acute to subacute onset weakness, unexplained skeletal fractures, profound hypophosphatemia, and kidney phosphate wasting.63 The condition resolves promptly after tumor resection.

Drug-induced hypophosphatemia. Hypophosphatemia may be caused by specific drugs. Tenofovir disoproxil fumarate (TDF) is associated with an acquired Fanconi syndrome that includes kidney phosphate wasting.64 IV iron repletion with ferric carboxymaltose is associated with an abrupt rise in serum FGF-23, kidney phosphate wasting, and severe hypophosphatemia.65 This drug is suspected to stabilize FGF-23 in the circulation. Imatinib mesylate, a tyrosine kinase inhibitor, and sorafenib, a vascular endothelial growth factor (VEGF) inhibitor, are both associated with hypophosphatemia66; the mechanism remains unclear.

Continuous kidney replacement therapies. Hypophosphatemia is commonly seen in patients receiving continuous venovenous hemofiltration or hemodialysis for AKI because of the constant removal of phosphate by these modalities. Phosphate repletion or the addition of phosphate to the replacement fluid is often required to maintain serum phosphate concentrations within the normal range.

Clinical Manifestations

Clinical manifestations of hypophosphatemia depend on the rate of onset more than the severity or total body phosphate deficit. In practice, hypophosphatemia is not clinically evident until serum phosphate concentrations are less than 0.65 mmol/L (2.0 mg/dL). Manifestations include metabolic encephalopathy, red and white blood cell dysfunction, sometimes hemolysis, and thrombocytopenia. Reduced muscle strength and decreased myocardial contractility (with occasional rhabdomyolysis and cardiomyopathy, respectively) may also occur.

Treatment

Hypophosphatemia is generally not an emergency. First, the mechanism involved should be defined to determine the most appropriate treatment. Inherited conditions characterized by FGF-23 excess (hypophosphatemic rickets) are treated by phosphate repletion and calcitriol replacement. A recombinant human immunoglobulin G1 (IgG1) monoclonal antibody to FGF-23 (Burosumab) has been developed and approved for the treatment of X-linked hypophosphatemic rickets.67 This treatment has also been used in cases of tumor-induced osteomalacia in which the tumor cannot be surgically resected. For kidney transplant recipients with hypophosphatemia, treatment is directed toward refractory hyperparathyroidism, which is the usual underlying cause along with elevated FGF-23. Initial treatments include supplementation with cholecalciferol and, if serum phosphate concentrations are extremely low (<0.5 mmol/L), oral phosphate replacement. Management of refractory hyperparathyroidism in kidney transplantation shares similarities with primary hyperparathyroidism: Consideration for parathyroidectomy is based on the severity of hypercalcemia and accompanying bone and other complications of the disease. Cinacalcet may be considered for nonsurgical candidates.

When phosphate deficiency is diagnosed, oral treatment by milk products or phosphate salts should be tried first whenever possible, except in the presence of nephrocalcinosis or nephrolithiasis with urinary phosphate wasting. In severe symptomatic deficiency, phosphate can also be infused by IV in divided doses over 24 hours. In patients undergoing parenteral nutrition, 10 to 25 mmol potassium phosphate should be given for each 1000 kcal, with care taken to avoid hyperphosphatemia because of the risk of inducing soft tissue calcification.

Dipyridamole (300 mg divided into four doses per day) reduces the urinary excretion of phosphate in patients with a low renal phosphate threshold.

Distribution of Magnesium in
Extracellular and Intracellular Spaces
Magnesium

Intracellular
0.5 mmol/L
(1.2 mg/dL)

Extracellular
0.75–1.0 mmol/L
(1.8–2.4 mg/dL)

Protein-bound
30%

Diffusible
(ultrafilterable)
70%

Ionized free
55%

Ionized
free 10%

Bound
90%

Complexed
15%

Fig. 11.21 Magnesium Distribution in Extracellular and Intracellular Spaces. Intracellular magnesium concentration is that of free, not total, magnesium.

MAGNESIUM HOMEOSTASIS AND DISORDERS OF MAGNESIUM METABOLISM

Distribution of Magnesium in the Organism and Magnesium Homeostasis

Magnesium is the second most abundant cation in the intracellular fluid after potassium. Magnesium contributes to the regulation of mitochondrial function, inflammatory processes, growth, neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure. The distribution of magnesium within the intracellular and extracellular spaces is shown in Fig. 11.21. Similar to calcium and phosphate, circulating magnesium concentrations $[Mg^{2+}]$ represent only a minute fraction of total body magnesium.

Fig. 11.22 shows the balance of ingestion, body distribution, and excretion of magnesium in healthy individuals. Unlike calcium and phosphate, there is no hormonal system known to specifically regulate whole-body magnesium homeostasis. Magnesium moves into and out of cells through active transport systems. Insulin promotes magnesium influx into cells, whereas stimulation of β-adrenoceptors favors magnesium efflux.[68,69]

Intestinal and Kidney Handling of Magnesium

Magnesium is present in a wide variety of foods, especially nuts, seeds, and beans. Sufficient dietary intake is about 300 mg/day (12 mmol/day). Intestinal magnesium absorption varies from 25% to 60% with a mean of approximately 30%. Compared with calcium and phosphate, magnesium absorption occurs more distally in the GI tract, including the colon.

Transcellular magnesium transport in the intestine is mediated by the melastatin-related transient receptor potential cation channels 6 and 7 (TRPM6 and TRPM7).70 71

The kidneys are the primary route of magnesium elimination because losses through intestinal secretion and sweat are small under normal conditions. Approximately 70% of circulating $[\mathrm{Mg}^{2+}]$ is filtered in the glomerulus (104 mmol or 2500 mg/day). Tubular reabsorption occurs primarily in the thick ascending loop of Henle (65%) with additional reabsorption in the proximal tubules (25%) and distal convoluted tubules (5%; Fig. 11.23).72 Under normal conditions, the

Magnesium Homeostasis
in the Healthy Adult
Intracellular (non-bone)
compartment 500 mmol

12 mmol

?
5 mmol

?

Extracellular
compartment
10 mmol
1 mmol
Intestine

?

Bone
compartment

100 mmol
500 mmol

8 mmol

Kidney

4 mmol

Fig. 11.22 Magnesium Homeostasis in Healthy Adults. Net zero balance results from net intestinal uptake (absorption minus secretion) equaling urinary loss. After its passage into the extracellular fluid, Mg^{2+} enters the intracellular space, is deposited in bone or soft tissue, or is eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude; however, precise values of exchange are still debated.

urinary excretion of magnesium represents approximately 5% of the filtered load (4–5 mmol or 100 mg/day). This value constitutes a general cut point for assessing conditions of kidney magnesium wasting; a fractional magnesium excretion greater than 5% in the presence of hypomagnesemia suggests inappropriate urinary losses.

The bulk reabsorption of salt and water in the proximal tubules drives parallel reabsorption of chloride, potassium, and calcium. Yet the proximal tubules are relatively impermeable to magnesium accounting for its proportionately small reabsorption in this segment.73 Members of the claudin family of proteins are suspected to facilitate magnesium transport in the proximal tubules; however, the specific components remain unknown.

In the TAL, magnesium is transported via paracellular claudin channels in tight junctions. Specifically, claudins 16 and 19 are hypothesized to include a cation-selective pore that facilitates calcium and magnesium reabsorption.74 This transport is driven by reabsorption of Na^+, K^+, and 2Cl through the apical NKCC2 cotransporter, which generates an electrical lumen-positive gradient (see Fig. 11.9). The renal outer medullary potassium (ROMK) channel promotes NKCC2 activity by recycling potassium into the lumen, thereby enhancing magnesium reabsorption. Stimulation of the basolateral CaSR by calcium or magnesium directly decreases paracellular permeability, reducing magnesium reabsorption. Defects in NKCC2 caused by genetic disorders, specific drugs, or electrolyte imbalances lead to kidney magnesium wasting (see later discussion).28 Approximately 5% of the filtered Mg2+ load is reabsorbed in the distal convoluted tubule

Magnesium Reabsorption in the Kidney
Plasma ultrafilterable Mg:
0.5–0.7 mmol/L
Glomerulus

Distal convoluted tubule
5%

Filtered load:
100 mmol/day
Cortex
Proximal
convoluted
tubule
25%

Collecting
tubule
₀2%

Thick
ascending
limb

Outer
medulla

65%

Inner
medulla

151

Loop of
Henle
Urinary
output:
5 mmol/day
5%

Fig. 11.23 Sites of Magnesium Reabsorption in Various Segments. Percentage absorbed in various segments of the renal tubule from the glomerular ultrafiltrate. (Redrawn from Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiologic role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113[4]:561–568.)

Causes of Hypermagnesemia
Renal failure:
acute, chronic
Acromegaly
Familial
hypocalciuric
hypercalcemia

Hypermagnesemia

Adrenal
insufficiency

Treatment with compounds
containing magnesium
Administration of
pharmacologic doses
of magnesium
Use of magnesiumcontaining oral purgatives
or rectal enemas
Infants born to mothers
treated with magnesium
for eclampsia

Causes of Hypomagnesemia
Decreased
intake
Proteincalorie
malnutrition
Prolonged
fasting
or IV
therapy

Miscellaneous
Acute pancreatitis
Chronic alcoholism
Bartter syndrome
Acute intermittent porphyria
associated with inappropriate
vasopressin secretion
Idiopathic hypomagnesemia

Hypomagnesemia

Fig. 11.24 Causes of hypermagnesemia.

via the identical TRPM6 channel found in the intestine. This channel colocalizes with the thiazide-sensitive Na^+ Cl cotransporter (NCC).[75] Conditions that impair NCC activity lead to reductions in magnesium reabsorption in the distal tubule.

Tubular magnesium transport is modulated by circulating $[Mg^{2+}]$ and $[Ca^{2+}]$ and by extracellular fluid volume. An increase in serum $[Mg^{2+}]$ or $[Ca^{2+}]$ reduces kidney magnesium reabsorption.[76] Extracellular volume expansion suppresses the reabsorption of sodium, chloride, potassium, and, to a lesser extent, magnesium in the proximal tubules.[77] Other hormones that can increase magnesium reabsorption include PTH, vasopressin, calcitonin, and glucagon.[78]

Hypermagnesemia

Elevated serum [Mg2] can be seen in patients with acute kidney disease and CKD because of decreased elimination; however, enhanced single-nephron magnesium excretion in CKD tends to prevent overt hypermagnesemia. Elevated serum [Mg2+] may also be observed with an increase in magnesium intake or administration, such as pharmacologic doses of magnesium for treating preeclampsia, oral magnesiumcontaining laxatives or rectal enemas, and Epsom salts (Fig. 11.24).79
Mild hypermagnesemia may also occur in patients with adrenal insufficiency, acromegaly, and familial hypocalciuric hypercalcemia.

Clinical Manifestations

Symptoms and signs of hypermagnesemia are the result of the pharmacologic effects of magnesium on the nervous and cardiovascular systems. At concentrations of up to 1.5 mmol/L (3.6 mg/dL), hypermagnesemia is usually asymptomatic. Deep tendon reflexes are typically reduced or lost when serum [Mg2+] exceeds 3.0 mmol/L (7.2 mg/dL). Respiratory paralysis, hypotension, abnormal cardiac conduction, and loss of consciousness may occur as serum [Mg2+] approaches 5.0 mmol/L (12 mg/dL).

Treatment

Treatment of hypermagnesemia consists of cessation of magnesium administration and IV infusion of isotonic fluids and calcium salts, which promote kidney excretion. For management of symptomatic hypermagnesemia, calcium gluconate may be administered by IV as 1 g in 10 mL over 5 to 10 minutes (each gram of calcium gluconate is equal to approximately 90 mg of elemental calcium). Loop diuretics may also be used, where appropriate, to enhance kidney magnesium elimination.

HYPOMAGNESEMIA AND MAGNESIUM DEFICIENCY

Magnesium deficiency refers to a deficit in total body magnesium stores, whereas hypomagnesemia refers to low circulating magnesium

Administration of drugs (increased urinary losses)
Aminoglycoside
Amphotericin
Cisplatin
Cyclosporine
Pentamidine
Thiazide diuretics

Gastrointestinal diseases
Malabsorption syndromes (nontropical sprue, steatorrhea)
Massive resection of the small intestine
Neonatal selective magnesium malabsorption
Intestinal and biliary fistulae
Excessive use of purgatives

Increased urinary losses
Drug administration (see above)
High urinary output states (polyuric phase of acute renal failure, postobstructive polyuria,

post-transplantation polyuria)
Hypercalcemic states
Prolonged infusions with excessive sodium content
Primary aldosteronism
Metabolic acidosis
Diabetes (glycosuric and ketoacidotic states)
Hyperthyroidism
Phosphate depletion
Idiopathic renal wasting
Gitelman syndrome

Fig. 11.25 Causes of hypomagnesemia.

concentrations. Although serum concentrations do not directly reflect total body magnesium stores, there is no practical test for wholebody deficiency. Therefore, clinical focus relates to hypomagnesemia. Causes can be broadly classified into conditions of reduced GI intake and disorders of kidney wasting (Fig. 11.25). The fractional excretion of magnesium can be used to distinguish between these mechanistic processes.

Dietary and Gastrointestinal Causes

A temporary reduction in dietary magnesium intake does not usually cause magnesium deficiency because of the remarkable ability of the kidneys to conserve magnesium. However, prolonged and severe dietary deficiency of less than 0.5 mmol/day can produce symptomatic deficiency. Chronic alcoholism is among the most common causes of hypomagnesemia in hospitalized patients predominantly because of marked nutritional deficiency and some degree of inappropriate kidney wasting.[69] Decreased intestinal absorption may also be seen in malabsorption syndromes, such as nontropical sprue, diarrheal illnesses, and after bowel resection. Proton pump inhibitors can inhibit intestinal magnesium absorption; chronic use of these medications is associated with hypomagnesemia.[80] Hypomagnesemia and hypocalcemia are also observed in patients with acute pancreatitis because of saponification in necrotic fat.

Kidney Causes

Diuretics are the most common acquired cause of kidney magnesium wasting in adults. Loop diuretics block the NKCC2 cotransporter, reducing the driving force for adjacent paracellular reabsorption. Thiazide diuretics block the NCC cotransporter in the distal tubule, which colocalizes with TRPM6, leading to reduced kidney magnesium reabsorption. Several other medications interfere with kidney magnesium reabsorption and are associated with hypomagnesemia: gentamicin, cisplatin, amphotericin, calcineurin inhibitors (cyclosporine and tacrolimus), and monoclonal antibodies to the epidermal growth factor receptor (cetuximab and panitumumab).81

Hypercalcemia can also induce kidney magnesium wasting by activating the CaSR in the thick ascending limb.

Primary inherited conditions causing kidney magnesium wasting are Bartter and Gitelman syndromes. Bartter syndrome is an autosomal recessive disorder caused by mutations in genes encoding major ion transporters in the TAL.82 These include the basolateral Cl channel (encoded by CLCNKB), the NKCC2 cotransporter (encoded by SLC12A1), and the ROMK channel (encoded by KCNJ1). Genetically mediated dysfunction of this kidney segment leads to a “loop diureticlike effect” with loss of potassium, calcium, and magnesium in the urine. Bartter syndrome typically presents in childhood with features of growth retardation, polyuria, metabolic alkalosis, hypokalemia, and hypomagnesemia.

Gitelman syndrome is an autosomal recessive disorder caused by inactivating mutations in the gene encoding the NaCl transporter NCC (SLC12A3).83 Genetic disruption of NCC produces a thiazide diuretic–like effect with loss of sodium, potassium, and magnesium in the urine but with increased reabsorption of calcium. In contrast to Bartter syndrome, Gitelman syndrome typically presents in adulthood with muscle cramps, fatigue, hypokalemia, and hypomagnesemia. Bartter and Gitelman syndromes can be distinguished by the kidney handling of calcium. By mimicking the action of loop diuretics, Bartter syndrome is associated with kidney calcium wasting. In contrast, by mimicking the action of thiazide diuretics, Gitelman syndrome is associated with enhanced tubular calcium reabsorption.

The presence of Bartter or Gitelman syndrome is suggested by a constellation of chronic metabolic alkalosis, hypokalemia, and hypomagnesemia in the context of normal to low blood pressures and absence of known diuretic treatment. Two conditions that share these metabolic features are volume depletion caused by vomiting and the surreptitious use of diuretics. The urinary chloride concentration can be helpful for excluding vomiting in this situation (urinary chloride concentration typically <20 mEq/L in states of volume depletion). Differentiating covert diuretic use from Bartter or Gitelman syndromes is difficult because these genetic conditions mimic the effects of loop and thiazide diuretics, respectively.

Clinical Manifestations

Specific clinical manifestations of hypomagnesemia may be difficult to appreciate because of concomitant hypocalcemia and hypokalemia. Moreover, moderate degrees of magnesium deficiency can be difficult to detect because clinical manifestations may be absent, and blood levels may not reflect total body magnesium. Clinical manifestations of moderate to severe magnesium depletion include generalized weakness and neuromuscular hyperexcitability with hyperreflexia, carpopedal spasm, seizure, tremor, and, rarely, tetany. Cardiac findings may include a prolonged QT interval, ST depression, torsades de pointes, and potentiation of digoxin toxicity. The role of magnesium deficiency in seizure activity is demonstrated by its effectiveness as a treatment; among women with eclampsia, IV magnesium administration is more effective than phenytoin for the treatment of seizures.84

An important physiologic consequence of hypomagnesemia is blunting of the PTH response to calcium, leading to a state of relative hypoparathyroidism. Reduced PTH secretion consequently results in hypocalcemia and reduced calcitriol synthesis.

Treatment

Magnesium deficiency is managed by administration of magnesium salts. Magnesium sulfate is generally used for parenteral therapy (1500–3000 mg [150–300 mg elemental magnesium] per day). A variety of magnesium salts are available for oral administration, including oxide, hydroxide, sulfate, lactate, chloride, carbonate, and pidolate. The use of oral magnesium is often limited by GI side effects, particularly diarrhea, at higher dosages.

In Bartter and Gitelman syndromes, magnesium and potassium supplementation along with increased sodium intake are initially used to address the attendant electrolyte disturbances. Amiloride, which blocks distal sodium and potassium exchange, can help restore serum potassium and magnesium concentrations if concomitant volume contraction can be avoided. The defective loop sodium transport in Bartter syndrome stimulates prostaglandin synthesis and activates the renin-angiotensin-aldosterone system. These metabolic disturbances are countered by nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors, respectively, promoting their use in Bartter syndrome with careful monitoring of kidney function.

SELF-ASSESSMENT QUESTIONS

1. Which is the most common cause of hypercalcemia in patients with a low serum PTH level?
A. Secondary hyperparathyroidism
B. Cholecalciferol or ergocalciferol therapy
C. Malignant neoplasias
D. Familial hypocalciuric hypercalcemia
E. Hypomagnesemia

2. Which is a primary cause of hypocalcemia in patients with chronic kidney disease?
A. Primary hypoparathyroidism
B. Secondary hyperparathyroidism
C. Impaired calcitriol synthesis
D. Blunted response to FGF-23
E. Treatment with phosphate binders

3. Which kidney tubular segment is responsible for regulating phosphate balance?
A. Proximal tubule
B. Thick ascending limb

C. Distal tubule
D. Outer collecting duct
E. Inner collecting duct

4. Hypophosphatemic rickets describe a group of genetic conditions characterized by an increase in circulating concentrations of which molecule?
A. Calcitriol
B. Parathyroid hormone
C. Calcium
D. FGF-23
E. Phosphate-regulating endopeptidase on the X chromosome

5. Which of the following is most helpful in distinguishing a genetic cause of hypomagnesemia from surreptitious vomiting?
A. Serum calcium
B. Serum phosphate
C. Urinary chloride
D. Urinary potassium
E. Prolonged QT interval

REFERENCES

1. Kumar R. Vitamin D and calcium transport. Kidney Int. 1991;40:1177–1189.
2. Magno AL, Ward BK, Ratajczak T. The calcium-sensing receptor: a molecular perspective. Endocr Rev. 2011;32:3–30.
3. Hoenderop JG, Bindels RJ. Epithelial Ca2+ and Mg2+ channels in health and disease. J Am Soc Nephrol. 2005;16(1):15–26.
4. Christakos S. Recent advances in our understanding of 1,25-dihydroxyvitamin D(3) regulation of intestinal calcium absorption. Arch Biochem Biophys. 2012;523:73–76.
5. Wilkinson R. Absorption of calcium, phosphate, and magnesium. In: Nordin BEC, ed. Calcium and Magnesium Metabolism. Edinburgh: Churchill Livingstone; 1976:36–112.
6. Kovacs CS. Maternal mineral and bone metabolism during pregnancy, lactation, and post-weaning recovery. Physiol Rev. 2016;96(2):449–547.
7. Kinyamu HK. Association between intestinal vitamin D receptor, calcium absorption, and serum 1,25 dihydroxyvitamin D in normal young and elderly women. J Bone Miner Res. 1997;12:922–928.
8. Harada S GAR. Control of osteoblast function and regulation of bone mass. Nature. 2003;12:922–928.
9. Martin T, Gooi JH, Sims NA. Molecular mechanisms in coupling of bone formation to resorption. Crit Rev Eukaryot Gene Expr. 2009;19:73–88.
10. Puschett JB. Renal handling of calcium. In: Massry SG, Glassock RJ, eds. Textbook of Nephrology. Baltimore: Williams & Wilkins; 1989:293–299.
11. Loupy A, Ramakrishnan SK, Wootla B, et al. PTH-independent regulation of blood calcium concentration by the calcium-sensing receptor. J Clin Invest. 2012;122(9):3355–3367.
12. Mensenkamp AR, Hoenderop JG, Bindels RJ. Recent advances in renal tubular calcium reabsbsorption. Curr Opin Nephrol Hypertens. 2006;15:524–529.
13. Stewart AF. Clinical practice. hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373–379.
14. Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). Mol Cell Endocrinol. 2014;386(1–2):2–15.
15. Thakker RV. Diseases associated with the extracellular calcium–sensing receptor. Cell Calcium. 2004;35:275–282.
16. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018;32(5):609–619.
17. Vargas-Poussou R, Mansour-Hendili L, Baron S, et al. Familial hypocalciuric hypercalcemia types 1 and 3 and primary hyperparathyroidism: similarities and differences. J Clin Endocrinol Metab. 2016;101(5):2185–2195.
18. Thosani S, Hu MI. Denosumab: a new agent in the management of hypercalcemia of malignancy. Future Oncol. 2015;11(21):2865–2871.
19. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90(1):135–141.
20. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350(15):1516–1525.
21. Thiele S, Mantovani G, Barlier A, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network. Eur J Endocrinol. 2016;175(6):P1–P17.
22. Markowitz GS, Stokes MB, Radhakrishnan J, D’Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. J Am Soc Nephrol. 2005;16:3389–3396.
23. Portale AA, Halloran BP, Murphy MM, Morris Jr RC. Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in humans. J Clin Invest. 1986;77(1):7–12.
24. Ix JH, Anderson CA, Smits G, Persky MS, Block GA. Effect of dietary

phosphate intake on the circadian rhythm of serum phosphate concentrations in chronic kidney disease: a crossover study. Am J Clin Nutr. 2014;100(5):1392–1397.

25. Miyaji T, Kawasaki T, Togawa N, Omote H, Moriyama Y. Type 1 sodiumdependent phosphate transporter acts as a membrane potential-driven urate exporter. Curr Mol Pharmacol. 2013;6(2):88–94.

26. Hattenhauer O, Traebert M, Murer H, Biber J. Regulation of small intestinal Na-P(i) type IIb cotransporter by dietary phosphate intake. Am J Physiol. 1999;277(4):G756–G762.

27. Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: molecular mechanisms. Physiol Rev. 2000;80(4):1373–1409.

28. Ohkido I, Segawa H, Yanagida R, Nakamura M, Miyamoto K. Cloning, gene structure and dietary regulation of the type-IIc Na/Pi cotransporter in the mouse kidney. Pflugers Arch. 2003;446(1):106–115.

29. Tenenhouse HS. Regulation of phosphorus homeostasis by the type iia na/phosphate cotransporter. Annu Rev Nutr. 2005;25:197–214.

30. Jono S, McKee MD, Murry CE, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000;87(7):E10–E17.

31. David S, Ferreira J, Quenez O, et al. Identification of partial SLC20A2 deletions in primary brain calcification using whole-exome sequencing. Eur J Hum Genet. 2016;24(11):1630–1634.

32. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(2):257–264.

33. Xu H, Bai L, Collins JF, Ghishan FK. Age-dependent regulation of rat intestinal type IIb sodium-phosphate cotransporter by 1,25-(OH)(2) vitamin D(3). Am J Physiol Cell Physiol. 2002;282(3):C487–C493.

34. Bland R, Zehnder D, Hughes SV, Ronco PM, Stewart PM, Hewison M. Regulation of vitamin D-1alpha-hydroxylase in a human cortical collecting duct cell line. Kidney Int. 2001;60(4):1277–1286.

35. Ix JH, Isakova T, Larive B, et al. Effects of nicotinamide and lanthanum carbonate on serum phosphate and fibroblast growth factor-23 in CKD: the COMBINE trial. J Am Soc Nephrol. 2019;30(6):1096–1108.

36. Isakova T, Gutierrez O, Shah A, et al. Postprandial mineral metabolism and secondary hyperparathyroidism in early CKD. J Am Soc Nephrol. 2008;19(3):615–623.

37. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005;16(7):2205–2215.

38. Kempson SA, Lotscher M, Kaissling B, Biber J, Murer H, Levi M. Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. Am J Physiol. 1995;268(4 Pt 2):F784–F791.

39. Bowe AE, Finnegan R, Jan de Beur SM, et al. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. Biochem Biophys Res Commun. 2001;284(4):977–981.

40. Weinman EJ, Biswas RS, Peng G, et al. Parathyroid hormone inhibits renal phosphate transport by phosphorylation of serine 77 of sodium-hydrogen exchanger regulatory factor-1. J Clin Invest. 2007;117(11):3412–3420.

41. Kurosu H, Ogawa Y, Miyoshi M, et al. Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem. 2006;281(10):6120–6123.

42. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113(4):561–568.

43. Armbrecht HJ, Hodam TL, Boltz MA. Hormonal regulation of 25-hydroxyvitamin D3-1alpha-hydroxylase and 24-hydroxylase gene transcription in opossum kidney cells. Arch Biochem Biophys. 2003;409(2):298–304.

44. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A. 2001;98(11):6500–6505.

45. Slatopolsky E, Brown A, Dusso A. Calcium, phosphorus and vitamin D disorders in uremia. Contrib Nephrol. 2005;149:261–271.
46. Neyra JA, Hu MC, Moe OW. Fibroblast growth factor 23 and alphaKlotho in acute kidney injury: current status in diagnostic and therapeutic applications. Nephron. 2020;144(12):665–672.
47. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–528.

References

48. Gutierrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009;119(19):2545–2552.
49. Moe SM, Abdalla S, Chertow GM, et al. Effects of cinacalcet on fracture events in patients receiving hemodialysis: the EVOLVE trial. J Am Soc Nephrol. 2015;26(6):1466–1475.
50. Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. N Engl J Med. 2003;349(10):1006–1007.
51. Kamenicky P, Mazziotti G, Lombes M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. Endocr Rev. 2014;35(2):234–281.
52. Farrow EG, Imel EA, White KE. Miscellaneous non-inflammatory musculoskeletal conditions. Hyperphosphatemic familial tumoral calcinosis (FGF23, GALNT3 and alphaKlotho). Best Pract Res Clin Rheumatol. 2011;25(5):735–747.
53. Prie D, Beck L, Urena P, Friedlander G. Recent findings in phosphate homeostasis. Curr Opin Nephrol Hypertens. 2005;14(4):318–324.
54. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019;15(7):435–455.
55. Yuan B, Takaiwa M, Clemens TL, et al. Aberrant Phex function in osteoblasts and osteocytes alone underlies murine X-linked hypophosphatemia. J Clin Invest. 2008;118(2):722–734.
56. White KE, Carn G, Lorenz-Depiereux B, Benet-Pages A, Strom TM, Econs MJ. Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. Kidney Int. 2001;60(6):2079–2086.
57. Feng JQ, Ward LM, Liu S, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet. 2006;38(11):1310–1315.
58. Norden AG, Lapsley M, Igarashi T, et al. Urinary megalin deficiency implicates abnormal tubular endocytic function in Fanconi syndrome. J Am Soc Nephrol. 2002;13(1):125–133.
59. Batuman V. Proximal tubular injury in myeloma. Contrib Nephrol. 2007;153:87–104.
60. Malloy PJ, Feldman D. Genetic disorders and defects in vitamin d action. Endocrinol Metab Clin North Am. 2010;39(2):333–346, table of contents.
61. Insogna KL. Primary hyperparathyroidism. N Engl J Med. 2018;379(11):1050–1059.
62. Bhan I, Shah A, Holmes J, et al. Post-transplant hypophosphatemia: tertiary ‘hyper-Phosphatoninism’? Kidney Int. 2006;70(8):1486–1494.
63. Hautmann AH, Hautmann MG, Kolbl O, Herr W, Fleck M. Tumorinduced osteomalacia: an up-to-date review. Curr Rheumatol Rep. 2015;17(6):512.
64. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis. 2011;57(5):773–780.
65. Schaefer B, Wurtinger P, Finkenstedt A, et al. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. PLoS One. 2016;11(12):e0167146.
66. Osorio S, Noblejas AG, Duran A, Steegmann JL. Imatinib mesylate induces hypophosphatemia in patients with chronic myeloid leukemia in late chronic phase, and this effect is associated with response. Am J Hematol. 2007;82(5):394–395.

67. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med. 2018;378(21):1987–1998.
68. Keenan D, Romani A, Scarpa A. Differential regulation of circulating Mg2+ in the rat by beta 1- and beta 2-adrenergic receptor stimulation. Circ Res. 1995;77(5):973–983.
69. Romani AM, Matthews VD, Scarpa A. Parallel stimulation of glucose and

Mg(2+) accumulation by insulin in rat hearts and cardiac ventricular myocytes. Circ Res. 2000;86(3):326–333.

70. Nadler MJ, Hermosura MC, Inabe K, et al. LTRPC7 is a Mg.ATPregulated divalent cation channel required for cell viability. Nature. 2001;411(6837):590–595.

71. Groenestege WM, Hoenderop JG, van den Heuvel L, Knoers N, Bindels RJ. The epithelial Mg2+ channel transient receptor potential melastatin 6 is regulated by dietary Mg2+ content and estrogens. J Am Soc Nephrol. 2006;17(4):1035–1043.

72. Wong NL, Dirks JH, Quamme GA. Tubular reabsorptive capacity for magnesium in the dog kidney. Am J Physiol. 1983;244(1):F78–F83.

73. Brunette MG, Vigneault N, Carriere S. Micropuncture study of magnesium transport along the nephron in the young rat. Am J Physiol. 1974;227(4):891–896.

74. Hou J, Shan Q, Wang T, et al. Transgenic RNAi depletion of claudin-16 and the renal handling of magnesium. J Biol Chem. 2007;282(23):17114–17122.

75. Voets T, Nilius B, Hoefs S, et al. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption. J Biol Chem. 2004;279(1):19–25.

76. Quamme GA. Effect of hypercalcemia on renal tubular handling of calcium and magnesium. Can J Physiol Pharmacol. 1982;60(10):1275–1280.

77. Poujeol P, Chabardes D, Roinel N, De Rouffignac C. Influence of extracellular fluid volume expansion on magnesium, calcium and phosphate handling along the rat nephron. Pflugers Arch. 1976;365(2–3):203–211.

78. Di Stefano A, Wittner M, Nitschke R, et al. Effects of parathyroid hormone and calcitonin on Na+, Cl-, K+, Mg2+ and Ca2+ transport in cortical and medullary thick ascending limbs of mouse kidney. Pflugers Arch. 1990;417(2):161–167.

79. Onishi S, Yoshino S. Cathartic-induced fatal hypermagnesemia in the elderly. Intern Med. 2006;45(4):207–210.

80. Famularo G, Gasbarrone L, Minisola G. Hypomagnesemia and protonpump inhibitors. Expert Opin Drug Saf. 2013;12(5):709–716.

81. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658–1664.

82. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. Bartter’s syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. Nat Genet. 1996;13(2):183–188.

83. Bettinelli A, Bianchetti MG, Borella P, et al. Genetic heterogeneity in tubular hypomagnesemia-hypokalemia with hypocalcuria (Gitelman’s syndrome). Kidney Int. 1995;47(2):547–551.

84. Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev. 2010;(10):CD000128.

12

Normal Acid-Base Balance

Biff F. Palmer

The acid-base status of the body is carefully regulated to maintain arterial pH between 7.35 and 7.45 and intracellular pH between 7.0 and 7.3. This regulation occurs in the setting of continuous production of acidic metabolites and is accomplished by intracellular and extracellular buffering processes with respiratory and renal regulatory mechanisms. This chapter reviews the normal physiology of acid-base homeostasis.

buffer source as acid-induced dissolution of bone apatite releases alkaline Ca^{2+} salts and HCO_3 into the ECF. With chronic metabolic acidosis, this can result in osteomalacia and osteoporosis. The calcium released can result in hypercalciuria and an increased likelihood of renal stones. Within the intracellular fluid (ICF) compartment, pH is maintained by intracellular buffers such as hemoglobin, cellular proteins, organophosphate complexes, and HCO_3 as well as by the H^+ HCO_3 mechanisms that transport acid and alkali in and out of the cell.

NET ACID PRODUCTION

RESPIRATORY SYSTEM IN REGULATION OF PH

Both acid and alkali are generated from diet. Lipid and carbohydrate metabolism results in production of carbon dioxide (CO_2), a volatile acid, at the rate of approximately 15,000 mmol/day. Protein metabolism yields amino acids, which can be metabolized to form nonvolatile acid and alkali. Amino acids such as lysine and arginine yield acid on metabolism, whereas the amino acids glutamate and aspartate and organic anions such as acetate and citrate generate alkali. Sulfurcontaining amino acids (methionine, cysteine) are metabolized to sulfuric acid (H_2SO_4), and organophosphates are metabolized to phosphoric acid (H_3PO_4). In general, animal foods are high in proteins and organophosphates and provide a net acid diet; plant foods are higher in organic anions and provide a net alkaline load. In addition to acid and alkali generated from diet, there is a small daily production of organic acids, including acetic acid, lactic acid, and pyruvic acid. Also, a small amount of acid is generated by the excretion of alkali into the stool. Under normal circumstances, daily net nonvolatile acid production is approximately 1 mmol of hydrogen ions (H^+) per kilogram of body weight (Fig. 12.1).

Removal of acid or alkali from the body is accomplished by the lungs and kidneys. The lungs regulate CO_2 tension (P_{CO_2}), and the kidneys regulate serum bicarbonate concentration [HCO_3]. Although the [HCO_3]-CO_2 buffer system is not the only buffer system, all extracellular buffer systems are in equilibrium. Because serum [HCO_3] is much greater than that of other buffers, changes in the HCO_3 -CO_2 buffer pair easily titrate other buffer systems and thus set pH. The Henderson-Hasselbalch equation explains how the lungs and kidneys function in concert: pH is determined by the ratio of HCO_3 to CO_2. Conditions associated with similar fractional changes in [[HCO_3]] and [CO_2], such as when both are halved, will not change blood pH. The lungs defend pH by altering alveolar ventilation, which alters the CO_2 excretion rate and thereby controls the arterial CO_2 tension (Pa_{CO_2}) of body fluids. Systemic acidosis stimulates the respiratory center, resulting in increased respiratory drive that lowers the Pa_{CO_2}. As a result, the fall in blood pH is less than would have occurred in the absence of respiratory compensation. If the fractional change in P_{CO_2} were similar to that in serum [[HCO_3]], blood pH would not change. However, respiratory compensation rarely normalizes blood pH, and thus the fractional change in Pco2 is less than the change in serum [[HCO3]]. Quantitatively, the normal respiratory response in metabolic acidosis is a 1.2 mm Hg decrease in Paco2 for every 1 mmol/L decrease in HCO3 ; the increase in Paco2 in response to metabolic alkalosis averages 0.7 mm Hg for every 1 mmol/L increase in HCO3 above baseline.1

DEFINITION

BUFFER SYSTEMS IN REGULATION OF PH

Intracellular and extracellular buffer systems minimize the change in pH during the addition of acid or base equivalents but do not remove acid or alkali from the body. The most important buffer system is bicarbonate ion and carbon dioxide (HCO3 -CO2). In this system, carbon dioxide concentration [CO2] is maintained at a constant level set by respiratory control. Addition of acid (HA) leads to conversion of HCO3 to CO2 according to the reaction HA + NaHCO3 → NaA + H2 O + CO2 . HCO3 is consumed, but [CO2] does not change because this is maintained by respiration. The net result is that the acid load has been buffered and pH changes are minimal.

Although the HCO3 -CO2 buffer system is the most important of the buffers in extracellular fluid (ECF), other buffers such as plasma proteins and phosphate ions also participate in the maintenance of a stable pH. During metabolic acidosis, the skeleton becomes a major

KIDNEY REGULATION OF pH

Buffer systems and respiratory excretion of CO2 help maintain normal acid-base balance, but the kidneys provide a critical role in acidbase homeostasis. The kidneys normally generate sufficient net acid excretion (NAE) to balance nonvolatile acid produced from normal metabolism. NAE has three components, titratable acids, ammonium (NH4+), and bicarbonate, and is calculated by the following formula:

NAE = V UAm + UTA − UHCO3

Acid and Alkali Generated from Diet

Fat and
carbohydrate

Complete metabolism
to volatile acid
excreted by lung

H_2O and
15,000 mmol/d
CO_2

Incomplete
metabolism
(lactate– and acetate–)

Animal foods
Nonvolatile acid production
Sulfur-containing AA
-Methionine, cysteine
Cationic AA
-Arginine, lysine
Organophosphates (phosphoric acid)
Organic acids
-Uric acid, oxalic acid

$HA + NaHCO_3 \rightarrow A^- + H_2O + CO_2$
Daily stool loss
of HCO_3^- is
equivalent to acid
gain to body

Nonvolatile base
Anionic AA
-Glutamate
-Aspartate
Organic anions
-Citrate, acetate
Plant foods

Fig. 12.1 Acid and Alkali Generated From the Diet. A nonvolatile acid is an acid produced from sources other than CO_2 and is not excreted by the lungs. Nonvolatile acids are produced from incomplete metabolism of carbohydrates, fats, and proteins and from metabolism of animal foods. Plant foods tend to produce an alkali load. AA, Amino acids.

where UAmV is the rate of NH_4^+ excretion, UTAV is the rate of titratable acid excretion, and U_{HCO_3} V is the rate of HCO_3 excretion. Under basal conditions, approximately 40% of NAE is in the form of titratable acids and 60% is in the form of ammonia (NH_3); urinary bicarbonate concentrations and excretion are essentially zero under normal conditions.

Titratable acidity refers to weak acids filtered at the glomerulus that can act as buffers in the urine. These buffers are referred to as titratable because they are measured by determining the amount of alkali required to titrate the urine back to a pH of 7.4. To serve as a titratable buffer, a buffer must have a pKa near the range of tubular fluid pH.

The most important titratable buffer is phosphate (HPO_4^{2-} ↔ H_2PO_4) because it has a favorable pKa of 6.80 and there is a relatively high rate of urinary excretion. However, when acid production increases, the increase in acid excretion is almost entirely caused by an increase in excretion of NH_4^+ because the ability to increase urinary phosphate is limited.

KIDNEY TRANSPORT MECHANISMS OF HYDROGEN AND BICARBONATE IONS

Glomerulus

The glomerulus is not normally considered a participant in acid-base regulation. However, the glomerulus filters an amount of HCO_3 equivalent to serum [[HCO_3]] multiplied by the glomerular filtration rate (GFR). Under normal circumstances, the filtered load of HCO_3 averages approximately 4000 mmol/day. Normal acid-base homeostasis requires both the reabsorption of this filtered bicarbonate and the generation of “new” bicarbonate; the latter replenishes bicarbonate and other alkaline buffers consumed in the process of titrating endogenous acid production. From the standpoint of prevention or correction of acidosis, GFR is not regulated by alterations in acid or base and therefore does not contribute to acid-base homeostasis.

Proximal Tubule

The proximal tubule reabsorbs approximately 80% of the filtered load of HCO_3 In addition, by titration of luminal pH from 7.4 down to approximately 6.7, the majority of phosphate, the major form of titratable acid, is titrated to its acid form. Finally, ammonia synthesis occurs in the proximal tubule.

Fig. 12.2 shows the acid-base transport mechanisms of the proximal tubule cell. HCO_3 absorption from the tubular lumen is mediated by H^+ secretion across the membrane.2 This H^+ secretion is active in that the electrochemical gradient favors H^+ movement from lumen to cell. Two mechanisms mediate active apical H^+ secretion. Approximately two-thirds occurs through the apical membrane Na^+ H^+ antiporter NHE3.3 This protein uses the inward Na^+ gradient to drive H^+ secretion. The Na^+-H^+ exchanger has a 1:1 stoichiometry and is electroneutral. In parallel with the Na^+-H^+ antiporter, there is an apical membrane H^+-ATPase that mediates approximately one-third of basal proximal tubular HCO_3 absorption.

Both these H^+ transporters generate base in the cell, which must exit across the basolateral membrane to effect transepithelial transport. This primarily occurs through a basolateral Na^+- HCO_3 -CO_3^{2-} cotransporter.4 Because this protein transports the equivalent of two net negative charges, the negative cell voltage generated by the basolateral Na^+,K^+-ATPase provides a strong favorable driving force for base efflux. The Na^+ carried on this transporter is moved out of the cell without requiring ATP. The Na^+ $3HCO_3$ cotransporter NBCe1, encoded by the gene SLC4A4, mediates most of the exit of base from the proximal tubule.5

Carbonic anhydrase II is present in the proximal tubular cell cytoplasm, and carbonic anhydrase IV is on the apical and basolateral membranes. Carbonic anhydrase (carbonate dehydratase) has a number of functions in the proximal tubule. Apical membrane carbonic anhydrase allows secreted H^+ ions to react with luminal HCO_3 , forming H_2CO_3, which rapidly dissociates to CO_2 + H_2O. This CO_2 diffuses across the apical plasma membrane into the cell. There the

Proximal Tubule NaHCO 3 Reabsorption

Hydrogen and Bicarbonate Ion Transport
in the Thick Ascending Limb
Lumen

Lumen

Na+

HCO3
Carbonic
anhydrase
CO2 + OH

H+

H+

H2O

Na+
H+

Blood

Interstitium
3Na+
H2O

3Na+

2K+

2K+

K+

H+ + OH
H+

H+ Carbonic
anhydrase

Na+
HCO3

Na+
CI

Active transport

CO32

CO32

CO2

Voltage
+1 mV

Na^+
HCO_3

Na^+
CI
70 mV

Channel

Na^+

KCC4
HCO_3

NHE3
H^+
Carbonic
anhydrase

$H_2O + CO_2$

HCO_3

AE2
Cl

0 mV

Passive transport

Fig. 12.2 Proximal tubule Sodium Bicarbonate ($NaHCO_3$) Reabsorption. The secretion of H^+ into the proximal tubule lumen involves a Na^+-H^+ antiporter and an H^+-ATPase. Apical membrane H^+ secretion generates OH , which reacts with CO_2 to form HCO_3 and CO_3^{2-}, and these exit with a Na^+ on the basolateral membrane Na^+-HCO_3 -CO_3^{2-} cotransporter. The Na^+ absorbed by the Na^+-H^+ antiporter exits the cell on the basolateral membrane Na^+,K^+-ATPase and the Na^+-HCO_3 -CO_3^{2-} cotransporter. The K^+ that enters the cell on the Na^+,K^+-ATPase exits on a basolateral membrane K^+ channel. Carbonic anhydrase catalyzes the conversion of HCO_3 to CO_2 and OH in the lumen and the reverse reaction in the cell. Electrogenic H^+ secretion generates a small, lumen-positive voltage that generates a current flow across the paracellular pathway.

process is reversed, with use of cytoplasmic carbonic anhydrase, generating intracellular H^+ and HCO_3 . This H^+ “replenishes” the H^+ secreted across the apical membrane, resulting in net movement of the HCO_3 from the luminal solution to the cell cytoplasm. The intracellular HCO_3 is then secreted across the basolateral plasma membrane, as described previously.

Thick Ascending Limb of the Loop of Henle

Tubular fluid arriving at the early distal tubule has a pH and serum [[HCO_3]] similar to that in the late proximal tubule. Because there is significant water extraction in the loop of Henle, maintenance of a constant serum HCO_3 concentration requires reabsorption of HCO_3 . The majority of this HCO_3 absorption occurs in the thick ascending limb (TAL) through mechanisms similar to those present in the proximal tubule (Fig. 12.3). The majority of apical membrane H^+ secretion is mediated by the Na^+-H^+ antiporter NHE3. As in the proximal tubule, the low intracellular Na^+ concentration maintained by the basolateral Na^+,K^+ ATPase provides the primary driving force for the antiporter. Base efflux across the basolateral membrane is mediated by a Cl HCO_3 exchanger (AE2) and K^+ HCO_3 cotransport likely mediated by the K^+-Cl cotransporter KCC4.6

These cells also possess an H+-ATPase. The contribution of this pump to overall acidification in this segment is not clear.

Distal Nephron

Approximately 80% of the filtered HCO3 is reabsorbed in the proximal tubule; most but not all of the remainder is absorbed in the TAL.

One function of the distal nephron is to reabsorb the remaining 5% of filtered HCO3 . In addition, the distal nephron must secrete a quantity of H+ equal to that generated systemically by metabolism to maintain acid-base balance.

Fig. 12.3 Hydrogen (H+) and Bicarbonate HCO3− Ion Transport in the Thick Ascending Limb. Apical H+ secretion is mediated by a Na+-H+ antiporter. The low intracellular Na+ concentration, maintained by the basolateral Na+,K+-ATPase, provides the primary driving force for the antiporter. Both Cl−-HCO3− exchange and K+-HCO3− cotransport mediate base exit across the basolateral membrane.

The distal nephron is subdivided into several distinct portions that differ in their anatomy and acid secretory properties. Most of these segments transport H+ and HCO3 into the luminal fluid, but the main segments appear to be in the collecting duct.7 The segments of the collecting duct include the cortical collecting duct (CCD), the outer medullary collecting duct, and the inner medullary collecting duct. There are two distinct cell types in the CCD that can be distinguished histologically: the principal cell and the intercalated (IC) cell. The principal cell reabsorbs Na+ and secretes K+ and is discussed later. Depending on chronic acid-base status, the CCD is capable of either H+ or HCO3 secretion. These functions are mediated by two types of IC cells: the acid-secreting α-IC cell and the base-secreting β-IC cell. Both IC cell types are rich in carbonic anhydrase II.

Reabsorption of HCO3 in the distal nephron is mediated by apical H+ secretion by the α-IC cell. Two transporters secrete H+: a vacuolar H+-ATPase and an H+-K+-ATPase (Fig. 12.4). The vacuolar H+ ATPase is an electrogenic pump related to the H+ pump present within lysosomes, the Golgi apparatus, and endosomes. The H+-K+-ATPase uses the energy derived from adenosine triphosphate hydrolysis to secrete H+ into the lumen and to reabsorb K+ in an electroneutral fashion. The activity of the H+-K+-ATPase increases in K+ depletion and thus provides a mechanism by which K+ depletion enhances both collecting duct H+ secretion and K+ absorption.8

Active H+ secretion by the apical membrane generates an intracellular base that must exit the basolateral membrane. A basolateral Cl HCO3 exchanger (AE1) is the mechanism by which this base exit occurs. The Cl that enters the cell in exchange for HCO3 exits the cell through a basolateral membrane Cl conductance channel (see Fig. 12.4).

The HCO3 -secreting β-IC cell is a mirror image of the α-IC cell (Fig. 12.5). It possesses an H+-ATPase on the basolateral membrane, which mediates active H+ extrusion. Alkali that is generated within the cell then exits on an apical membrane Cl HCO3 exchanger. This Cl HCO3 exchanger is distinct from the basolateral Cl HCO3 exchanger present in the α-IC cell and functions as an anion exchanger or Cl channel in the luminal membrane of epithelial cells.9 The SLC26A4 protein (pendrin) is a family member that mediates apical Cl HCO3 exchange in the β-IC cell of the kidney. The Na+-driven Cl HCO3

Secretion of H+ in the -Intercalated Cell
of the Cortical Collecting Duct
Lumen

Bicarbonate Secretion by Cortical
Collecting Duct -Intercalated Cell

Interstitium
H+

H2O

H+

2CI

Pendrin
2HCO3

H+ + OH

H+

H+

K+

K+

K+

Carbonic
anhydrase

CO2

Voltage
+10 mV

Active transport

HCO3

HCO3
CI

CI
CI

?

K+

CI

H+
Carbonic
anhydrase II

Channel

0 mV

Passive transport

Fig. 12.4 Hydrogen (H+) Secretion in the Cortical Collecting Duct α-Intercalated Cell. Secretion of hydrogen ions into the lumen by an H+-ATPase and an H+-K+-ATPase. Apical membrane H+ secretion generates OH , which reacts with CO2 to form HCO3 . This bicarbonate exits across the basolateral membrane on a Cl -HCO3 exchanger, a member of the anion exchanger-1 (AE1) family and a truncated form of the red blood cell AE1 Cl -HCO3 exchanger. The Cl that enters the cell on the exchanger recycles across a basolateral membrane Cl channel. The K+ that enters the cell on the H+-K+-ATPase appears to be able either to recycle across the apical membrane or exit across the basolateral membrane, depending on the potassium balance of the individual. Carbonic anhydrase catalyzes the conversion of CO 2 and OH to HCO3 in the cell. Electrogenic H+ secretion generates a lumen-positive voltage that generates a current flow across the paracellular pathway.

exchanger (NDCBE) colocalizes with pendrin on the apical membrane and together may explain a component of electroneutral NaCl reabsorption in the collecting duct that is thiazide sensitive.10

The other cortical collecting tubule cell type is the principal cell, which also regulates acid-base transport, although indirectly. Principal cells mediate electrogenic Na+ reabsorption that results in a net negative luminal charge (Fig. 12.6). The greater this negative charge, the lesser is the electrochemical gradient for electrogenic proton secretion and therefore the greater the rate of net proton secretion. Thus, factors that stimulate Na+ reabsorption indirectly regulate the H+ secretory rate.

The medullary collecting duct possesses mechanisms only for H+ secretion. This H+ secretion is mediated by α-IC cells but also by cells that appear morphologically distinct from IC cells but are functionally similar.

Net Acid Excretion

For the kidney to generate NAE, it must both reabsorb filtered HCO3 and excrete titratable acids and ammonia. Several weak acids, such as phosphate, creatinine, and uric acid, are filtered at the glomerulus and can buffer secreted protons. Of these, phosphate is the most important because of its favorable pKa of 6.80 and its relatively high rate of urinary excretion (~25–30 mmol/day). However, the capacity of phosphate to buffer protons is maximized at a urine pH of 5.8, and acid-base disturbances generally do not induce substantial changes in urinary phosphate excretion. Other titratable acids, such as creatinine and uric acid, are limited by their lower excretion rate, which is not

Cl

H2O + CO2

2HCO3
Na+

NDCBE
Cl

Na+
AE4
HCO3

CI
30 mV

H+

β–Intercalated cells

Fig. 12.5 Bicarbonate Secretion by the Cortical Collecting Duct β-Intercalated Cell. H+ is secreted into the interstitium by an H +-ATPase. The OH generated by basolateral membrane H + secretion reacts with CO2 to form HCO3 , which exits across the apical membrane on a Cl -HCO3 exchanger (pendrin). The Cl that enters the cell on the exchanger exits across a basolateral membrane Cl channel. Carbonic anhydrase catalyzes the conversion of CO 2 and OH to HCO3 in the cell. The Na+-driven Cl -HCO3 exchanger (NDCBE) colocalizes with pendrin on the apical membrane and mediates thiazide-sensitive electroneutral NaCl reabsorption in this segment.

Transport of Na+ in the Principal Cell
of the Cortical Collecting Duct
Lumen

Interstitium

Na+

Na+

K+

3Na+

3Na+

2K+

2K+
K+

CI−

CI−
Voltage
−10 mV

−80 mV

Active transport

0 mV

Channel

Fig. 12.6 Sodium Transport in the Cortical Collecting Duct Principal Cell. Electrogenic Na+ absorption is mediated by the Na+ channel. The Na+ enters the cell across the apical membrane channel and exits the cell on the basolateral membrane Na+,K+-ATPase. The K+ that enters the cell on the basolateral Na+,K+-ATPase can be secreted into the luminal fluid by an apical membrane K+ channel. Electrogenic Na+ absorption establishes a lumen-negative voltage that drives a paracellular current.

dramatically changed in response to acid-base disturbances. Titratable acid excretion is a minor component of the increase in NAE in response to metabolic acidosis (Fig. 12.7).

Changes in Net Acid Excretion in Response to Chronic Metabolic Acidosis

Increase in net acid excretion
(mmol per day)

120
100

Ammonia

80
60
40
Titratable acid
20
0
Day 0

Day 1

Day 3

Day 5

Day of acid loading

Fig. 12.7 Changes in Net Acid Excretion. Chronic metabolic acidosis increases net acid excretion dramatically over several days; shown quantitatively are the increases in the two major components of net acid excretion: titratable acids and ammonia. Titratable acid excretion increases slightly and predominantly in the first 24 to 48 hours. In contrast, urinary ammonia excretion progressively increases over 7 days and is responsible for most of the increase in net acid excretion in chronic metabolic acidosis. (Data from Elkinton JR, Huth EJ, Webster GD Jr, McCance RA. The renal excretion of hydrogen ion in renal tubular acidosis. I. Quantitative assessment of the response to ammonium chloride as an acid load. Am J Med. 1960;36:554–575.)

Ammonia Metabolism

Quantitatively, the most important component of NAE is the NH_3/NH_4^+ system.[12] Unlike for titratable acids, the rate of ammonia (NH_3) production and excretion varies according to physiologic needs. Under normal circumstances, ammonia excretion accounts for approximately 60% of total NAE, and in chronic metabolic acidosis, almost the entire increase in NAE is caused by increased NH_3 metabolism. Ammonia metabolism involves interplay among the proximal tubule, TAL, and collecting duct.

The proximal tubule is responsible for both ammonia production and luminal secretion. Ammonia is synthesized in the proximal tubule predominantly from glutamine metabolism through enzymatic processes in which phosphoenolpyruvate carboxykinase and phosphatedependent glutaminase are the rate-limiting steps. This results in production of two ammonium (NH_4^+) and two HCO_3 ions from each glutamine ion. Ammonia is then preferentially secreted into the lumen. The primary mechanism for this luminal secretion appears to be NH_4^+ transport by the apical Na^+-H^+ antiporter NHE3[13] (Fig. 12.8). Metabolic acidosis increases the mobilization of glutamine from skeletal muscle and intestinal cells. Glutamine is preferentially taken up by the proximal tubular cell through the Na^+- and H^+-dependent glutamine transporter SNAT3. This transporter is a member of the SCL38 gene family of Na+-coupled neutral amino acid transporters. SNAT3 expression increases several-fold in metabolic acidosis, and it is preferentially expressed on the cell’s basolateral surface, where it is poised for glutamine uptake.14 The increase in plasma cortisol that typically accompanies metabolic acidosis plays a role in this transporter’s upregulation.15 Metabolic acidosis also causes increased expression and activity of phosphate-activated glutaminase and glutamate dehydrogenase.

Most of the ammonia that leaves the proximal tubule does not reach the distal tubule. Thus, there is transport of ammonia out of the

loop of Henle. This ammonia transport appears to occur predominantly in the TAL and is mediated by at least three mechanisms16 (Fig. 12.9). First, the lumen-positive voltage provides a driving force for passive paracellular NH4+ transport out of the TAL. Second, NH4+ can be transported out of the lumen by the furosemide-sensitive Na+-K+ 2Cl transporter. Third, NH4+ can leave the lumen across the apical membrane K+ channel of the TAL cell. NH4+ exits the cell via the Na+ H+ exchanger NHE4, functioning in Na+-NH4+ mode.

In addition, ammonia is secreted by the collecting duct. Although the traditional thought was that NH3/NH4+ then enters the collecting duct by nonionic diffusion driven by the acid luminal pH, increasing evidence suggests that the nonerythroid glycoproteins Rhbg and Rhcg may be involved in collecting duct ammonia secretion.17 18

Ammonia excretion can be regulated by three mechanisms. First, ammonia synthesis in the proximal tubule can be regulated. Chronic acidosis and hypokalemia increase ammonia synthesis, whereas hyperkalemia suppresses ammonia synthesis. Second, ammonia delivery from the proximal tubule to the medullary interstitium can be regulated. In particular, chronic metabolic acidosis increases expression of both NHE3 and the loop of Henle Na+-K+-2Cl cotransporter. Hyperkalemia can inhibit NH4+ reabsorption from the TAL. The combined effects of decreased NH3 synthesis in the proximal tubule and interference in NH4+ reabsorption in the thick limb may explain the low urinary [NH4+] found in hyperkalemic distal renal tubular acidosis. The reduced availability of ammonia to serve as a urinary buffer leads to a reduction in distal H+ secretion and development of metabolic acidosis. Also, any interstitial renal disease that destroys renal medullary anatomy may decrease medullary interstitial [NH3/NH4+] transfer. Third, mechanisms that regulate collecting duct H+ secretion or ammonia transporter expression can regulate ammonia entry into the collecting duct and ammonia excretion. Importantly, the primary mechanisms require synthesis of new proteins to increase both ammonia production and transport. Accordingly, changes in ammonia excretion may be delayed, and the maximal renal response to chronic metabolic acidosis requires 4 to 7 days.

REGULATION OF KIDNEY ACIDIFICATION

The regulation of acid-base balance requires an integrated system that precisely regulates proximal tubular H+ HCO3 transport, distal nephron H+ HCO3 transport, and ammonia synthesis and transport.

Blood pH

The regulation of acid-base balance requires that net H+ excretion increase in states of acidosis and decrease in states of alkalosis. This form of regulation involves both acute and chronic mechanisms. In the proximal tubule, acute decreases in blood pH increase the rate of HCO3 absorption, and acute increases in blood pH inhibit HCO3 absorption. These alterations in the rate of HCO3 absorption occur [whether]the change in pH is the result of changes in Paco2 or serum HCO3[. Similarly,
in the collecting duct, acute changes in peritubular
]
serum HCO3 and pH regulate the rate of H+ secretion.

In addition to acute regulation, mechanisms exist for chronic regulation. Chronic acidosis or alkalosis leads to parallel changes in the activities of the proximal tubule apical membrane Na+-H+ antiporter and basolateral membrane Na+ HCO3 -CO32− cotransporter.

Metabolic acidosis acutely increases the kinetic activity of NHE3 through direct pH effects and by phosphorylation; chronic acidosis increases the number of NHE3 transporters.19 20 In addition, chronic acidosis increases proximal tubular ammonia synthesis by increasing the activities of the enzymes involved in ammonia metabolism.

Ammonia Synthesis and Transport in the Proximal Tubule
Glutamine
Lumen

Blood

SNAT3

Na+
NH3

Mitochondria

NH3

NBC1

3HCO3

Glutamine
+

H

H+

NH4+
NH4+

H+
+

Na

H+
NHE3

+

Na

CA II

Glutaminase

NH4

Kir4.2

H2O

Glutamate
+

CO2

OH

Glutamate
dehydrogenase

α-ketoglutarate

(–)

H+

K+
GLUT

Glucose
PEPCK

NH4+

Fig. 12.8 Ammonia Synthesis and Transport in the Proximal Tubule. Metabolic acidosis and hypokalemia stimulate proximal ammonia synthesis by stimulating the uptake of glutamine through SNAT3 and increasing the activities of the enzymes involved in ammonia metabolism. The generation of ammonia is the result of glutamine metabolism by enzymes closely linked to gluconeogenesis. Hyperkalemia suppresses ammoniagenesis by increasing cell pH. Increased extracellular K+ concentration leads to depolarization of the proximal tubular cell (decrease in electronegativity of the cell) as sensed through the inwardly rectifying K + subchannel Kir4.2 encoded by Kcnj15 located on the basolateral membrane. This change results in less HCO 3 exit coupled to Na+ via NBCe1 because the cotransporter carries a net negative charge and is driven by intracellular electronegativity. The net effect is increased cell pH and downregulation of proteins involved in ammoniagenesis.

Ammonia Transport in the Thick Ascending
Limb of Henle's Loop
Lumen

Blood

NH4+

NH4+

Na+
2CI
NH4+

Na+
2CI
NH4+

Lumen (+)
potential

NH4
NHE4
Na+
NBCn1

Na+
HCO3

NH4+

Fig. 12.9 Ammonia Transport in the Thick Ascending Limb of Henle’s Loop. In addition to reabsorption through the paracellular pathway driven by the lumen-positive potential, ammonium can substitute for K + on the Na+-K+-2Cl− transporter and the apical membrane K+ channel. NH4+ exits the cell via the Na+-H+

exchanger NHE4. The basolateral Na^+-HCO_3^- cotransporter (NBCn1) functions to maintain an optimal cell pH to facilitate the large transcellular ammonium flux.

The CCD is also modified by chronic acid-base changes. Long-term increases in dietary acid lead to an increase in H^+ secretion, whereas long-term increases in dietary alkali lead to an increased capacity for HCO_3 secretion.[21] This effect is mediated by changes in the relative number of α- and β-IC cells. For example, during metabolic acidosis, the number of α-IC cells increases and the number of β-IC cells decreases, without a change in the total number of IC cells. Recent evidence suggests that the extracellular protein hensin may be involved in the switch between the predominant IC cell types.[22]

Mineralocorticoids, Distal Sodium Delivery, and Extracellular Fluid Volume

Mineralocorticoid hormones are key regulators of distal nephron and collecting duct H^+ secretion. Two mechanisms appear to be involved. First, mineralocorticoid hormone stimulates Na^+ absorption in principal cells of the CCD (see Fig. 12.6). This leads to a more lumennegative voltage that then stimulates H^+ secretion. This mechanism is indirect in that it requires the presence of Na^+ and of Na^+ transport. The second mechanism is the direct activation of H^+ secretion by mineralocorticoids. This effect is chronic, requiring long exposure, and involves parallel increases in apical membrane H^+-ATPase and basolateral membrane Cl HCO_3 exchanger activity.

Plasma Volume

Changes in plasma volume have important effects on acid-base homeostasis. This effect appears to be related to a number of factors. First, volume contraction is associated with a decreased GFR, which lowers the filtered load of HCO_3 and decreases the load placed on the tubules to maintain NAE. Volume contraction also acutely decreases the paracellular permeability of the proximal tubule. This will decrease HCO_3 backleak around cells, thereby increasing net bicarbonate reabsorption by the proximal tubule. Third, chronic volume contraction is associated with an adaptive increase in the activity of the proximal tubule apical membrane Na^+-H^+ antiporter NHE3. Because this transporter contributes to both $NaHCO_3$ and NaCl absorption, both these capacities will be increased with chronic volume contraction. Further, volume contraction limits distal delivery of chloride. In the presence of chronic metabolic alkalosis, the CCD is poised for HCO_3 secretion. However, collecting duct HCO_3 secretion requires luminal Cl and is inhibited by Cl deficiency.

Potassium

Potassium deficiency is associated with an increase in renal NAE. This effect is multifactorial. First, chronic K^+ deficiency increases the proximal tubule apical membrane Na^+-H^+ antiporter and basolateral membrane Na^+ HCO_3 -CO_3^{2-} cotransporter activities. This effect is similar to that seen with chronic acidosis and may be caused by intracellular acidosis. Chronic K^+ deficiency also increases proximal tubular ammonia production. Finally, chronic K^+ deficiency leads to an increase in collecting duct H^+ secretion. This appears to be related to increased activity of the apical membrane H^+-K^+-ATPase. Such an effect increases the rate of H^+ secretion and the rate of K^+ reabsorption in the collecting duct. In addition, ammonia, whose production is stimulated by hypokalemia, has direct effects that stimulate collecting duct H^+ secretion. Counterbalancing these effects is that K^+ deficiency decreases aldosterone secretion, which can inhibit distal acidification. Thus, in normal individuals, the net effect of K^+ deficiency is typically a minor change in acid-base balance. However, in patients with nonsuppressible mineralocorticoid secretion (e.g., hyperaldosteronism, Cushing syndrome), K^+ deficiency can greatly stimulate renal acidification and cause profound metabolic alkalosis.

Hyperkalemia appears to have opposite effects on renal acidification. The most notable effect of hyperkalemia is inhibition of ammonia synthesis in the proximal tubule and ammonia absorption in the loop of Henle, resulting in inappropriately low levels of urinary ammonia excretion. This contributes to the metabolic acidosis seen in patients with hyperkalemic distal (type 4) renal tubular acidosis.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is true regarding the effect of chronic K^+ deficiency on renal acidification?
A. Decreases basolateral membrane Na^+- HCO_3^--CO_3^{2-} cotransporter activity
B. Increases proximal tubular ammonia production
C. Decreases collecting duct H^+ secretion
D. Increases aldosterone secretion

2. Which one of the following is true regarding ammonia handling in the kidney?
A. Ammonia synthesized in the proximal tubule is primarily reabsorbed in the cortical collecting duct.
B. Ammonia is reabsorbed passively in the thick ascending limb driven by the lumen-negative voltage.

C. NH_4^+ is transported into the lumen of the thick ascending limb by the Na^+-K^+-Cl transporter.
D. Nonthyroid glycoproteins Rhbg and Rhcg are involved in collecting duct ammonia secretion.

3. Which of the following is true regarding net acid production by the kidney?
A. Sulfur-containing amino acids are metabolized to CO_2
B. Metabolism of lysine and arginine yield base on metabolism.
C. Animal foods are high in protein and organophosphates and provide a net acid diet.
D. Daily volatile acid production is approximately 1 mmol H^+

REFERENCES

1. Palmer BF. Approach to fluid and electrolyte disorders and acid-base problems. Prim Care. 2008;35:195–213.
2. Alpern RJ. Cell mechanisms of proximal tubule acidification. Physiol Rev. 1990;70:79–114.
3. Bobulescu A, Moe OW. Luminal Na+/H+ exchange in the proximal tubule. Pflugers Arch. 2009;458:5–21.
4. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. Clin J Am Soc Nephrol. 2014;9:1627–1638.
5. Romero M. Molecular pathophysiology of SLC4 bicarbonate transporters. Curr Opin Nephrol Hypertens. 2005;14:495–501.
6. Mount DB. Thick ascending limb of the loop of Henle. Clin J Am Soc Nephrol. 2014;9(11):1974–1986.
7. Alpern RJ, Preisig P. Renal acid base transport. In: Schrier RW, ed. Diseases of the Kidney and Urinary Tract. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:183–195.
8. Roy A, Al-bataineh MM, Pastor-Soler NM. Collecting duct intercalated cell function and regulation. Clin J Am Soc Nephrol. 2015;10(2):305–324.
9. Dorwart M, Shcheynikov N, Yang D, Muallem S. The solute carrier 26 family of proteins in epithelial ion transport. Physiology (Bethesda). 2008;23:104–114.
10. Wall SM. The role of pendrin in blood pressure regulation. Am J Physiol Renal Physiol. 2016;310(3):F193–F203.
11. Elkinton JR, Huth EJ, Webster Jr GD, McCance RA. The renal excretion of hydrogen ion in renal tubular acidosis. I. quantitative assessment of the response to ammonium chloride as an acid load. Am J Med. 1960;36:554–575.
12. Knepper MA, Packer R, Good DW. Ammonium transport in the kidney. Physiol Rev. 1989;69:179–249.

13. Bignon Y, Pinelli L, Frachon N, et al. Defective bicarbonate reabsorption in Kir4.2 potassium channel deficient mice impairs acid-base balance and ammonia excretion. Kidney Int. 2020;97:304–315.
14. Moret C, Dave M, Schulz N, et al. Regulation of renal amino acid transporters during metabolic acidosis. Am J Physiol Renal Physiol. 2007;292:F555–F566.
15. Karinch A, Lin C, Meng Q, et al. Glucocorticoids have a role in renal cortical expression of the SNAT3 glutamine transporter during chronic metabolic acidosis. Am J Physiol Renal Physiol. 2007;292:F448–F455.
16. Olson J, Svendsen S, Berg P, et al. NBCn1 Increases NH4+ reabsorption across thick ascending limbs, the capacity for urinary NH4+ excretion, and early recovery from metabolic acidosis. J Am Soc Nephrol. 2021.
17. Weiner ID, Verlander J. Role of NH3 and NH4 transporters in renal acidbase transport. Am J Physiol Renal Physiol. 2011;300:F11–F23.
18. Kim H, Verlander J, Bishop J, et al. Basolateral expression of the ammonia transporter family member Rh C glycoprotein in the mouse kidney. Am J Physiol Renal Physiol. 2009;296:F543–F555.
19. Moe OW. Acute regulation of proximal tubule apical membrane Na/H exchanger NHE-3: role of phosphorylation, protein trafficking, and regulatory factors. J Am Soc Nephrol. 1999;10:2412–2425.
20. Ambuhl P, Amemiya M, Danczkay M, et al. Chronic metabolic acidosis increases NHE3 protein abundance in rat kidney. Am J Physiol. 1996;271:F917–F925.
21. McKinney TD, Burg MB. Bicarbonate transport by rabbit cortical collecting tubules: effect of acid and alkaline loads in vivo on transport in vitro. J Clin Invest. 1977;60:766–768.
22. Vijayakumar S, Erdjument-Bromage H, Tempst P, Al-Awqati Q. Role of integrins in the assembly and function of hensin in intercalated cells. J Am Soc Nephrol. 2008;19:1079–1091.

13

Metabolic Acidosis

Biff F. Palmer

DEFINITION

Metabolic acidosis is defined as a low arterial blood pH in conjunction with a reduced serum bicarbonate concentration $[HCO_3\ ]$.

Respiratory compensation results in a decrease in arterial carbon dioxide tension ($Paco_2$). A low serum $[HCO_3\ ]$ alone is not diagnostic of metabolic acidosis because it also results from the kidney compensation to chronic respiratory alkalosis. Measurement of the arterial pH differentiates between these two possibilities. Box 13.1 shows the expected compensatory responses for metabolic and respiratory acidbase disorders.[1]

After the diagnosis of metabolic acidosis is confirmed, the first step in the examination of the patient is to calculate the serum anion gap. The anion gap equals the difference between the serum concentrations of the major cation sodium ($[Na^+]$) and the major measured anions chloride and bicarbonate ($[Cl\ ]$ and $[HCO_3\ ]$) and is given by the following formula:

$$\text{Anion gap} = Na^+ - ([Cl\ ] + [HCO_3\ ])$$

In healthy individuals, the normal value of the anion gap is approximately 12 ± 2 mmol/L. Because many of the unmeasured anions consist of albumin, the normal anion gap is decreased by approximately 2.5 mmol/L for each 1 g/dL decrease in the serum albumin concentration below normal. The total number of cations must equal the total number of anions, so a decrease in the serum HCO_3 concentration must be offset by an increase in the concentration of other anions.

If the anion accompanying excess H^+ is Cl , the decrease in serum $[HCO_3\ ]$ is matched by an equal increase in serum $[Cl\ ]$. This acidosis is classified as a normal anion gap, a non–anion gap, or a hyperchloremic metabolic acidosis. In contrast, if excess H^+ is accompanied by an anion other than Cl , the decreased $[HCO_3\ ]$ is balanced by an increase in the concentration of the unmeasured anion. $[Cl\ ]$ remains the same. In this setting, the acidosis is said to be a high anion gap or anion gap metabolic acidosis.

The normal value for the anion gap has tended to fall over time because of changes in how serum Na^+ and Cl are measured.[2] Flame photometry for Na^+ measurement and a colorimetric assay for Cl have been replaced by the use of ion-selective electrodes, with which the serum Na^+ values have largely remained the same, whereas the serum Cl values have tended to be higher. As a result, the normal value for the anion gap has decreased to as low as 6 mmol/L in some reports. Recognizing this change, some laboratories have adjusted the calibration set point for Cl to return the normal value for the anion gap to the 12 ± 2 mmol/L range. The clinician needs to be aware that the average anion gap and range of normal values will vary across different facilities.

Fig. 13.1 provides a recommended approach to a patient with metabolic acidosis and lists the common causes of metabolic acidosis according to the anion gap.

NON–ANION GAP (NORMAL ANION GAP) METABOLIC ACIDOSIS

A non–anion gap metabolic acidosis can result from either kidney or extrarenal causes. Kidney causes of metabolic acidosis occur when renal bicarbonate generation, which results from net acid excretion, does not balance the loss of bicarbonate and other alkali buffers consumed in the buffering of normal endogenous acid production. This failure of net acid excretion is termed renal tubular acidosis (RTA). Extrarenal causes occur when exogenous acid loads, endogenous acid production, or endogenous bicarbonate losses are elevated and exceed kidney net acid excretion. The most common extrarenal cause of non–anion gap metabolic acidosis is chronic diarrhea.

Kidney and extrarenal causes of metabolic acidosis can be distinguished by measuring urinary ammonia excretion.[3] The primary response of the kidney to metabolic acidosis is to increase urinary ammonia excretion, each millimole of urinary ammonia excreted resulting in the generation of 1 mmol of “new” bicarbonate. Thus, kidney causes of metabolic acidosis are characterized by low urinary ammonia excretion rates. In contrast, in extrarenal metabolic acidosis, urinary ammonia excretion is elevated. Because most laboratories do not measure urinary ammonia, one can indirectly assess ammonia excretion by measuring the urinary anion gap (UAG):

$$UAG = (UNa^+ + UK^+) - UCl^-$$

The UAG is normally a positive value, ranging from +30 to +50 mmol/L. A negative value for the UAG suggests increased kidney excretion of an unmeasured cation (i.e., cation other than Na^+ or K^+). One such cation is NH_4^+. With chronic metabolic acidosis because of extrarenal causes, urinary ammonia concentrations, in the form of NH_4Cl, can reach 200 to 300 mmol/L. As a result, the measured cation concentration will be less than the measured anion concentration, which includes the increased urinary Cl^-, and the UAG will be less than zero and frequently less than −20 mmol/L.

The UAG only indirectly reflects the urinary ammonia concentration and, if other unmeasured ions are excreted, can give misleading results. Examples include diabetic ketoacidosis, associated with substantial urinary excretion of sodium ketoacid salts, and toluene exposure (discussed later), associated with increased urinary excretion of sodium hippurate and sodium benzoate. In these settings, the UAG value may remain positive despite an appropriate increase in urinary ammonia excretion because of the increased urinary excretion of Na^+ acid-anion salts. A similar situation occurs when urinary NH_4^+ is excreted with an anion other than Cl^-, such as β-hydroxybutyrate, acetoacetate, bicarbonate, or hippurate. In these settings, and even when NH_4^+ is excreted with Cl^-, the urine osmolal gap (UOG) can be used as a surrogate for NH_4^+

Expected Compensatory
Responses to Acid-Base Disorders

BOX 13.1

Acute Respiratory Acidosis
For every 10 mm Hg rise in Pco_2, HCO_3 increases by 1 mmol/L
Chronic Respiratory Acidosis
For every 10 mm Hg rise in Pco_2, HCO_3 increases by 3.5 mmol/L
Acute Respiratory Alkalosis
For every 10 mm Hg fall in Pco_2, HCO_3 decreases by 2 mmol/L

Assessment of Low Serum HCO_3^-
Concentration
Low serum
HCO_3^- concentration

Check arterial blood
gases to exclude chronic
respiratory alkalosis

Chronic Respiratory Alkalosis
For every 10 mm Hg decrease in Pco_2, HCO_3 decreases by 5 mmol/L
Metabolic Acidosis
1.2 mm Hg decrease in Pco_2 for each 1 mmol/L fall in HCO_3
$Pco_2 = HCO_3 + 15$
Pco_2 = Last digits of pH

Calculate serum
anion gap

Normal
anion gap

Metabolic Alkalosis
Pco_2 increases by 0.7 for each mmol/L HCO_3

concentration. The UOG is the difference between the measured
and the calculated urine osmolality (mOsmol/kg):
$2 \times Na^+ + K^+ +$ [Urea nitrogen (mg/dL)/ 2.8]
+ [Glucose (mg / dL)/18]

Calculate urine
anion gap

Raised anion gap
Renal origin
Uremic acidosis (GFR
usually <15–20 mL/min)
Extrarenal origin
Lactic acidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Poisoning (ethylene glycol,
methanol, salicylate)
Pyroglutamic acidosis

In SI units, the formula is:
$2 \times Na^+ + K^+$ mmol/L + Urea (mmol/L) + Glucose (mmol/L)

The normal value of the UOG is approximately 10 to 100 mOsmol/kg. NH4+ salts are generally the only other major urinary solute that contributes importantly to the urine osmolality, so values appreciably greater than 100 mOsmol/kg reflect increased excretion of NH4+ salts.

Urine pH, in contrast to the UAG or UOG, does not reliably differentiate acidosis of kidney origin from that of extrarenal origin. For example, an acid urine pH does not necessarily indicate an appropriate increase in net acid excretion. If renal ammonia metabolism is inhibited, as occurs with chronic hyperkalemia, there is decreased ammonia available in the distal nephron to serve as a buffer, and small amounts of distal H+ secretion can lead to significant urine acidification. In this setting, the urine pH is acid, but net acid excretion is low because of the low ammonia excretion. Similarly, alkaline urine does not necessarily imply a renal acidification defect. In conditions in which ammonia metabolism is stimulated, distal H+ secretion can be massive and yet the urine remains relatively alkaline because of the buffering effects of ammonia.

Metabolic Acidosis of Renal Origin

An overall approach to patient assessment for workup of metabolic acidosis of kidney origin is shown in Fig. 13.2

Proximal Renal Tubular Acidosis (Type 2)

Normally, 80% to 90% of the filtered load of HCO3 is reabsorbed in the proximal tubule. In proximal (type 2) RTA, the proximal tubule has a decreased capacity to reabsorb filtered bicarbonate. When serum bicarbonate concentration is normal or nearly normal, the amount of bicarbonate filtered by the glomerulus exceeds proximal tubule bicarbonate reabsorptive capacity. When this happens, there is increased bicarbonate delivery to the loop of Henle and distal nephron that exceeds their capacity to reabsorb bicarbonate. As a result, some filtered bicarbonate appears in the urine. The net effect is that serum [HCO3] decreases. Eventually, the filtered bicarbonate load decreases to the point at which the proximal tubule is able to reabsorb sufficient filtered bicarbonate that the bicarbonate load to the loop of Henle and the distal nephron is within their reabsorptive capacity. When this occurs, no further bicarbonate is lost in the urine, net acid excretion normalizes, and a new steady-state serum [HCO3] develops, although at a lower-than-normal level.

Positive value
Proximal renal tubular acidosis (type 2 RTA)
Hypokalemic distal renal tubular acidosis (type 1 RTA)
Hyperkalemic distal renal tubular acidosis (type 4 RTA)
Renal tubular acidosis of renal impairment (GFR usually >15–20 mL/min)

Negative value
Diarrhea
Gastrointestinal ureteral connections
External loss of pancreatic or biliary secretions

Fig. 13.1 Approach to the patient with low serum HCO 3− concentration. GFR, Glomerular filtration rate; RTA, renal tubular acidosis.

Hypokalemia is present in proximal RTA. Kidney NaHCO3 losses lead to intravascular volume depletion, which in turn activates the renin-angiotensin-aldosterone system. Distal Na+ delivery is increased as a result of the impaired proximal reabsorption of NaHCO3. Because of the associated hyperaldosteronism and increased distal nephron Na+ reabsorption, there is increased K+ secretion. The net result is kidney potassium wasting and the development of hypokalemia. In the

Assessment of a Patient With
Renal Tubular Acidosis
Renal tubular
acidosis (RTA)
Abnormal proximal
tubular function:
proximal RTA
(type 2 RTA)

Assess proximal
tubular function

Proximal tubular
function normal

Measure plasma
K^+ levels

Raised plasma
K^+ levels:
hyperkalemic
RTA (type 4 RTA)

Measure
urine pH

pH < 5.5
Low
mineralocorticoid
secretion

pH > 5.5
Collecting
duct
abnormality

Normal or
low plasma
K^+ levels

Measure urine
pH and plasma K^+ levels

Plasma $[K^+]$
< 3.5 mmol/L
Urine pH > 5.5
Hypokalemic distal
RTA (type 1 RTA)

Plasma $[K^+]$
3.5–5.0 mmol/L
Urine pH < 5.5
RTA or renal
impairment

Fig. 13.2 Approach to the patient with renal tubular acidosis.

BOX 13.2

steady state, when virtually all the filtered HCO_3 is reabsorbed in the proximal and distal nephron, kidney potassium wasting is less, and the degree of hypokalemia tends to be mild.

Proximal RTA may occur as an isolated defect in acidification but more commonly occurs in the setting of widespread proximal tubule dysfunction (Fanconi syndrome). In addition to decreased HCO3 reabsorption, patients with Fanconi syndrome have impaired reabsorption of glucose, phosphate, uric acid, amino acids, and lowmolecular-weight proteins. Various inherited and acquired disorders have been associated with the development of Fanconi syndrome and proximal RTA (Box 13.2). The most common inherited cause in children is cystinosis (see Chapter 50). Most adults with Fanconi syndrome have an acquired condition that is related to an underlying dysproteinemic condition, such as multiple myeloma.

Skeletal abnormalities are common in these patients. Osteomalacia can develop from chronic hypophosphatemia caused by renal phosphate wasting if Fanconi syndrome is present. These patients also may have a deficiency in the active form of vitamin D because of an inability to convert 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D in the proximal tubule.

In contrast to distal RTA, proximal RTA is not associated with nephrolithiasis or nephrocalcinosis. One exception is the use of topiramate,4 5 an antiepileptic drug that is increasingly used to treat a variety of neurologic and metabolic disorders. The drug exerts an inhibitory effect on kidney carbonic anhydrase activity, resulting in a proximal acidification defect similar to that observed with acetazolamide. Topiramate also is associated with hypocitraturia, hypercalciuria, and elevated urine pH, leading to an increased risk for kidney stone disease.

Proximal RTA should be suspected in a patient with a normal anion gap acidosis and hypokalemia who has an intact ability to acidify the urine to below 5.5 while in a steady state.6 Proximal tubular dysfunction, such as euglycemic glycosuria, hypophosphatemia, hypouricemia, and mild proteinuria, helps support this diagnosis. The UAG is

Causes of Proximal (Type 2) Renal Tubular Acidosis

Not Associated With Fanconi Syndrome
- Sporadic
- Familial

Dysproteinemic States
- Myeloma kidney
- Light chain deposition disease

Disorder of Carbonic Anhydrase
- Drugs: acetazolamide, sulfanilamide, topiramate
- Carbonic anhydrase II deficiency

Hyperparathyroidism
- Primary
- Secondary

Associated With Fanconi Syndrome
- Selective (no systemic disease present)
- Sporadic

Drugs and Toxins
- Tenofovir
- Outdated tetracycline
- Ifosfamide
- Gentamicin
- Streptozocin
- Lead
- Cadmium
- Mercury

Familial
- Autosomal recessive proximal RTA with ocular abnormalities: Na+-HCO3

cotransporter (NBCe1) defect
- Autosomal recessive proximal RTA with osteopetrosis and cerebral calcification: carbonic anhydrase II defect
- Generalized (systemic disorder present)
- Genetic disorders
- Cystinosis
- Wilson disease
- Hereditary fructose intolerance
- Lowe syndrome
- Metachromatic leukodystrophy

RTA, Renal tubular acidosis.

Tubulointerstitial Disease
- Posttransplantation rejection
- Balkan nephropathy
- Medullary cystic disease

Others
- Bone fibroma
- Osteopetrosis
- Paroxysmal nocturnal hemoglobinuria

greater than zero, indicating the lack of increase in net acid excretion. The metabolic acidemia in the steady state is maintained by a low rate of NH_4^+ excretion. The lesion causing impaired reabsorption of HCO_3^- in the proximal tubule leads to a more alkaline intracellular pH exerting an inhibitory effect on glutamine metabolism and suppressing ammoniagenesis.

Treatment of proximal RTA is difficult. Administration of alkali increases serum [HCO_3^-], which increases urinary bicarbonate losses and thereby minimizes subsequent increases in the serum [HCO_3^-]. Moreover, the increased distal sodium load, in combination with increased circulating plasma aldosterone, results in increased kidney potassium wasting and worsening hypokalemia. As a result, substantial amounts of alkali, often in the form of a potassium salt, such as potassium citrate, are required to prevent worsening hypokalemia. Children with proximal RTA should be aggressively treated to normalize their serum [HCO_3^-] to minimize growth retardation. These children may require large amounts of alkali therapy, typically 5 to 15 mmol/kg/day. Adults with proximal RTA are frequently not treated as aggressively as children are because of the lack of systemic metabolic abnormalities or bone disease. Many clinicians administer alkali therapy if serum [HCO_3^-] is less than 18 mmol/L to prevent severe acidosis. Whether more aggressive therapy to normalize serum [HCO_3^-] is beneficial remains unknown. However, the large amounts of alkali required, about 700 to 1000 mmol/day for a 70-kg individual, make this approach problematic.

Hypokalemic Distal Renal Tubular Acidosis (Type 1)

In contrast to proximal RTA, patients with distal RTA are unable to acidify their urine, either under basal conditions or in response to metabolic acidosis.[7,8] Type 1 RTA results from a reduction in net H^+ secretion in the distal nephron and prevents urinary acidification, thereby minimizing titratable acid excretion and urinary ammonia excretion. As a result, these patients are unable to match net acid excretion to endogenous acid production, and acid accumulation ensues. The subsequent metabolic acidosis stimulates reabsorption of bone matrix to release the calcium alkali salts present in bone. During prolonged periods, this can result in progressive osteopenia in adults and in osteomalacia in children. Distal RTA can be caused by either impaired H^+ secretion (secretory defect) or an abnormally permeable distal tubule, resulting in increased backleak of normally secreted H^+ (gradient defect); it may be genetic or acquired. Certain medications, especially amphotericin, result in increased backleak of protons across the apical plasma membrane, leading to a gradient defect form of distal RTA.

For patients with a secretory defect, the inability to acidify the urine below pH 5.5 results from abnormalities in any of the proteins involved in collecting duct H^+ secretion. Some patients may have an isolated defect in the H^+-K^+-ATPase that impairs H^+ secretion and K^+ reabsorption.[9] A defect confined to the vacuolar H^+-ATPase also results in kidney potassium wasting.[10] The development of systemic acidosis tends to diminish net proximal fluid reabsorption with an increase in distal delivery, resulting in volume contraction and activation of the renin-aldosterone system. Increased distal Na^+ delivery coupled to increased circulating levels of aldosterone then leads to increased kidney K^+ secretion.[11] Defects in the basolateral anion exchanger (AE1) also can cause distal RTA. In this case the lack of basolateral HCO_3^- exit leads to intracellular alkalinization, which inhibits apical proton secretion.

Patients with distal RTA have low ammonia secretion rates. The decreased secretion is caused by the failure to trap ammonia in the tubular lumen of the collecting duct as a result of the inability to lower luminal fluid pH. In addition, there is often impaired medullary transfer of ammonia because of interstitial disease. Interstitial disease is frequently present in such patients through an associated underlying disease or as a result of nephrocalcinosis or hypokalemia-induced interstitial fibrosis.

In contrast to proximal RTA, nephrolithiasis and nephrocalcinosis are common.[12] Urinary Ca^{2+} excretion is high secondary to acidosisinduced bone mineral dissolution. Luminal alkalinization also inhibits calcium reabsorption, resulting in further increases in urinary calcium excretion.[13] Calcium phosphate solubility is also greatly lowered at alkaline pH, and calcium phosphate stone formation is accelerated. Stone formation is further enhanced as a result of low urinary citrate excretion. Citrate is metabolized to HCO_3^-, and its kidney reabsorption is stimulated by metabolic acidosis, thereby minimizing the severity of metabolic acidosis. Urinary citrate also chelates urinary calcium, decreasing ionized calcium concentrations. Accordingly, the decreased citrate excretion that occurs in chronic metabolic acidosis as a result to distal RTA further contributes to both nephrolithiasis and nephrocalcinosis.

Distal RTA may be a primary disorder, either idiopathic or inherited, but it most often occurs in association with a systemic disease, one of the most common of which is Sjögren syndrome (Box 13.3). Hypergammaglobulinemic states as well as drugs and toxins also may cause this disorder.

A common cause of acquired distal RTA is glue sniffing. Inhalation of toluene from the fumes of model glue, spray paint, and paint thinners can give rise to hypokalemic normal anion gap acidosis through multiple mechanisms. First, toluene inhibits collecting duct proton secretion. Second, metabolism of toluene produces the organic acids hippuric and benzoic acid. These are buffered by sodium bicarbonate, resulting in metabolic acidosis and the production of sodium hippurate and sodium benzoate. If plasma volume is normal, these salts are rapidly excreted in the urine, and a non–anion gap metabolic acidosis develops. If plasma volume is decreased, urinary excretion is limited, these salts accumulate, and an anion gap metabolic acidosis develops.

Distal RTA should be considered in all patients with a non–anion gap metabolic acidosis and hypokalemia who have an inability to lower the urine pH maximally. A urine pH above 5.5 in the patient with systemic acidosis suggests distal RTA, and a UAG value greater than zero or lack of an increase in the UOG is confirmatory. Depending on the duration of the distal RTA, the metabolic acidosis can be mild or very severe, with a serum [HCO_3^-] as low as 10 mmol/L. Urinary potassium losses lead to the development of hypokalemia. Severe hypokalemia (<2.5 mmol/L) may result in musculoskeletal weakness and nephrogenic diabetes insipidus. The latter occurs because hypokalemia decreases aquaporin 2 (AQP2) expression in the collecting duct, thereby minimizing the ability to concentrate urine. An abdominal ultrasound scan or radiograph may reveal nephrocalcinosis.

In patients with minimal disturbances in blood pH and plasma [HCO_3^-], a test of urinary acidification is required. Traditionally, such a test involved oral NH_4Cl administration to induce metabolic acidosis with assessment of the kidney response by serial measurement of urine pH. Many patients poorly tolerate NH_4Cl ingestion because of gastric irritation, nausea, and vomiting. An alternative way to test the capacity for distal acidification is to administer furosemide and the mineralocorticoid fludrocortisone simultaneously.[14] The combination of both increased distal Na^+ delivery and mineralocorticoid effect will stimulate distal H^+ secretion by both an increase in the luminal electronegativity and a direct stimulatory effect on H^+ secretion. Unaffected individuals will have urine pH lowered below 5.5 with either maneuver.

Correction of the metabolic acidosis in distal RTA can be achieved by administration of alkali in an amount only slightly greater than daily acid production, usually 1 to 2 mmol/kg/day. In patients with

Differentiation of Renal Tubular Acidosis Types

BOX 13.3

Causes of Hypokalemic Distal (Type 1) Renal Tubular Acidosis (RTA)

TABLE 13.1

Primary
- Idiopathic
- Familial

Factor

Type 1

Type 2

Type 4

Serum K^+

Low

Low

High

Kidney function

Normal or near normal

Normal or near normal

Stage 3, 4, or 5 chronic kidney disease

Urine pH during acidosis

High

Low

Low or high

Serum HCO_3^- (mmol/L)

10–20

16–18

16–22

Urine citrate

Low

High

Low

Fanconi syndrome

No

May be
present

No

Secondary
Autoimmune Disorders
- Hypergammaglobulinemia
- Sjögren syndrome
- Primary biliary cirrhosis
- Systemic lupus erythematosus

Genetic Diseases
- Autosomal dominant RTA: anion exchanger 1 defect
- Autosomal recessive RTA: H^+-ATPase A4 subunit
- Autosomal recessive with progressive nerve deafness: H^+-ATPase B1 subunit

Drugs and Toxins
- Amphotericin B
- Toluene

Disorders With Nephrocalcinosis
- Hyperparathyroidism
- Vitamin D intoxication
- Idiopathic hypercalciuria

Tubulointerstitial Disease
- Obstructive uropathy
- Renal transplantation

severe K^+ deficits, correction of the acidosis with HCO_3 , particularly if it is done with sodium alkali salts such as $NaHCO_3$, can lower serum potassium concentration to dangerous levels. In this setting, potassium replacement should begin before the acidosis is corrected. In general, a combination of sodium alkali and potassium alkali is required for long-term treatment of distal RTA. For patients with recurrent kidney stone disease caused by distal RTA, treatment of the acidosis increases urinary citrate excretion, which slows the rate of further stone formation and may even lead to stone dissolution.

Hyperkalemic Distal Renal Tubular Acidosis (Type 4)

Type 4 RTA is characterized by distal nephron dysfunction, resulting in impaired kidney excretion of both H^+ and K^+ and causing hyperchloremic normal gap acidosis and hyperkalemia.[15] (Note that the term type 3 RTA is most often applied to a rare autosomal recessive syndrome resulting from carbonic anhydrase II deficiency with features of both proximal and distal RTA.)

Type 4 RTA occurs most frequently with mild to moderate impairment in kidney function; however, the magnitude of hyperkalemia and acidosis is disproportionately severe for the observed glomerular filtration rate (GFR). Whereas hypokalemic distal (type 1) RTA is also a disorder of distal nephron acidification, type 4 is distinguished from type 1 RTA on the basis of several important characteristics (Table 13.1).

Type 4 RTA is also a much more common form of RTA, particularly in adults.

Hyperkalemic distal RTA results from deficient circulating aldosterone or abnormal cortical collecting duct (CCD) function, or is related to hyperkalemia. In either case, a defect in distal H+ secretion develops. Impaired Na+ reabsorption by the principal cell leads to a decrease in the luminal electronegativity of the CCD, which impairs distal acidification as a result of the decrease in driving force for H+ secretion into the tubular lumen. The H+ secretion is further impaired in this segment as well as in the medullary collecting duct as a result of either the loss of the direct stimulatory effect of aldosterone on H+ secretion or an abnormality in the H+-secreting cell.

A consequence of the decrease in luminal electronegativity in the CCD is impaired kidney K+ excretion. In addition, a primary abnormality in CCD transport can also impair K+ secretion. The development of hyperkalemia adds to the defect in distal acidification by decreasing the amount of ammonia available to act as a urinary buffer. Some studies suggest that hyperkalemia itself, through its effects on ammonia metabolism, is the primary mechanism by which metabolic acidosis develops in type 4 RTA.

The etiology of type 4 RTA includes disorders associated with decreased circulating levels of aldosterone and conditions associated with impaired CCD function. The most common disease associated with type 4 RTA in adults is diabetes mellitus. In these patients, primary NaCl retention leads to volume expansion and suppression and atrophy of the renin-secreting juxtaglomerular apparatus. Several common drugs, such as nonsteroidal antiinflammatory agents (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and high doses of heparin, as used for systemic anticoagulation, can lead to decreased mineralocorticoid synthesis. Impaired function of the CCD can be a feature of structural damage to the kidney, as in interstitial renal diseases such as sickle cell nephropathy, urinary tract obstruction, and lupus. CCD function also may be impaired from use of drugs such as amiloride, triamterene, spironolactone, and finerenone.16

Type 4 RTA should be suspected in a patient with a normal gap metabolic acidosis associated with hyperkalemia. The typical patient is in the fifth to seventh decade of life with a long-standing history of diabetes mellitus with a moderate reduction in the GFR. Plasma $[\mathrm{HCO}_3\ ]$ is usually 18 to 22 mmol/L and serum [K+] between 5.5 and 6.5 mmol/L. Most patients are asymptomatic; however, the hyperkalemia may occasionally be severe enough to cause muscle weakness or cardiac arrhythmias. The UOG is not increased and the UAG value is slightly positive, indicating minimal ammonia excretion in the urine. When the disorder is caused by a defect in mineralocorticoid activity, patients typically have urine pH below 5.5, reflecting a more severe defect in ammonia availability than occurs with a defect in H+ secretion (Fig. 13.3). In patients with structural damage to the collecting duct, the urine pH may be alkaline, reflecting both impaired H+ secretion and decreased urinary ammonia excretion.

Urine pH in Type 4 Renal Tubular Acidosis
Type 4 RTA

Decreased distal
H^+ secretion

Decreased
K^+ secretion

Raised plasma
K^+ levels

Decreased
NH_3/NH_4^+ synthesis

Urine pH >5.5

Net acid excretion
decreased

Urine pH < 5.5

Fig. 13.3 Urine pH in Hyperkalemic Distal (Type 4) Renal Tubular Acidosis. Net acid excretion is always decreased; however, the urine pH can be variable. In structural disease of the kidney, the predominant defect is usually decreased distal H^+ secretion and the urine pH is >5.5. In disorders associated with decreased mineralocorticoid activity, urine pH is usually <5.5.

Treatment of patients with type 4 RTA is directed at both the hyperkalemia and the metabolic acidosis. In many patients, lowering serum $[K^+]$ will simultaneously correct the acidosis.[17] Correction of the hyperkalemia allows kidney ammonia production to increase, thereby increasing the buffer supply for distal acidification. The first consideration in treatment is to discontinue any nonessential medication that might interfere in either the synthesis or activity of aldosterone or the ability of the kidneys to excrete potassium (Box 13.4). ACE inhibitors and angiotensin receptor blockers usually should be continued because of the beneficial effects on cardiovascular disease and their renoprotective benefits in patients with chronic kidney disease (CKD). In patients with aldosterone deficiency who are neither hypertensive nor fluid overloaded, administration of a synthetic mineralocorticoid such as fludrocortisone 0.1 mg/day can be effective. In patients with hypertension or volume overload, particularly in association with CKD, administration of either a thiazide or a loop diuretic is frequently effective. Loop diuretics are required in patients with estimated GFR below 30 mL/min. Loop and thiazide diuretics increase distal Na^+ delivery and thus stimulate K^+ and H^+ secretion in the collecting duct. Alkali therapy (e.g., $NaHCO_3$) also can be used to treat the acidosis and hyperkalemia, but the patient must be closely monitored to avoid volume overload and worsening hypertension. One can also consider chronic use of a gastrointestinal K^+ binding drug such as patiromer or sodium zirconium cyclosilicate.[18]

Renal Tubular Acidosis in Chronic Kidney Disease

Metabolic acidosis in advanced CKD is caused by failure of the tubular acidification process to excrete the normal daily acid load. As functional kidney renal mass is reduced by disease, there is an adaptive increase in ammonia production and H^+ secretion by the remaining nephrons. Despite increased production of ammonia from each remaining nephron, overall production may be decreased secondary to the decrease in total kidney mass. In addition, less ammonia is delivered to the medullary interstitium secondary to disrupted medullary anatomy.[19] The ability to lower the urinary pH remains intact, reflecting the fact

Causes of Hyperkalemic Distal (Type 4) Renal Tubular Acidosis

BOX 13.4

Mineralocorticoid Deficiency

Low Renin, Low Aldosterone
- Diabetes mellitus
- Drugs
- NSAIDs
- Cyclosporine, tacrolimus
- β-Blockers

High Renin, Low Aldosterone
- Adrenal destruction
- Congenital enzyme defects
- Drugs
- ACE inhibitors
- ARBs
- Heparin
- Ketoconazole

Abnormal Cortical Collecting Duct
- Absent or defective mineralocorticoid receptor
- Drugs
- Spironolactone, eplerenone
- Triamterene
- Amiloride
- Trimethoprim
- Pentamidine
- Chronic tubulointerstitial disease

ACE, Angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAIDs, nonsteroidal antiinflammatory drugs.

that the impairment in distal nephron H^+ secretion is less than that in ammonia secretion. Quantitatively, the total amount of H^+ secretion is small, and the acidic urine pH is the consequence of very little buffer in the urine. The lack of ammonia in the urine is reflected by a positive value for the UAG and lack of an increase in the UOG. Differentiation of RTA from type 4 RTA can be difficult because it is based on the clinician’s determination of whether the severity of metabolic acidosis is out of proportion to the degree of kidney dysfunction.

Patients with CKD may develop a hyperchloremic normal gap metabolic acidosis associated with normokalemia or mild hyperkalemia as GFR decreases to less than 30 mL/min. With more advanced CKD (GFR <15 mL/min), the acidosis may change to an anion gap metabolic acidosis, reflecting a progressive inability to excrete phosphate, sulfate, and various organic acids. At this stage, the acidosis is commonly referred to as uremic acidosis

Correction of the metabolic acidosis in patients with CKD is achieved by treatment with $NaHCO_3$, 0.5 to 1.5 mmol/kg/day, beginning when the HCO_3 level is less than 22 mmol/L. In some patients, non–sodium citrate formulations can be used. Loop diuretics are often used in conjunction with alkali therapy to prevent volume overload. If the acidosis becomes refractory to medical therapy, dialysis needs to be initiated. Recent evidence suggests that metabolic acidosis in the patient with CKD should be aggressively treated because chronic acidosis is associated with metabolic bone disease, is associated with faster progression of kidney disease, and may lead to an accelerated catabolic state in patients with CKD.[20,21]

Metabolic Acidosis of Extrarenal Origin

Diarrhea

Intestinal secretions from sites distal to the stomach are rich in HCO3 . Accelerated loss of this HCO3 rich solution can result in metabolic acidosis. The resultant volume loss signals the kidney to increase NaCl reabsorption; this combined with the intestinal $NaHCO_3$ losses generates a normal anion gap metabolic acidosis. The kidney response is to increase net acid excretion by increasing urinary excretion of ammonia.[22] Hypokalemia, as a result of gastrointestinal losses, and the low serum pH both stimulate the synthesis of ammonia in the proximal tubule. The increase in availability of ammonia to act as a urinary buffer allows a maximal increase in H^+ secretion by the distal nephron.

The increase in urinary ammonia excretion associated with an extrarenal normal anion gap acidosis results in a negative UAG value and an increase in the UOG. Urine pH can be misleading and in chronic diarrhea may be above 6.0 because of substantial increases in renal ammonia metabolism that result in increased urine pH from the buffering ability of the ammonia. Although the clinical history should distinguish between these two possibilities, in a patient with surreptitious laxative abuse, this may not be helpful because diarrhea may not be reported. Colonoscopy may be required to demonstrate characteristic findings of laxative abuse (e.g., melanosis coli) if this diagnosis is being considered.

Treatment of diarrhea-associated metabolic acidosis is based on treatment of the underlying diarrhea. If this is not possible, alkali treatment, possibly including potassium alkali to treat hypokalemia and metabolic acidosis simultaneously, is indicated.

Ileal Conduits

Surgical diversion of the ureter into an ileal pouch is used in the treatment of the patient with neurogenic bladder or after cystectomy. The procedure may be associated rarely with development of a hyperchloremic normal anion gap metabolic acidosis. Acidosis in part is caused by reabsorption of urinary NH_4Cl by the intestine. The ammonia is transported through the portal circulation to the liver or is metabolized to urea to prevent hyperammonemic encephalopathy. This metabolic process consumes equimolar amounts of bicarbonate and therefore can result in the development of metabolic acidosis. Metabolic acidosis also may develop because urinary Cl can be exchanged for HCO_3 through activation of a Cl -HCO_3 exchanger on the intestinal lumen.

In some patients, a kidney defect in acidification can develop and exacerbate the degree of acidosis. Such a defect may result from tubular damage caused by pyelonephritis or high colonic pressures, secondarily causing urinary obstruction.

The severity of acidosis relates to the length of time the urine is in contact with the bowel and the total surface area of bowel exposed to urine. In patients with a ureterosigmoid anastomosis, these factors are increased and the acidosis tends to be more common and more severe than in patients with an ileal conduit. The ileal conduit was designed to minimize the time and area of contact between urine and intestinal surface. Patients with surgical diversion of the ureter who develop metabolic acidosis should be evaluated for an ileal loop obstruction because this would lead to an increase in contact time between the urine and intestinal surface.

ANION GAP METABOLIC ACIDOSIS

Lactic Acidosis

Lactic acid is the end product in the anaerobic metabolism of glucose and is generated by the reversible reduction of pyruvic acid by lactic acid dehydrogenase and reduced nicotinamide adenine dinucleotide (NADH), as shown in the following formula:

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{Lactate} + \text{NAD}^+$$

Under normal conditions, the reaction is shifted toward the right and the normal lactate-to-pyruvate ratio is approximately 10:1. The

BOX 13.5

Causes of Lactic Acidosis

Type A (Tissue Underperfusion or Hypoxia)
Cardiogenic shock
Septic shock
Hemorrhagic shock
Acute hypoxia
Carbon monoxide poisoning
Anemia
Type B (Absence of Hypotension and Hypoxia)
Hereditary enzyme deficiency (glucose 6-phosphatase)
Drugs or toxins
- Phenformin, metformin
- Cyanide
- Salicylate, ethylene glycol, methanol
- Propylene glycol26
- Linezolid24
- Propofol25
- Nucleoside reverse transcriptase inhibitors: stavudine, didanosine24
- Clenbuterol27
- Isoniazid

Thiamine deficiency
Systemic disease
- Liver failure
- Malignancy

reactants in this pathway are interrelated, as shown in the following equation:

$$Lactate = K (pyruvate)(NADH)(H^+) / NAD^+$$

where K is the equilibrium constant.

On the basis of this relationship, it is evident that lactate can increase for three reasons.23 First, lactate can increase because of increased pyruvate production alone. In this situation, the normal 10:1 lactate-to-pyruvate ratio will be maintained. An isolated increase in pyruvate production can be seen in the setting of intravenous glucose infusions, intravenous administration of epinephrine, and respiratory alkalosis. Lactate levels in these conditions are minimally elevated, rarely exceeding 5 mmol/L. Second, lactate can increase as a result of an increased NADH:NAD+ ratio. Under these conditions, the lactateto-pyruvate ratio can increase to very high values. Third, lactate can increase with a combination of increased pyruvate production and increased NADH:NAD+ ratio. This is common in severe lactic acidosis.

Lactic acidosis occurs when there is an imbalance between the production and the use of lactic acid. The net result is an accumulation of serum lactate and development of metabolic acidosis. The accumulation of the non–chloride anion lactate accounts for the increase in anion gap. Severe exercise and grand mal seizures are examples of lactic acidosis developing as a result of increased production. The short-lived nature of the acidosis in these conditions suggests that a concomitant defect in lactic acid use is present in most conditions of sustained and severe lactic acidosis.

Some of the disorders associated with the development of lactic acidosis are listed in Box 13.5. Type A lactic acidosis is characterized by underperfusion of tissue or acute hypoxia, such as hypotension, sepsis, acute tissue hypoperfusion, cardiopulmonary failure, severe anemia, hemorrhage, and carbon monoxide poisoning. Type B lactic acidosis occurs in the absence of overt hypoperfusion or hypoxia, such as with congenital defects in glucose or lactate metabolism, diabetes mellitus, liver disease, effects of drugs (especially overdose of isoniazid) and toxins, and neoplastic diseases.24-29

Thiamine deficiency is increasingly recognized as a cause of type B lactic acidosis in subjects with alcoholism, persistent vomiting, and severe malnutrition. In clinical practice, many patients will often exhibit features of type A and type B lactic acidosis simultaneously.

Therapy is aimed at correction of the underlying disorder. Restoration of tissue perfusion and oxygenation is attempted if these are compromised. The role of alkali in the treatment of patients with lactic acidosis is controversial; some experimental models and clinical observations suggest that administration of HCO_3^- may depress cardiac function and exacerbate the acidemia. In addition, such therapy may be complicated by volume overload, hypernatremia, and rebound alkalosis after the acidosis has resolved.[30] In general, HCO_3^- should be given when the systemic pH decreases to below 7.1 because hemodynamic instability becomes much more likely with severe acidemia. In such patients, alkali therapy should be directed at increasing the pH above 7.1; attempts to normalize the pH or $[HCO_3^-]$ should be avoided. Acute hemodialysis is rarely beneficial for lactic acidosis induced by tissue hypoperfusion. The hemodynamic instability that can occur with hemodialysis in these critically ill patients may worsen the underlying difficulty in tissue oxygenation.

Diabetic Ketoacidosis

Diabetic ketoacidosis results from the accumulation of acetoacetic acid and β-hydroxybutyric acid. The development of ketoacidosis is the result of insulin deficiency and a relative or absolute increase in glucagon.[31] These hormonal changes lead to increased fatty acid mobilization from adipose tissue and alter the oxidative machinery of the liver such that delivered fatty acids are primarily metabolized into ketoacids. In addition, peripheral glucose use is impaired, and the gluconeogenic pathway in the liver is maximally stimulated. The resultant hyperglycemia causes an osmotic diuresis and volume depletion.

Ketoacidosis results when the rate of hepatic ketoacid generation exceeds renal excretion, causing increased blood ketoacid concentrations. The H^+ accumulation in the extracellular fluid (ECF) decreases HCO_3^- concentration, whereas the ketoacid anion concentration increases. An anion gap metabolic acidosis is the more common finding in the patient with diabetic ketoacidosis, but a normal gap metabolic acidosis also can be seen. In early stages of ketoacidosis, when the ECF volume is almost normal, ketoacid anions that are produced are rapidly excreted by the kidney as Na^+ and K^+ salts. Excretion of these salts is equivalent to the loss of potential HCO_3^-. This loss of potential HCO_3^- in the urine at the same time the kidney is retaining NaCl results in a normal gap metabolic acidosis. As volume depletion develops, kidney ketoacid excretion cannot match production rates and ketoacid anions are retained within the body, thus increasing the anion gap.[32]

During treatment, the anion gap metabolic acidosis transforms once again into a normal gap acidosis. Treatment leads to a termination in ketoacid production. As the ECF volume is restored, there is increased kidney excretion of the Na^+ salts of the ketoacid anions. The loss of this potential HCO_3^-, combined with the retention of administered NaCl, accounts for the redevelopment of the hyperchloremic normal gap acidosis. In addition, K^+ and Na^+ administered in solutions containing NaCl and KCl enter cells in exchange for H^+. The net effect is infusion of HCl into the ECF. The reversal of the hyperchloremic acidosis takes several days as the HCO_3^- deficit is corrected by the kidney.

Diabetic ketoacidosis can result in a severe metabolic acidosis with serum bicarbonate levels below 5 mmol/L. This diagnosis should be considered in patients with simultaneous metabolic acidosis and hyperglycemia. Diagnosis is confirmed by demonstration of retained ketoacids with nitroprusside tablets or reagent strips in the urine.

However, these tests detect only acetone and acetoacetate and not βhydroxybutyrate. In the patient with lactic acidosis or alcoholic ketoacidosis, acetoacetate may be converted to β-hydroxybutyrate to an extent that depends on the $NADH/NAD^+$ ratio. With treatment of the diabetic ketoacidosis, acetoacetate is generated as this ratio falls, and the nitroprusside test result may suddenly become strongly positive.

The limitations of the nitroprusside test can be prevented by direct measurement of β-hydroxybutyrate. With uncontrolled diabetes, a serum β-hydroxybutyrate level above 3.0 mmol/L in adults and above 3.8 mmol/L in children confirms diabetic ketoacidosis.[33]

Compared with urinary ketone measurements, capillary blood levels of β-hydroxybutyrate better correlate with both the degree of acidosis and the response to therapy.[34]

Treatment consists of insulin and intravenous fluids to correct volume depletion. Deficiencies in K^+, Mg^{2+}, and phosphate are common; therefore these electrolytes are typically added to intravenous solutions, especially after the initial fluid resuscitation. However, diabetic ketoacidosis typically manifests with hyperkalemia secondary to the insulin deficiency. Potassium should be administered only as hypokalemia develops, usually during insulin treatment of diabetic ketoacidosis. If there is significant hypokalemia at presentation, potassium supplementation may be needed before insulin administration to avoid life-threatening worsening of hypokalemia. Alkali therapy is generally not required because administration of insulin leads to the metabolic conversion of ketoacid anions to HCO_3^- and allows partial correction of the acidosis. However, HCO_3^- therapy may be indicated in patients who present with severe acidemia ($pH < 7.1$).[35]

d-Lactic Acidosis

d-Lactic acidosis is a form of metabolic acidosis that can occur in the patient with small bowel resections or in patients with a jejunoileal bypass. Such short bowel syndromes create a situation in which carbohydrates that are normally extensively reabsorbed in the small intestine are delivered in large amounts to the colon. In the presence of colonic bacterial overgrowth, these substrates are metabolized into d-lactate and absorbed into the systemic circulation. Accumulation of d-lactate produces an anion gap metabolic acidosis in which the serum lactate concentration is normal because the standard test for lactate is specific for l-lactate. These patients typically present after ingestion of a large, high-carbohydrate meal, with neurologic abnormalities including confusion, slurred speech, and ataxia. Ingestion of low-carbohydrate meals and antimicrobial agents to decrease the degree of bacterial overgrowth are the principal treatments.

Starvation Ketosis

Abstinence from food can lead to a mild anion gap metabolic acidosis secondary to increased production of ketoacids. The pathogenesis of this disorder is similar to that of diabetic ketoacidosis in that starvation leads to relative insulin deficiency and glucagon excess. As a result, there is increased mobilization of fatty acids while the liver is set to oxidize fatty acids to ketoacids. With prolonged starvation, the blood ketoacid level can reach 5 to 6 mmol/L. The serum [HCO_3^-] is rarely less than 18 mmol/L. More fulminant ketoacidosis is aborted because ketone bodies stimulate the pancreatic islets to release insulin and lipolysis is held in check. This break in the ketogenic process is notably absent in patients with insulin-dependent diabetes.[36] No specific therapy is indicated in starvation ketosis.

Alcoholic Ketoacidosis

Ketoacidosis develops in patients with a history of chronic ethanol abuse, decreased food intake, and often a history of nausea and vomiting. As with starvation ketosis, a decrease in the insulin-to-glucagon ratio leads to accelerated fatty acid mobilization and alters the enzymatic machinery of the liver to favor ketoacid production. However, features unique to this disorder differentiate alcoholic ketoacidosis from simple starvation ketosis. First, the alcohol withdrawal combined with volume depletion and starvation greatly increases the levels of circulating catecholamines. As a result, the peripheral mobilization of fatty acids is much greater than typically found with starvation alone. This sometimes-massive mobilization of fatty acids can lead to marked ketoacid production and severe metabolic acidosis. Second, the metabolism of ethanol leads to accumulation of NADH. The increase in NADH/NAD+ is reflected by a higher ratio of β-hydroxybutyrate to acetoacetate. As mentioned previously, the nitroprusside reaction may be diminished by this redox shift despite the presence of severe ketoacidosis. Treatment of patients with alcoholic ketoacidosis focuses on glucose administration, which leads to the rapid resolution of the acidosis; stimulation of insulin release leads to diminished fatty acid mobilization from adipose tissue, as well as decreased hepatic output of ketoacids.37

Ethylene Glycol and Methanol Intoxications

Ethylene glycol and methanol intoxications are characteristically associated with the development of a severe anion gap metabolic acidosis.

Metabolism of ethylene glycol by alcohol dehydrogenase generates various acids, including glycolic, oxalic, and formic acids. Ethylene glycol is present in antifreeze and solvents and is ingested by accident or as a suicide attempt. The initial effects of intoxication are neurologic and begin with drunkenness but can quickly progress to seizures and coma. If left untreated, cardiopulmonary symptoms such as tachypnea, noncardiogenic pulmonary edema, and cardiovascular collapse may appear. From 24 to 48 hours after ingestion, patients may develop flank pain and acute kidney injury, often accompanied by abundant calcium oxalate crystals in the urine (Box 13.6). A fatal dose of ethylene glycol is approximately 100 mL.

Methanol is also metabolized by alcohol dehydrogenase and forms formaldehyde, which is then converted to formic acid. Methanol is found in a variety of commercial preparations, such as shellac, varnish, and deicing solutions, and is also known as wood alcohol. As with ethylene glycol, methanol can be ingested either by accident or as a suicide attempt.

Clinically, methanol ingestion is associated with an acute inebriation followed by an asymptomatic period lasting 24 to 36 hours. Abdominal pain caused by pancreatitis, seizures, blindness, and coma may develop. The blindness is caused by direct toxicity of formic acid on the retina. Methanol intoxication is also associated with hemorrhage in the white matter and putamen, which can lead to the delayed onset of a parkinsonian syndrome (see Box 13.6). The lethal dose of methanol is 60 to 250 mL.

Lactic acidosis is also a feature of methanol and ethylene glycol poisoning and contributes to the elevated anion gap. Together with an elevated anion gap, an osmolar gap is an important clue to the diagnosis of ethylene glycol and methanol poisoning. The osmolar gap is the difference between the measured and calculated osmolality. The formula for the calculated osmolality is as follows:

2 × Na+ + BUN/2 8 + Glucose/18 + EtOH/4 6

where the blood urea nitrogen (BUN), glucose, and ethanol concentrations are in milligrams per deciliter. Inclusion of the ethanol concentration in this calculation is important because many patients ingest ethylene glycol or methanol while inebriated from ethanol ingestion.

The normal value for the osmolar gap is less than 10 mOsm/kg. Each 100 mg/dL (161 mmol/L) of ethylene glycol will increase the osmolar gap by 16 mOsm/kg. Methanol contributes 32 mOsm/kg for each 100 mg/dL (312 mmol/L).

In addition to supportive measures, the patient with ethylene glycol and methanol poisoning is treated with fomepizole (4-methylpyrazole),

BOX 13.6

Ethylene Glycol and Methanol

Time course of clinical symptoms and signs after ingestion

- Ethylene glycol
  - 0–12 hours: inebriation progressing to coma
  - 12–24 hours: tachypnea, noncardiogenic pulmonary edema
  - 24–36 hours: flank pain, renal failure, urinary calcium oxalate crystals
- Methanol
  - 0–12 hours: inebriation followed by asymptomatic period
  - 24–36 hours: pancreatitis, retinal edema progressing to blindness, seizures
  - >48 hours: putamen and white matter hemorrhage leading to Parkinsonlike state

Increased anion gap metabolic acidosis

Increased osmolar gap

Treatment

- Supportive care
- Fomepizole (4-methylpyrazole) is agent of choice (competitor of alcohol dehydrogenase): 15 mg/kg IV loading dose, then 10 mg/kg every 12 hours for 48 hours. After 48 hours, increase dose to 15 mg/kg every 12 hours; increase frequency of dosing to every 4 hours during hemodialysis.
- Intravenous ethanol (5% or 10% solution) if fomepizole unavailable: Loading dose of 0.6 g/kg, followed by hourly maintenance dose of 66 mg/kg. Increase maintenance dose when the patient has history of chronic alcohol use and during hemodialysis.
- Hemodialysis to accelerate removal of parent compound and metabolites
- Bicarbonate therapy to treat acidosis

IV, Intravenous.

which inhibits alcohol dehydrogenase and prevents formation of toxic metabolites[38] (see Box 13.6). If fomepizole is unavailable, intravenous ethanol can be used to prevent the formation of toxic metabolites. Ethanol has more than a 10-fold greater affinity for alcohol dehydrogenase than that of other alcohols. Ethanol has its greatest efficacy when levels of 100 to 200 mg/dL are obtained. In addition to both fomepizole and ethanol therapy, the patient should receive hemodialysis to remove both the parent compound and its metabolites. Correction of the acidosis is accomplished with an HCO_3^--containing dialysate or by intravenous infusion of $NaHCO_3$

Salicylate

Aspirin (acetylsalicylic acid) is associated with a large number of accidental or intentional poisonings. At toxic concentrations, salicylate uncouples oxidative phosphorylation and, as a result, leads to increased lactic acid production. In children, ketoacid production also may be increased. The accumulation of lactic, salicylic, keto, and other organic acids leads to the development of an anion gap metabolic acidosis. At the same time, salicylate has a direct stimulatory effect on the respiratory center. Increased ventilation lowers the carbon dioxide tension (Pco_2), contributing to the development of a respiratory alkalosis.[39] Children primarily manifest an anion gap metabolic acidosis with toxic salicylate levels; a respiratory alkalosis is most evident in adults.

In addition to conservative management, the initial goals of therapy for salicylate poisoning are to correct systemic acidemia and increase the urine pH. By increasing systemic pH, the ionized fraction of salicylic acid will increase, resulting in less accumulation of the drug in the central nervous system. Similarly, an alkaline urine pH favors increased urinary excretion because the ionized fraction of the drug is poorly reabsorbed by the tubule. At serum concentrations above 80 when risk factors are present. The diagnosis of pyroglutamic acidosis should be considered in patients with unexplained anion gap metabolic acidosis and recent acetaminophen ingestion.

mg/dL or in the setting of severe clinical toxicity, hemodialysis can be used to accelerate drug elimination.

Pyroglutamic Acidosis

Pyroglutamic acid, also known as 5-oxoproline, is an intermediate in glutathione metabolism. An anion gap acidosis caused by pyroglutamic acid has been described rarely in critically ill patients receiving therapeutic doses of acetaminophen[40,41] (Fig. 13.4). Patients present with severe anion gap metabolic acidosis accompanied by alterations in mental status ranging from confusion to coma. High concentrations of pyroglutamic acid are found in the blood and urine. Risk factors include malnutrition, infection, antibiotic use, pregnancy, and kidney failure. In these settings, glutathione levels are reduced because of the oxidative stress associated with critical illness. The reduction in glutathione secondarily leads to increased production of pyroglutamic acid.

Even therapeutic doses of acetaminophen can precipitate this disorder

ALKALI TREATMENT OF METABOLIC ACIDOSIS

Treatment of metabolic acidosis usually involves either sodium bicarbonate or citrate[35] (Table 13.2). $NaHCO_3$ can be taken orally as tablets or powder or given intravenously as a hypertonic bolus or an isotonic infusion, which can be created by adding 150 mmol $NaHCO_3$ to 1 L 5% dextrose in water (D5W). This solution is useful if treatment requires both volume expansion and alkali administration.

Citrate may be taken orally as a liquid, as sodium citrate, potassium citrate, or citric acid, or a combination. Many patients find citratecontaining solutions more palatable than oral $NaHCO_3$ as a source of oral alkali therapy. Oral citrate therapy should not be combined with medications that include aluminum. Citrate, which has a −3 charge under normal conditions, can complex with aluminum (Al^{3+}) in the intestinal tract, resulting in an uncharged moiety that is rapidly absorbed across the intestinal tract and then can dissociate to release free aluminum. This can increase the rate of aluminum absorption dramatically and in some patients, particularly those with severe CKD, has resulted in acute aluminum encephalopathy.

The dose of alkali therapy administered is based on both the total body bicarbonate deficit and the desired rapidity of treatment. Under normal circumstances, the volume of distribution (VD) for bicarbonate is approximately 0.5 L/kg total body weight. Thus, the bicarbonate deficit, in millimoles, can be estimated from the following formula: $(0.5 \times LBW_{kg}) \times (24 - HCO_3^-)$, where LBW_{kg} is the lean body weight in kilograms and 24 is the desired resultant bicarbonate concentration. Several caveats regarding this equation should be understood. First, edema fluid contributes to the volume of distribution of bicarbonate. Accordingly, an estimation of the amount of edema fluid should be included in this calculation. Second, the volume of distribution for bicarbonate increases as the severity of the metabolic acidosis worsens. When serum $[HCO_3^-]$ is 5 mmol/L or less, the volume of distribution may increase to 1 L/kg or more.

When acute treatment is desired, 50% of the bicarbonate deficit should be replaced during the first 24 hours. If hypertonic $NaHCO_3$ is administered, the increase in serum $[HCO_3^-]$ will be mirrored by an increase in serum $[Na^+]$. After the initial 24 hours of therapy, the response to therapy and the patient’s current clinical condition are reevaluated before future therapy is decided. Acute hemodialysis solely for the treatment of metabolic acidosis, other than that associated with kidney failure, is rarely beneficial.

Mechanism of Pyroglutamic Acidosis
Glutamic acid
Cysteine

g-Glutamylcysteine
synthetase

ATP

5-Oxoprolinase
(low capacity)

ADP
g-Glutamylcyclotransferase

g-Glutamylcysteine
Feedback
inhibition
lost

Pyroglutamic
acidosis
(5-Oxoproline)

Glycine
Glutathione
synthetase

ATP
ADP

Acetaminophen
depletes glutathione

Glutathione
(g-Glutamylcysteine 1 glycine)

Fig. 13.4 Mechanism of Pyroglutamic Acidosis. Glutathione is formed from γ-glutamylcysteine and glycine in the presence of glutathione synthetase. Glutathione normally regulates the activity of γglutamylcysteine synthetase through feedback inhibition. Depletion of glutathione results in increased formation of γ-glutamylcysteine, which in turn is metabolized to pyroglutamic acid (5-oxoproline) and cystine through γ-glutamylcyclotransferase. Pyroglutamic acid accumulates because the enzyme responsible for its metabolism (5-oxoprolinase) is low capacity. ADP, Adenosine diphosphate; ATP, adenosine triphosphate.

TABLE 13.2

Alkali Treatment Options

Therapy	Route	Usual Dose per Unit
Sodium bicarbonate tablet	PO	650 mg = 8 mmol

May cause gastric gas

Sodium bicarbonate

IV

50 mmol in 50 mL

Hypertonic, may cause hypernatremia

5% Dextrose with water with NaHCO3

IV

150 mmol/L

Useful for simultaneous intravascular volume expansion
and alkali administration

Potassium citrate (tablet)

PO

5 and 10 mmol per tablet

Citric acid/potassium citrate/sodium
citrate (liquid)

PO

Na+

and and 2 mmol of
1 mmol of
citrate per milliliter

Avoid concomitant aluminum-containing medications
such as antacids and sucralfate 1 mmol citrate
equivalent to 3 mmol HCO3

Potassium citrate (liquid)

PO

2 mmol of K+ and 2 mmol of citrate per
milliliter

Avoid concomitant aluminum-containing medications

IV, intravenous; PO, oral.

K+

Comments

Useful for simultaneous K+ and alkali therapy

SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presents with the chief complaint of progressive weakness over the last several months. He is normotensive; physical examination is unremarkable with the following laboratory results (in mmol/L): Na+ 135, Cl 105, K+ 3.0, HCO3 18, creatinine 1.8, blood urea nitrogen, glucose 110, Pco2 28 mm Hg, pH 7.33, hematocrit 25%, white blood cells 5600/mm2, platelets 340,000/mm3, and urinalysis: trace protein, 1+ glucose, normal sediment, and 4.8 protein g/24 h. Which of the following is characteristic of the renal lesion present in this patient?

A. Nephrocalcinosis will be shown on a kidney, ureter, bladder radiograph of the abdomen.
B. Serum HCO3 concentration will increase after oral bicarbonate administration but then decrease to 18 mmol/L after therapy is discontinued.
C. Bicarbonate therapy will cause the serum K+ to decline slightly because of a shift into cells.
D. Urine pH will be persistently alkaline.
E. Urine anion gap will be negative.

2. A 35-year-old woman presents having ingested a large quantity of aspirin after breaking up with her boyfriend. Her medical history is unremarkable, and she is taking no medications. Physical examination shows blood pressure 130/80 mm Hg lying and 110/62 mm Hg standing, pulse 102 beats/min, and respiratory rate 24 breaths/min; the remainder of the examination is normal. Laboratory tests on admission (in mmol/L) are Na+ 138, K+ 3.2, Cl 100, HCO3 13, pH 7.48, and Pco2 21 mm Hg; urinalysis is 1+ ketone, normal sediment; and urine chemistry (in mmol/L) is Na+ 38, Cl <10, and K+ 45. Which of the following statements is true regarding salicylate poisoning?

A. A 5-year-old child who has accidently swallowed an unknown quantity of his mother’s aspirin is likely to present with similar acid-base findings.

B. The cause of hypokalemia is primarily due to a shift of K+ into cells because of respiratory alkalosis.
C. Serum uric acid levels are likely to be low in this patient.
D. The high urine Na+ is caused by proximal tubular dysfunction as a result of salicylate nephrotoxicity.
E. Measurement of serum lactic acid in this patient is likely to be normal.

3. A 65-year-old White man with an extensive smoking history and known chronic obstructive pulmonary disease is admitted to the hospital with hematemesis. On the day of admission, endoscopy shows a nonbleeding duodenal ulcer. The procedure was complicated by the development of aspiration pneumonia and respiratory failure. A continuous infusion of intravenous lorazepam was required to control agitation and minimize peak inspiratory pressures. Admission laboratory results (in mmol/L) were Na+ 142, K+ 4.3, Cl 105, HCO3 22, creatinine 1.4 mg/dL, blood urea nitrogen (BUN) 25 mg/dL, hematocrit 36, pH 7.35, Pco2 45, and Po2 75. On hospital day 4, gastrointestinal bleeding recurred, and the patient was taken to the operating room and underwent oversewing of a bleeding duodenal ulcer. The patient remained hemodynamically stable throughout the hospitalization but continued to require intravenous lorazepam for sedation. Laboratory results (in mmol/L) were Na+ 138, K+ 4.8, Cl 100, HCO3 10, creatinine 1.8 mg/dL, BUN 28 mg/dL, glucose 120 mg/dL, and serum osmolality 330 mOsm/l (osmolar gap = 37). Which of the following is the cause of this patient’s anion gap metabolic acidosis and increased

osmolar gap?
A. Propylene glycol toxicity
B. Diabetic ketoacidosis
C. Lactic acidosis
D. Uremic acidosis
E. Isopropyl alcohol administration

REFERENCES

1. Palmer BF. Approach to fluid and electrolyte disorders and acid-base problems. Prim Care. 2008;35:195–213.
2. Kraut J, Madias N. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2:162–174.
3. Halperin ML, Richardson RM, Bear R, et al. Urine ammonium: the key to the diagnosis of distal renal tubular acidosis. Nephron. 1988;50:1–4.
4. Vega D, Maalouf N, Sakhaee K. Increased propensity for calcium phosphate kidney stones with topiramate use. Expert Opin Drug Saf. 2007;6:547–557.
5. Welch B, Graybeal D, Moe O, et al. Biochemical and stone-risk profiles with topiramate treatment. Am J Kidney Dis. 2006;48:555–563.
6. Rodriguez S. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. 2002;13:2160–2170.
7. Kim S, Lee J, Park J, et al. The urine-blood Pco 2 gradient as a diagnostic index of H+-ATPase defect distal renal tubular acidosis. Kidney Int. 2004;66:761–767.
8. Nicoletta J, Schwartz G. Distal renal tubular acidosis. Curr Opin Pediatr. 2004;16:194–198.
9. Codina J, DuBose T. Molecular regulation and physiology of the H +,K+ATPases in kidney. Semin Nephrol. 2006;26:345–351.
10. Jefferies K, Cipriano D, Forgac M. Function, structure and regulation of the vacuolar H+-ATPases. Arch Biochem Biophys. 2008;476:33–42.
11. Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. J Am Soc Nephrol. 2011;22:1981–1989.
12. Evan A, Lingeman J, Coe F, et al. Renal histopathology of stone-forming patients with distal renal tubular acidosis. Kidney Int. 2007;71:795–801.
13. Bonny O, Rubin A, Huang C, et al. Mechanism of urinary calcium regulation by urinary magnesium and pH. J Am Soc Nephrol. 2008;19:1530–1537.
14. Walsh S, Shirley D, Wrong O, Unwin R. Urinary acidification assessed by furosemide and fludrocortisone treatment: an alternative to ammonium chloride. Kidney Int. 2007;71:1310–1316.
15. DuBose TD. Hyperkalemic hyperchloremic metabolic acidosis: pathophysiologic insights. Kidney Int. 1997;51:591–602.
16. Palmer BF. Managing hyperkalemia caused by inhibitors of the reninangiotensin-aldosterone system. N Engl J Med. 2004;351:585–592.
17. Sebastian A, Schambelan M, Lindenfeld S, Morris RC. Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. N Engl J Med. 1977;297:576–583.
18. Palmer BF, Kelepouris E, Clegg DJ. Renal tubular acidosis and management strategies: a narrative review. Adv Ther. 2021;38(2):949–968.
19. Buerkert J, Martin D, Trigg D, Simon E. Effect of reduced renal mass on ammonium handling and net acid formation by the superficial and juxtamedullary nephron of the rat. J Clin Invest. 1983;71:1661–1675.
20. Krieger N, Frick K, Bushinsky D. Mechanism of acid-induced bone resorption. Curr Opin Nephrol Hypertens. 2004;13:423–436.
21. Alpern RJ, Sakhaee K. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis. 1997;29:291–302.

22. Garibotto G, Sofia A, Robaudo C, et al. Kidney protein dynamics and ammonia genesis in humans with chronic metabolic acidosis. J Am Soc Nephrol. 2004;15:1606–1615.
23. Madias N. Lactic acidosis. Kidney Int. 1986;29:752–774.
24. Palenzuela L, Hahn N, Nelson R, et al. Does linezolid cause lactic acidosis by inhibiting mitochondrial protein synthesis? Clin Infect Dis. 2005;40:e113–e116.
25. Thoden J, Lebrecht D. Highly active antiretroviral HIV therapy–associated fatal lactic acidosis: quantitative and qualitative mitochondrial DNA lesions with mitochondrial dysfunction in multiple organs. AIDS. 2008;22:1093–1094.
26. Fodale V, La Monaca E. Propofol infusion syndrome: an overview of a perplexing disease. Drug Saf. 2008;31:293–303.

27. Zar T, Yusufzai I, Sullivan A, Graeber C. Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam. Nat Clin Pract Nephrol. 2007;3:515–520.
28. Hoffman R, Kirrane B, Marcus S. A descriptive study of an outbreak of clenbuterol-containing heroin. Ann Emerg Med. 2008;52:548–553.
29. Creagh-Brown B, Ball J. An under-recognized complication of treatment of acute severe asthma. Am J Emerg Med. 2008;26:514.e1–514.e3.
30. Kraut JA, Madias NE. Lactic acidosis: current treatments and future directions. Am J Kidney Dis. 2016;68:473–482.
31. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med. 1983;309:159–169.
32. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. N Engl J Med. 2015;373:548–559.
33. Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care. 2008;31:643–647.
34. Turan S, Omar A, Bereket A. Comparison of capillary blood ketone measurement by electrochemical method and urinary ketone in treatment of diabetic ketosis and ketoacidosis in children. Acta Diabetol. 2008;45:83–85.
35. Sabatini S, Kurtzman N. Bicarbonate therapy in severe metabolic acidosis. J Am Soc Nephrol. 2009;20:692–695.
36. Kraut J, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008;3:208–225.
37. Palmer BF, Clegg DJ. Electrolyte disturbances in patients with chronic alcohol-use disorder. N Engl J Med. 2017;377:1368–1377.
38. Palmer BF, Clegg DJ, Taylor SI, Weir MR. Diabetic ketoacidosis, sodium glucose transporter-2 inhibitors and the kidney. J Diabetes Complications. 2016;30:1162–1166.
39. Palmer BF, Clegg DJ. Salicylate toxicity. N Engl J Med. 2020;382:2544–2555.
40. Brooker G, Jeffery J, Nataraj T, et al. High anion gap metabolic acidosis secondary to pyroglutamic aciduria (5-oxoprolinuria): association with prescription drugs and malnutrition. Ann Clin Biochem. 2007;44:406–409.
41. Fenves A, Kirkpatrick H, Patel V, et al. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. Clin J Am Soc Nephrol. 2006;1:441–447.

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Metabolic Alkalosis

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Metabolic alkalosis is a primary acid-base disorder that increases the serum bicarbonate concentration [HCO_3] above 30 mmol/L,[1] causing the arterial blood [H^+] to fall and pH to increase into the alkaline range (>7.45). Most laboratories measure the venous [total CO_2] as a surrogate, which also includes dissolved CO_2 and H_2CO_3. The [total CO_2] exceeds the [HCO_3] by about 1 to 2 mmol/L.

Metabolic alkalosis, a very common acid-base disorder, is especially prevalent in critically ill patients.[2]

RESPIRATORY COMPENSATION

Uncomplicated metabolic alkalosis generates compensatory hypoventilation, which raises Pco_2, thereby reducing the pH toward the normal range. However, the arterial pH generally remains above 7.45. The magnitude of the hypoventilatory response to metabolic alkalosis is proportional to the degree of [HCO_3] elevation, but the response is quite variable (Fig. 14.1)[3-6] (M.A. Fallahzadeh et al., unpublished observations). Compensation occurs relatively rapidly, within minutes to hours.

Mild metabolic alkalosis generates a modest Pco_2 increase (45–50 mm Hg); more severe metabolic alkalosis increases the Pco_2 to the 50 to 55 mm Hg range. Although some patients with severe metabolic alkalosis develop higher Pco_2 values, these patients are usually also very hypokalemic, which can generate muscle weakness and respiratory acidosis.

SERUM CHLORIDE CONCENTRATION AND METABOLIC ALKALOSIS

Abnormal serum chloride concentration [Cl] usually indicates that a water/hydration disorder, an acid/base disorder, or both exist. Water/hydration disorders generate proportional changes of [Cl] and [Na^+]. Therefore, the [Cl]:[Na^+] ratio remains normal at 1:1.4. [Cl] and [Na^+] both increase proportionately with dehydration and decrease proportionately with overhydration. This proportional relationship is disrupted when certain acid-base disorders exist (i.e., metabolic alkalosis, hyperchloremic metabolic acidosis, or chronic respiratory disorders). Metabolic alkalosis elevates [HCO_3] and reciprocally reduces [Cl]. This disrupts the normal 1:1.4 [Cl]:[Na^+] ratio. The “anatomic” electrolyte profile, or “Gamblegram” (Fig. 14.2), shows why the increased [HCO_3], which exists with metabolic alkalosis, must be accompanied by an equal reduction of [Cl] (independent of [Na^+]), a reduction of the anion gap, or both.[7,8] In fact, metabolic alkalosis will commonly slightly increase the anion gap due to increased albumin concentration, increased albumin negative charge density, and accelerated generation of organic acids.[9,10] To the extent this occurs, the relative [Cl] decrease must be even greater.

An identical electrolyte pattern (increased [HCO_3] and proportionately reduced [Cl]) is also generated by compensation for chronic respiratory acidosis. Clinical assessment and blood pH measurement will

indicate the correct diagnosis. Blood pH is increased with metabolic alkalosis and low-normal/reduced with chronic respiratory acidosis. Venous blood pH, although less definitive than arterial pH, can be very helpful; add 0.03 pH units to the venous pH to approximate the arterial pH.[11]

PATHOGENESIS: GENERATION AND MAINTENANCE OF METABOLIC ALKALOSIS

Seldin and Rector used an extracellular fluid (ECF) volume–centered approach to explain how metabolic alkalosis develops and is maintained.[12] Subsequently, some have proposed that the “ECF volume–centric” approach should be replaced by a “chloride-centric” model,[13-16] whereas others have challenged this model.[17 18] From a practical and clinically relevant perspective, ECF volume contraction almost invariably equals “chloride depletion” and vice versa. We will use the traditional ECF volume–centered framework to direct the diagnostic and therapeutic approach to the metabolic alkaloses because it remains very useful and easy to understand.

Normal HCO_3^- Reclamation, Regeneration, and Generation

The metabolism of foods and endogenous substrates produces a large amount of nonvolatile organic acids (i.e., lactic, pyruvic, citric acids) that are oxidized to the volatile acid CO_2 and water. In addition, the typical Western European/American diet generates 80 to 100 mmol/day of nonvolatile strong acids, which cannot be metabolically oxidized (mainly sulfuric, phosphoric, and hydrochloric acids). These strong acids dissociate and release protons that mainly react with HCO_3 to form H_2CO_3, which then rapidly dehydrates to CO_2 and H_2O. To the extent this occurs, the serum [HCO_3] falls and is “replaced” by
2
the anions of the generated strong acids, for example, SO_4 , HPO_4^{2} , and Cl . Acid-base homeostasis must be restored/maintained by the kidney, which filters and/or secretes the anions of these acids, mainly as sodium salts. As the Na salts travel along the tubules, the Na^+ is reabsorbed in exchange for secreted H^+, which either binds to NH_3, forming NH_4^+, or binds to other H^+ binding molecules (i.e., titratable acids), mainly HPO_4^{2} to generate H_2PO_4 . Excretion of 80 to 100
2
mmol of H^+ together with the acid anions (e.g., SO_4 , HPO_4^{2} , Cl) thereby maintains acid-base equilibrium.

However, before this acid-base restorative process can occur, all the $NaHCO_3$ filtered by the glomeruli must first be reclaimed (i.e., removed from the filtrate) and returned to the body fluids. About 80% of the normal filtered HCO_3 load (about 4000–4500 mmol/day) is reclaimed by the proximal tubules via the process of H^+ secretion. The major features of proximal tubule Na^+ reabsorption and H^+ secretion are shown in Fig. 14.3. A large fraction of proximal Na^+ reabsorption occurs via the Na^+-H^+ exchanger 3 (NHE3) in the proximal luminal membrane. This exchange is energized by basolateral membrane

CHAPTER 14 Metabolic Alkalosis

Normal Acid-Base Status vs. Metabolic Alkalosis

Respiratory Compensation for Metabolic Alkalosis

100

AG

AG

90

HCO3

pCO2 TORR

80

HCO3

70
60

Na

Na

50

Cl

40

Cl

30
20

20

30

40

50

60

70

80

90

100

pCO2 = 0.8(HCO3) + 20 R2 = 0.8 (*)
(4)

$pCO_2 = 1.2(HCO_3) + 6$

$pCO_2 = HCO_3 + 15$

(6)

$pCO_2 = HCO_3 + 10$

(*)

$pCO_2 = 40 + 0.7(HCO_3 – 24)$

(5)

Fig. 14.1 Respiratory Compensation for Metabolic Alkalosis. Simultaneous Pco_2 and $[HCO_3]$ data points derived from a recent comprehensive literature review shows the best-fit linear regression line. Also shown are several commonly used equations that predict the $P co_2$ expected for the elevated $[HCO_3]$. (The references are indicated.) We show that the equation $Pco_2 = [HCO_3] + 10$ (dashed line) is very similar to the best-fit regression line for the HCO_3 range between 30 and 50 mmo/L. This is a relationship very easy to remember and use. If $[HCO_3]$ exceeds 55 mmol/L, the Pco_2 may increase markedly. This is likely the result of a coexisting respiratory muscle weakness, very likely due to severe hypokalemia that almost always exists. Pco_2 Partial pressure of carbon dioxide; 1 Torr = 133.32 Pa. Asterisk, Fallahzadeh M.A. et al., unpublished observations. (From Emmet M. Metabolic alkalosis: a brief pathophysiologic review. Clin J Am Soc Nephrol. 2020;15[12]:1848–1856.)

Na^+,K^+-ATPase, which reduces intracellular Na^+ and generates a negative intracellular electrical charge. The resulting strong electrochemical gradient drives Na^+ from the lumen into the cell in exchange for H^+ entering the lumen. Additionally, ATP-energized H^+ pumps in the luminal membrane of the proximal tubule are responsible for about 30% of proximal H^+ secretion.

Each H^+ that enters the proximal tubule lumen leaves 1 HCO_3 in the cytoplasm, which moves across the basolateral membrane to enter the ECF. The HCO_3 movement from within the cell to the ECF occurs largely via the NBCe1A transporter (which moves 1 Na^+ and 3 HCO_3 ions). The net effect of the secretion of 1 H^+ molecule is the disappearance of 1 HCO_3 molecule from the luminal fluid and appearance of 1 HCO_3 molecule in the ECF.

About 20% of the filtered HCO_3 load escapes proximal tubule reclamation and is delivered downstream, where most is reabsorbed by the thick ascending limb of Henle. Proton secretion here is largely accomplished by the same Na^+-H^+ exchanger (NHE3) as exists in the proximal tubule. The small fraction of HCO_3 delivered more distally is reabsorbed by mechanisms shown in Fig. 14.4

After HCO_3 has largely disappeared from the lumen in distal tubules/collecting ducts, further H^+ secretion generates “new” HCO_3 that restores, or “regenerates,” the HCO_3 that was decomposed by

Metabolic alkalosis

Normal

Fig. 14.2 Normal Acid-Base Status and Metabolic Alkalosis. The three major serum electrolytes are shown in the form of Gamblegrams. Note that when $[HCO_3^-]$ increases and the anion gap (AG) also increases slightly (which occurs with most forms of metabolic alkalosis), $[Cl^-]$ must fall, and the $[Cl^-]:[Na^+]$ ratio will fall below its normal 1:1.4 relationship.

sulfuric, phosphoric, and hydrochloric acids, for example. Also, the quantity of HCO_3 that has been lost in the stool must also be regenerated. If 80 to 100 mmol/day of nonvolatile acids have been generated, then 80 to 100 mmol/day of H^+ (plus any HCO_3 lost in stool) must be

excreted by the kidneys to maintain acid-base equilibrium.
As HCO3 disappears from the tubular fluid, the pH falls. However, the minimum tubule fluid/urine pH cannot be reduced below about 4.5, which represents only 0.03 mmol/L of free H+ (and therefore only 0.03 mmol/L of generated HCO3). Therefore, virtually the entire H+ load excreted in the urine must be bound to buffers in the urine: HPO42 , which is titrated to H2 PO4 , represents most of the titratable acid in urine, and NH3 binds to H+ to form NH4+

Metabolic Alkalosis: Source of Excess HCO 3

Metabolic alkalosis usually indicates an accumulation of “excess” HCO3 in the body. The HCO3 source can be exogenous, endogenous, or both.

Exogenous Sources

Exogenous sources include Na+ or K+ HCO3 or salts of HCO3 precursors (organic anions such as lactate, acetate or citrate, which generate HCO3 when completely oxidized). These salts may be ingested/absorbed and/or infused. (Box 14.1).

Endogenous Sources

The two most important potential sources of endogenous of HCO3 are the stomach and kidney, as described below.

Stomach

HCO3 is added to the ECF whenever HCl is secreted into gastric lumen. Essentially, 1 HCO3 ion replaces 1 Cl in the ECF. However, net HCO3 accumulation in the ECF requires the secreted HCl to be lost from the body, usually via vomiting and/or gastric suction (for further explanation, see the section Classic Example: Gastric Alkalosis).

Major Proximal Tubule Cellular and Luminal Events in HCO_3

LUMEN

Carbonic
anhydrase IV

Na^+
HCO_3^-

$3Na^+$
Na^+ K^+
ATPase
H^+

$Na^+ + H^+$
HCO_3^-

BLOOD

PROXIMAL TUBULE CELL

ATPase

$2K^+$

H^+

Na^+
NBCe1A

Carbonic
anhydrase IV

$3HCO_3^-$
HCO_3^-

H^+
H^+

H_2CO_3

NHE3

Carbonic
anhydrase II

Na^+
$CO_2 + H_2O$

H_2CO_3

AQP1

$H_2O + CO_2$

Fig. 14.3 Major Proximal Tubule Cellular and Luminal Events That Participate in HCO_3^- Reclamation.
Intracellular H_2O combines with CO_2 to generate H_2CO_3, which rapidly dissociates to H^+ and HCO_3^- ions.

These reactions are catalyzed by the cytoplasmic enzyme carbonic anhydrase II. Na^+,K^+-ATPase in the basolateral membrane creates a steep Na^+ electrochemical gradient that energizes Na^+ reabsorption via the Na^+-H^+ exchanger 3 (NHE3). When H^+ moves into the lumen, it reacts with filtered HCO_3^- to form H_2CO_3. The H_2CO_3 dehydrates to H_2O and CO_2, a reaction catalyzed by intraluminal carbonic anhydrase IV (this enzyme is anchored by a glycosylphosphatidylinositol tail to the luminal membrane). The generated CO_2 flows into the cell, largely via the aquaporin 1 (AQP1) channel. The HCO_3^- ions generated within the cells move across the basolateral membrane into peritubular capillaries, primarily via an Na^+-$3HCO_3^-$ cotransporter (the electrogenic NBCe1A transporter is a product of the Solute Carrier Family 4 Member A4 [SLC4A4] gene). The net effect of the secretion of 1 H^+ molecule and reabsorption of 1 Na^+ molecule is the addition of 1 $NaHCO_3$ molecule to the extracellular fluid and the disappearance of 1 $NaHCO_3$ molecule from the lumen. In addition, a smaller component of proximal tubule H^+ secretion (HCO_3^- reclamation) is accomplished via a V-type H^+-ATPase pump complex.
Under normal conditions, about 80% of the filtered $NaHCO_3$ is reclaimed in the proximal tubule.

Kidney

+

Normal excretion of H^+ in the urine (as NH_4 and titratable acid) generates the quantity of HCO_3^- required to replace the HCO_3^- decomposed by nonvolatile acids derived from dietary metabolism plus any HCO_3^- lost in the stool. To the extent the kidney generates additional HCO_3^- above these replacement requirements, that quantity represents

“excess” HCO_3^- and can generate metabolic alkalosis. “Excess” kidney HCO_3^- generation generally occurs when the following conditions coexist:

1. The more distal kidney tubules/ducts are stimulated to avidly reabsorb Na^+ (e.g., because aldosterone activity is high), and

Principal Cells and Type A and Type B Intercalated Cells

Metabolic Alkalosis: Bicarbonate Sources and Mechanisms of Generation

BOX 14.1

- Ingest/absorb and/or infuse NaHCO3 and/or NaHCO3 precursors, such as Na acetate, Na citrate, or Na gluconate.
- Generation of excess HCO3 by distal renal tubules/collecting ducts (increased H+ secretion).
- Generous delivery of NaCl (or other Na salts, such as Na2SO4 or Na penicillin) to distal tubules/collecting ducts, which are actively reabsorbing Na+ (and therefore secreting K+ and H+).
- K+ depletion, shifting H+ into cells, thereby generating extracellular fluid HCO3
- Remove HCl from body (vomiting/nasogastric suction/chloride-rich diarrhea).

2. Salt and volume delivery to these distal reabsorbing sites is relatively large.

Several examples of kidney bicarbonate overproduction include:

1. Primary hyperaldosteronism and other disorders, which mimic primary hyperaldosteronism (especially when a high-salt diet is ingested) (Box 14.2)
2. Loop and/or thiazide diuretics
3. Certain inherited kidney salt-wasting syndromes (i.e., Bartter, Gitelman, and related syndromes)
4. The infusion of Na+ salts of poorly absorbed anions (e.g., HPO42 , SO42 , penicillin) when distal tubule Na+ reabsorption is stimulated by mineralocorticoids and/or volume contraction19 20

Another important endogenous source of “excess” ECF HCO3 is the movement of K+ out of cells into the ECF (in response to hypokalemia), which is partially balanced by movement of H+ into cells. This generates HCO3 in the ECF.21 22 The ECF [HCO3] can also increase when ECF volume contracts around a fixed quantity of HCO3 (see the section Classic Example: Gastric Alkalosis).23

Maintenance of Metabolic Alkalosis

Fig. 14.4 Principal Cells and Type A and Type B Intercalated Cells. These cells are located in the late distal convoluted tubule, the connecting tubule, and cortical collecting duct. Principal cell transport is energized primarily by electrogenic Na +,K+-ATPase pumps in the basolateral membrane. The resulting low intracellular [Na +] and negative intracellular potential difference combine to create a large gradient for Na + to move from the lumen into these cells. Flow occurs mainly through the epithelial sodium channel (ENaC, which is composed of α, β, and γ subunits, each a product of a different gene). Inward flow of Na + ions is more rapid than the sum of outward movement of K + (mainly through the renal outer medullary potassium [ROMK] channel) and inward flow of Cl (mainly via the paracellular space). Therefore, the Na + influx generates a negative potential difference (PD, approximately −40 mv) in the lumen. The H + secreted by the type A intercalated cells into the lumen initially reacts with any HCO3 remaining in the lumen; this represents HCO3 reclamation. As the luminal fluid pH falls, additional secreted H + combines with buffers such as HPO42 and NH3 to generate urine titratable acid (i.e., H2 PO42) and NH4+, which creates equimolar quantitates of systemic HCO 3 . See Fig.

14.5 for a more detailed description of intercalated cell ion transport.

If metabolic alkalosis develops and glomerular filtration rate (GFR) is not markedly reduced, correction of the alkalosis should be relatively straightforward: merely excrete a large fraction of the filtered HCO3 (which will be supernormal because of the high serum/filtered [HCO3]). A brisk HCO3 diuresis would then reduce the [HCO3] and restore normal acid-base status. This obviously has not occurred when metabolic alkalosis persists. Why has a brisk HCO3 diuresis not developed to rapidly restore normal acid-base status? The answer to this question depends on the underlying cause of the alkalosis, and the precise explanations continue to be refined and debated. The major mechanisms responsible for the maintenance of metabolic alkalosis are shown in Box 14.3

Normal individuals can ingest, and their kidneys will efficiently excrete, up to 1000 mmol/day of NaHCO3 over several weeks with only a minimal increase in serum [HCO3].24 Consequently, when metabolic alkalosis develops and persists despite a relatively normal GFR, this indicates the kidney is avidly reclaiming HCO3 at a supernormal rate. Most patients with metabolic alkalosis have both increased proximal and distal HCO3 reabsorption. The major factors responsible increasing proximal HCO3 are reduced intravascular, or effective intraarterial, blood volume, and hypokalemia.12 (Metabolic acidosis and chronic respiratory acidosis also stimulate proximal tubule HCO3 reabsorption, but these disorders are not relevant to the current discussion.)

Metabolic alkalosis is also usually associated with accelerated distal HCO3 reabsorption and generation. Generous distal Na+ delivery, combined with avid distal Na+ reabsorption (e.g., because of high aldosterone levels), accelerates distal H+ and K+ secretion. This occurs

BOX 14.2

Causes of Metabolic Alkalosis

ECF Volume Contracted: Urine [Cl] <20 mmol/L

- Gastric alkalosis: vomiting/nasogastric suction
- Chloride-rich diarrhea (congenital chloridorrhea)
- Status post–chronic hypercapnia (acute reversal of chronic respiratory acidosis)
- Cystic fibrosis with major sweating
- Some villous adenomas
- Thiazide or loop diuretics after their renal tubule diuretic effect has dissipated

ECF Volume Expanded: Urine [Cl] >20 mmol/L

- Primary hyperaldosteronism (unilateral adenoma/bilateral hyperplasia/glucocorticoid-sensitive hyperaldosteronism)
- Severe Cushing syndrome (especially with ectopic adrenocorticotropic hormone secretion)
- Exogenous mineralocorticoids
- Reduced 11-β (OH)-steroid dehydrogenase activity
- Chronic licorice/carbenoxolone ingestion
- Congenital apparent mineralocorticoid excess syndrome (inactivating mutation of 11-β hydroxysteroid dehydrogenase (type 2)
- Renin-secreting tumors
- Some forms of congenital adrenal hyperplasia
- 11-β hydroxylase deficiency
- 17-α hydroxylase deficiency
- Liddle syndrome (persistent open epithelial sodium channel–renal tubule epithelial channels

ECF Volume Contracted: But Urine [Cl] >20 mmol/L (Generally Indicates a Renal Tubule NaCl Reabsorptive Defect)

- Thiazide and/or loop diuretics actively inhibiting renal tubule NaCl reabsorption
- Bartter syndromes (defective Na reabsorption in loop of Henle, a furosemide-like lesion)
- Gitelman syndrome (defective Na reabsorption by the neutral NaCl transporter, a thiazide-like lesion)

Metabolic Alkalosis: Other

- Very severe potassium deficiency
- Milk (calcium) alkali syndrome
- $NaHCO_3$ loads in patients with markedly reduced glomerular filtration rate.
- Refeeding after prolonged fasting

ECF, Extracellular fluid.

in large part because distal tubule Na^+ reabsorption, mainly via the epithelial sodium channel (ENaC) in principal cells, generates a lumen negative electric potential (potential difference [PD] = −40 mv), which drives paracellular and transcellular anion (mostly Cl) reabsorption and enhances the secretion of H^+ and K^+. Also, multiple neurohormonal stimuli that increase distal Na^+ absorption also increase type A intercalated cell activity25 (Fig. 14.4).

Three different types of intercalated cells are shown in Fig. 14.5. The type B intercalated cell secretes HCO_3 in exchange for Cl and therefore contributes to the correction of metabolic alkalosis. However, generous distal delivery of Cl is required to enable this cell to secrete major quantities of HCO_3 , and Cl delivery is usually reduced when ECF, or effective intraarterial volume, is reduced. Intercalated cells also contribute to NaCl reabsorption and volume regulation as discussed in Fig. 14.5 25-31

Of course, if GFR is markedly reduced, the filtered HCO3 load will fall sharply. However, metabolic alkalosis does not usually develop in patients with very low GFR. These patients more often develop metabolic acidosis. Nonetheless, occasionally metabolic alkalosis does develop, and under these conditions the reduced GFR impairs excretion of the HCO3 load. A reduced GFR is a major contributor to the maintenance of metabolic alkalosis in patients with milk-alkali or calcium-alkali syndrome[32,33] and when patients with severe kidney dysfunction ingest bicarbonate salts, bicarbonate generating salts, vomit, or require nasogastric (NG) suction.[34]

Metabolic Alkalosis:
Mechanisms of Maintenance

BOX 14.3

- Increased proximal renal tubule HCO3 reclamation
- True extracellular fluid contraction or “effective intraarterial” volume contraction
- K+ depletion
- Continuous or intermittent generation of new HCO3
- In the distal kidney tubules and collecting ducts
- Gastric HCl losses
- Exogenous alkali
- Reduced NaHCO3 filtration due to kidney failure

METABOLIC ALKALOSES: ETIOLOGIC CLASSIFICATION BASED ON ECF VOLUME STATUS

The generation, maintenance, and resolution of several prototypical types of metabolic alkalosis in each ECF volume status category are described.

ECF Volume Contracted With Persistently Reduced Urine [Cl−]

Classic Example: Gastric Alkalosis

Generation. Gastric fluid osmolality is about 300 mOsm/L with a [Cl] of about 150 mmol/L and a similar total cation concentration of about 150 mmol/L. The [H+] varies between 40 and 140 mmol/L, [K+] between 10 and 15 mmol/L, and [Na+] makes up the balance.[35] Secretion of HCl (via gastric type H+/K+ ATPase and Cl channels) into the gastric lumen adds an equal quantity of HCO3 to the ECF. (The net effect of HCl secretion is the “replacement” of ECF Cl by HCO3 .) Normally, gastric HCl secretion does not result in metabolic alkalosis because the secreted HCl is not externally lost from the body. The HCl secreted into the gastric lumen usually enters the small bowel where the H+ reacts with HCO3 , mainly secreted by the pancreas (with a small component derived from bile and intestinal epithelium). This reaction generates CO2 and water in the small bowel lumen. Because the quantity of HCO3 that enters the small bowel lumen and reacts with H+ equals the quantity of H+ delivered from the stomach, these two processes neutralize one another so that neither alkalosis nor acidosis develops. However, if the HCl secreted into the stomach is removed from the body, via vomiting or aspiration, this prevents the HCl from reaching the small bowel. Consequently, HCO3 is either not secreted into the intestinal lumen, for neutralization by HCl, or is reabsorbed. The net effect is the addition of a gastric derived load of HCO3 to the ECF and loss of an equal quantity of Cl from the body. This represents the initial source of HCO3 in patients with “gastric alkalosis.”

Later in the development of gastric alkalosis, hypokalemia (generated by renal K+ loss) results in systemic K+/H+ cell shifts, which generate additional ECF

HCO3 (described later).

Intercalated Cells

Fig. 14.5 Intercalated Cells: Three different intercalated cell types have been identified: type A intercalated cells, type B intercalated cells, and non–type A/non–type B intercalated cells. Each is rich in carbonic anhydrase II and is capable of generating abundant HCO_3^- and H^+ from H_2CO_3. Type A intercalated cells: H^+ is secreted into the lumen mainly via V-type H^+-ATPase and to a smaller extent via H^+-K^+-ATPase. The generated cytoplasmic HCO_3^- moves into the peritubular capillary in exchange for Cl^-, via anion exchanger 1 (AE1; a product of the Solute Carrier Family 4 Member 1 [SLC4A1] gene). This transporter is also called the erythrocyte membrane protein band 3 when it is located in red blood cells. Type B intercalated cells: H^+ is secreted into the peritubular capillary by V-type H^+-ATPase in the basolateral membrane (the same proton transporter as found in type A intercalated cells but in the opposite, or luminal, membrane). The HCO_3^- generated in this cell is secreted into the lumen via an anion exchanger named pendrin (a product of the Solute Carrier Family 26 Member A4 [SLC26A4] gene), which exchanges 1 HCO_3^- for 1 Cl^-. Pendrin is a distinct and different exchanger than the AE1 present in the basolateral membrane of the type A cells. A Na^+/3 HCO_3^- cotransporter AE4 (anion exchanger 4; a product of the Solute Carrier Family 4 Member A4 or [SLC4A4] gene) is present in the basolateral membrane. These cells also have the sodiumdriven bicarbonate chloride exchanger (NDBCE; a product of the Solute Carrier Family 4 Member A8 [SLC4A8] gene) in the luminal membrane (see later discussion). Non–type A/non–type B intercalated cells: this is the third type of intercalated cell. Both a V-type H^+-ATPase, pumping H^+, and pendrin, exchanging HCO_3^- for Cl^- coexist in the lumen membrane. AE4 is a major Na^+/3 HCO_3^- transporter in the basolateral membrane, moving these ions into the peritubular capillary. Although intercalated cells were originally identified as major kidney acid-base–regulating cells, it is now clear that these cells also play an important role in salt and volume regulation.[32,33] The NDBCE in the luminal membrane of the type B intercalated cells is an electrically neutral ion exchanger moving 1 Na^+ and 2 HCO_3^- ions into the cell while moving 1 Cl^- into the lumen. The net effect of two pendrin cycles (2 HCO_3^- ions enter the lumen in exchange for uptake of 2 Cl^- ions) and 1 NDBCE cycle (2 HCO_3^- ions and 1 Na^+ ion enter the cell and 1 Cl^- ion enters the lumen) has the net effect of the reabsorption on 1 NaCl molecule. These acid-base and salt reabsorption interactions of intercalated cells may explain why some patients with Pendred syndrome, a genetic defect of pendrin, develop severe salt depletion and metabolic alkalosis when treated with thiazide diuretics.[34] (Pendrin is also a major transporter in the ear, and patients with Pendred syndrome are usually congenitally deaf.)

Maintenance. Initially, as HCO_3^- is added to the ECF and slightly raises the $[HCO_3^-]$, as a result of vomiting or gastric suction, most is filtered and excreted by the kidneys largely as $NaHCO_3$.

The loss of gastric fluid combines with kidney loss of $NaHCO_3$ and fluid to produce ECF volume contraction, and this activates a neurohormonal cascade that stimulates the kidneys to avidly retain salt and fluid. Secondary hyperaldosteronism develops and results in the conversion of much of the $NaHCO_3$ delivered to the distal tubules to $KHCO_3$.[36]

Systemic hypokalemia develops causing K^+ to shift out of cells in exchange for ECF H^+ entering cells. This generates ECF HCO_3^-.[21,22]

This K^+/H^+ shift acidifies kidney tubule cells, which further stimulates H^+ secretion and thereby drives kidney HCO_3^- reclamation and generation.

Systemic hypokalemia also reduces pendrin activity and type B intercalated cell density, which reduces HCO_3^- secretion and contributes to the maintenance of metabolic alkalosis.[30,31]

Extracellular fluid volume contraction stimulates both proximal and distal Na^+ reabsorption. In the proximal tubules, this increases HCO_3^- reclamation. In the distal tubules, Na^+ reabsorption increases both H^+ and K^+ secretion. K^+ depletion further increases H^+ secretion by type A intercalated cells via both H^+ ATPase and H/K ATPase pumps (Figs. 14.3 and 14.4) and increases kidney NH_3 generation and excretion.[37,38] These effects all combine to increase kidney HCO_3^- reclamation and generation.

During the maintenance phase of gastric metabolic alkalosis, the urine electrolyte pattern typically fluctuates. Extracellular fluid volume contraction stimulates avid reabsorption of filtered Na^+, HCO_3^-, Cl^-, and water. This usually generates concentrated urine (an antidiuretic hormone effect) with low Na, Cl, and K concentrations and a relatively acid pH (denoted as paradoxical aciduria because systemic metabolic alkalosis exists). However, intermittently (e.g., immediately after loss of a bolus of HCl-rich gastric fluid), serum $[HCO_3^-]$ acutely increases, and for a limited period of time, the larger load of filtered HCO_3^- cannot be completely reclaimed despite the multiple neurohormonal factors generated by volume contraction. When this occurs, the urine excretion of $[HCO_3^-]$, $[Na^+]$, $[K^+]$, and pH all temporarily increase. This reduces the serum $[HCO_3^-]$ and further contracts ECF volume, and after a brief period of time the filtered load of Na^+ and HCO_3^- can again be completely reabsorbed. The urine electrolyte concentrations and urine pH again fall. However, it is very important to note that throughout these cyclic variations in urine $[Na^+]$, $[K^+]$, $[HCO_3^-]$, and pH, urine $[Cl^-]$ remains persistently low (because the intermittent loss of HCO_3^- in the urine mandates loss of Na^+ and/or K^+ but not Cl^-). Thus, a low urine $[Cl^-]$ (<20 mmol/L) generally indicates the ongoing response to reduced ECF/intraarterial blood volume (or very low Cl^- intake). Development of these urine electrolyte profiles presume that kidney tubule function is relatively intact and the absence of exogenous diuretic activity.

Resolution. The factors responsible for kidney HCO_3^- retention in these forms of metabolic alkalosis are largely reversed by adequate ECF volume expansion (NaCl infusion) and K^+ repletion. Restoration of ECF volume is associated with a rising urine $[Cl^-]$ and the development of a $NaHCO_3$ diuresis. Increased distal Cl^- delivery also stimulates HCO_3^- secretion in exchange for Cl^- via the pendrin exchanger in Type B intercalated cells. Systemic K^+ replacement is required to restore K^+ homeostasis. Some of the administered K^+ moves into cells in exchange for H^+ moving into the ECF. This simultaneously reduces the ECF $[HCO_3^-]$ and increases intracellular pH.

The term contraction alkalosis has been used to describe several different conditions in which the ECF “contracts” around a relatively fixed quantity of HCO3−. Although gastric alkalosis is an ECF volume contracted condition and the ECF contraction contributes importantly to both its generation and maintenance, the major origin of the increased blood [HCO3−] is not contraction of the ECF per se but rather generation of HCO3− owing to gastric HCl loss and cellular H+K+ shifts.21-23,36

Conversely, although ECF expansion with NaCl-rich fluids does directly dilute the ECF [HCO3−] to a small degree, the corrective action of NaCl in these patients is mainly the result of ECF volume expansion and resultant kidney HCO3− excretion.

Reducing or stopping the loss of gastric HCl is of course required to reverse the process at its initiation point. If the exogenous loss of gastric fluid losses cannot be stopped, then reducing the gastric fluid [HCl] concentration with an H+ blocker or proton pump inhibitor can be helpful.39

Box 14.2 lists the most common forms of metabolic alkalosis associated with ECF volume contraction. The urine [Cl−] is typically reduced to less than 20 mmol/L in each of these disorders.

ECF Volume Expanded

Classic Example: Primary Mineralocorticoid Excess Syndromes

Primary hyperaldosteronism is a condition of autonomous, or inappropriately upregulated, aldosterone secretion. This usually generates ECF volume expansion, hypertension, hypokalemia, and metabolic alkalosis. A unilateral adrenal adenoma secreting aldosterone is the prototypical cause of this disorder, but many conditions can duplicate or mimic the clinical and electrolyte and acid-base pathophysiology of a primary aldosterone-secreting adenoma (Box 14.2) (see Chapter 39).

ECF Volume Regulation of Renin and Aldosterone (Normal Physiology)

Extracellular fluid volume contraction in normal individuals reduces the GFR and sharply increases the reabsorption of NaCl and NaHCO3 in the proximal tubules. Volume contraction also generates secondary hyperaldosteronism (high aldosterone activity driven by high renin and angiotensin II activity). Reabsorption of Na+ in late distal tubules/collecting ducts is largely accomplished by the principal cells via ENaC channels in the luminal membranes (Fig. 14.4). When these channels are present in the luminal membrane and in an open state, the electrochemical gradient favors reabsorption of Na+, and this cation flux generates a lumen negative electrical potential (about −40 mv) that drives both Cl− reabsorption and also secretion of K+ and H+. Normally, ECF volume contraction generates a coordinated series of proximal and distal actions so that the potent aldosterone-driven stimulus to reabsorb Na+ in the distal tubules and collecting ducts is linked to a fall in GFR and increased proximal tubule salt reabsorption. These proximal tubule events sharply reduce distal salt and water delivery. The net effect is that reduced Na+ and volume delivery to the distal aldosterone-sensitive tubule sites acts to blunt the magnitude of distal Na+ reabsorption and the indirectly linked secretion of K+ and H+. Thus, metabolic alkalosis and hypokalemia do not usually develop despite physiologic secondary hyperaldosteronism.

An opposite series of events develop in response to ECF volume expansion in normal individuals. The GFR increases, proximal salt and water reabsorption fall, and distal delivery of salt and water is generous. Volume expansion reduces renin, angiotensin II, and aldosterone levels. Now generous distal salt and water delivery exists while aldosterone activity is minimal. Distal Na+ reabsorption, and indirectly linked K+ and H+ secretion, is moderate. Thus, metabolic acidosis and hyperkalemia do not develop despite physiologic secondary hypoaldosteronism.

These coordinated interactions describe the normal reciprocal physiologic balance that exists between the magnitude of proximal tubule salt and water reabsorption, distal delivery of salt and water, and the neurohormonal stimulation (largely via aldosterone) of distal Na^+ reabsorption and indirectly linked K^+ and H^+ secretion. This exquisite normal reciprocal balance is disrupted by autonomous hypersecretion of aldosterone.[12,40]

Generation. Autonomous hyperaldosteronism generates an inappropriate degree of distal Na^+ reabsorption, which expands the ECF, raises the GFR, and reduces proximal tubule salt and water reabsorption. This results in generous distal salt and water delivery. This occurs in the setting of persistently high aldosterone activity. These conditions result in the unphysiologic combination of high aldosterone activity linked with high distal tubule salt and water delivery. This pathophysiologic combination generates a high rate of distal Na^+ reabsorption and indirectly linked generous K^+ and H^+ secretion. Excess excretion of K^+ and H^+ exceeds physiologic requirements and produces hypokalemia and metabolic alkalosis.

The development of hypokalemia and K^+ depletion contribute importantly to additional systemic and kidney HCO_3^- generation. K^+ shifts out of cells in exchange for H^+ generating ECF HCO_3^-.[22] Systemic K^+ depletion also increases kidney H^+ secretion and ammonia generation and excretion (in part by reducing the pH of kidney tubule cells).[25,27] All these effects enhance kidney HCO_3^- reclamation and generation.

Maintenance phase. Expansion of the ECF usually increases the GFR, reduces proximal tubule salt and volume reabsorption, and decreases HCO_3^- reclamation. ECF expansion normally also reduces renin, angiotensin II, and aldosterone levels. Consequently, with “physiologic” ECF volume expansion, distal Na^+ reabsorption and K^+ and H^+ secretion remain modest despite high delivery rates. However, autonomous aldosterone secretion combines generous distal salt delivery with inappropriately high levels of distal Na^+ reabsorption and indirectly linked K^+ and H^+ excretion. Hypokalemia and K^+ depletion develop and contribute importantly to both ongoing kidney HCO_3^- reclamation and both kidney and systemic HCO_3^- generation and via K^+/H^+ cell shifts and cellular acidification. Hypokalemia also increases H^+/K^+-ATPase activity in type A intercalated cells (Figs. 14.4 and 14.5).[25,27] Additionally, aldosterone increases distal salt reabsorption via a sequence of pendrin-related events as described in Fig. 14.5.[28]

During the maintenance phase of various states of autonomous hyperaldosteronism, and related pathophysiologic conditions, urine electrolytes reflect the individual’s salt intake. Thus, the urine $[Cl^-]$ will generally be greater than 20 mmol/L, unless the patient is ingesting a very low NaCl diet.

Recovery phase. Successful resection of an adrenal aldosteronesecreting adenoma should theoretically reverse the entire syndrome.

In lieu of surgery, drugs that block the action of aldosterone can be very helpful. The physical and biochemical manifestations of primary hyperaldosteronism can also be markedly ameliorated by ingestion of a low-salt diet. This reduces distal salt delivery and thereby blunts H^+ and K^+ secretion and excretion. Conversely, the physical findings and electrolyte abnormalities are exacerbated by a high-salt diet.[40,41] Analogously, other mineralocorticoid excess syndromes and mineralocorticoid excess-like syndromes are improved or “cured” by eliminating the source of the problem and/or treated by blocking the downstream pathophysiology. However, when hypertension has existed for a long period of time, this may persist as a result of the development of structural vascular pathology.

ECF Volume Contracted With Intermittently Reduced Urine [Cl^-]

Classic Example: Thiazide and/or Loop Diuretics

Thiazide and/or loop diuretics often generate hypokalemia and metabolic alkalosis. Despite a relatively contracted ECF and effective arterial blood volume, the generation and maintenance mechanisms of these conditions have many similarities to the ECF volume-expanded condition of primary hyperaldosteronism.[40]

That is because distal tubule salt and volume delivery are high when diuretics are inhibiting reabsorption. Therefore, they generate the pathophysiologic combination of high distal salt/volume delivery and high levels of aldosterone activity (in this case due to secondary hyperaldosteronism).

Generation. Inhibition of the neutral Na/K/2Cl cotransporter in the thick limb of Henle by loop diuretics and/or inhibition of the neutral Na/Cl cotransporter in the diluting segment by thiazide diuretics increases NaCl and volume delivery to more distal sites. Diuretics also increase renin, angiotensin II, and aldosterone levels, generating secondary hyperaldosteronism. In the absence of diuretics, secondary hyperaldosteronism is typically associated with reduced distal salt and volume delivery, and this limits the magnitude of distal Na^+ reabsorption (and thereby H^+ and K^+ secretion). However, diuretic activity combines secondary hyperaldosteronism with generous distal tubule NaCl and volume delivery. Therefore, enhanced distal Na^+ reabsorption via principal cell ENaCs is linked with generous distal Na^+ and volume delivery, accelerating distal H^+ and K^+ secretion. This pathophysiologic combination generates metabolic alkalosis and hypokalemia. Hypokalemia also adds additional ECF HCO_3^- via cellular H^+/K^+ exchange described above.

During periods of diuretic activity, urine [Na^+] and [Cl^-] are both high. However, diuretics are typically administered intermittently, so that periods of diuretic activity cycle with periods of inactivity and recovery. During the “off-diuretic” phases, avid proximal kidney salt and water reabsorption markedly reduces distal NaCl delivery. This minimizes principal cell Na^+ reabsorption and distal K^+ and H^+ secretion. During these off-diuretic periods, urine [Cl^-] and [Na^+] fall to low levels, reflecting the patient’s relatively contracted ECF volume status. Then, when the diuretic is again ingested or administered, the urine [Cl^-] and [Na^+] increase. Thus, the concentration of these urine electrolytes cycles up and down depending on the presence or absence of diuretic activity.

Recovery phase. When diuretics are discontinued, distal delivery of salt and volume fall, and this reduces kidney tubule HCO_3^- generation. However, metabolic alkalosis will not resolve until the potent stimuli, which are accelerating proximal and distal salt reabsorption, are eliminated. Therefore, if diuretics were initiated to treat avid salt retention (e.g., due to heart failure, hepatic cirrhosis), the metabolic alkalosis will generally persist until the underlying pathology can be ameliorated. Reversing hypokalemia and K^+ depletion is also critical for the amelioration or reversal of metabolic alkalosis. If the clinical situation mandates continuing diuretics despite metabolic alkalosis, the addition or substitution of diuretics, which blunt distal tubule/collecting duct Na^+ reabsorption (i.e., potassium sparing diuretics such as triamterene or spironolactone) and/or “acidifying” diuretics, which block proximal tubule HCO_3^- reclamation (acetazolamide), can be very helpful. However, acetazolamide will generate marked K^+ wasting, so aggressive K^+ supplementation is often required when this diuretic is initiated.[42]

All three types of intercalated cells located in the distal tubule/collecting ducts play a major role in both acid/base regulation and also

volume regulation and salt balance.[43,44] These cells may be especially important in moderating the development of metabolic alkalosis in patients receiving thiazide diuretics[45] (Fig. 14.5).

OTHER METABOLIC ALKALOSES

Bartter and Gitelman syndromes and their related disorders are genetic diseases that result in impaired kidney tubule salt reabsorption. Therefore, these diseases have many similarities to persistent diuretic action. However, unlike patients who receive diuretics, these patients never experience an “off-drug” period. Therefore, these disorders are characterized by persistent, high urine [Cl] because an “off-diuretic–like” period never occurs.[46,47]

If large amounts of alkali are ingestion or infused in a patient with acute or chronic kidney disease, this can produce metabolic alkalosis, which may sometimes be of extreme severity.[48] The “milk alkali” or “calcium alkali” syndrome is generated by the ingestion of large quantities of $NaHCO_3$ or other alkalinizing salts together with excess calcium (in milk or $CaCO_3$) intake.[32,33] In these patients, kidney damage is partially generated by kidney calcium deposition, facilitated by high urine calcium concentrations in alkaline urine. Vomiting often also develops and will exacerbate the metabolic alkalosis. Citrate is an anticoagulant that is used in many blood products and is a HCO_3 precursor. Each mole of Na_3Citrate that is oxidized yields 3 moles of $NaHCO_3$. Therefore, metabolic alkalosis can occur after massive blood transfusions and when blood products, such as fresh frozen plasma, are infused in large volumes during procedures such as plasma exchange. These metabolic alkaloses are usually maintained because GFR is reduced, which impairs kidney HCO_3 excretion.

Compensation for chronic respiratory acidosis elevates plasma [HCO_3] and reduces the [Cl]. However, arterial pH remains acid due to the elevated Pco_2. If the chronically elevated Pco_2 is rapidly reduced, usually by mechanical ventilation, the plasma [HCO_3] concentration may remain elevated for a period of time and generate metabolic alkalosis. This is especially likely if the patient has a low effective arterial blood volume or reduced GFR. This is “posthypercapnic” metabolic alkalosis. This alkalosis will persist until enough NaCl is ingested or infused to replete the extracellular fluid volume.[49]

DIAGNOSTIC APPROACH TO METABOLIC ALKALOSIS

Most metabolic alkaloses are due to diuretics or external loss of gastric fluid. When the cause is not apparent from the history, drug review, and physical examination, it is helpful to categorize the disorder based on the kidney function and ECF or effective intraarterial volume status. If the GFR is reduced and major acidic gastrointestinal fluid losses do not exist, a source of exogenous bicarbonate should be sought. If the GFR is not markedly reduced, then it will be helpful to assess volume status integrating the history, physical examination, and spot urine [Cl] measurement. Urine [Cl] less than 20 mmol/L is consistent with a reduced ECF or effective intraarterial volume. Urine [Cl] greater than 20 mmol/L suggests a volume expanded state, or defective kidney salt reabsorption (i.e., diuretic activity or kidney tubule reabsorption defect). Consider the diagnoses listed in Box 14.2. If the patient exhibits signs of volume expansion, such as hypertension, then consider the ECF volume–expanded disorders in Box 14.2. Measurements of plasma renin and aldosterone levels can be helpful. If the patient appears volume contracted, yet has relatively high urine [Cl^-], kidney salt wasting may be responsible. Many of the genetic mutations responsible for Bartter and Gitelman syndromes can be identified by commercial laboratories. Recognize that diuretic-generated metabolic alkalosis is generally characterized by cyclic changes in urine [Cl−] as the diuretic effects wax and wane, and widely varying urine [Cl−] generally indicates intermittent diuretic use (which some patients may deny). Fig. 14.6 shows this diagnostic approach.

TREATMENT

Treatment of the volume-contracted metabolic alkaloses, such as those due to the external loss of HCl from vomiting or NG suction, was discussed earlier. Intravenous NaCl is required to expand the contracted ECF and KCl to replete K+ stores (the K+ deficit is usually in the 200–400 mmol range). If the HCl losses continue, proton pump inhibitors can be used to reduce the acid loss. Treatment of metabolic alkalosis generated by loop and/or thiazide diuretics include stopping (or reducing the dose of) diuretics whenever feasible, administering KCl to replete K deficits, and adding blockers of distal tubule Na reabsorption (which also reduce H and K loss), such as triamterene or amiloride, or blocking mineralocorticoid activity with spironolactone or eplerenone. Adding or switching to acetazolamide, a diuretic that increases kidney bicarbonate excretion, can also rapidly correct the metabolic alkalosis but will increase kidney K loss. The combination of volume contraction, metabolic alkalosis, and hypokalemia, which characterizes Bartter and Gitelman syndromes, is difficult to manage. In addition to generous oral NaCl and KCl intake, drugs that blunt distal Na+ reabsorption/K+ and H+ exchange (e.g., spironolactone, eplerenone, or amiloride) are helpful, and nonsteroidal antiinflammatory drugs may be useful. The Gitelman phenotype usually also generates marked urine magnesium wasting and hypomagnesemia requiring aggressive magnesium replacement.

Management of metabolic alkalosis and hypokalemia due to excessive (and physiologically inappropriate) mineralocorticoid activity can be definitively treated by removing the source of mineralocorticoid (i.e., resect an adenoma when present). If this is not possible (i.e., bilateral adrenal hyperplasia), then spironolactone or eplerenone are very helpful. For disorders that mimic physiologically inappropriately excessive mineralocorticoid activity (i.e., Liddle syndrome), triamterene or amiloride are used (the excessive mineralocorticoid-like activity in these disorders is independent of aldosterone activity; therefore, spironolactone or eplerenone are not effective). All the physiologically inappropriate increased mineralocorticoid activity disorders, and the disorders that mimic this pathophysiology, are exacerbated by high NaCl intake and ameliorated with low NaCl intake. Administration of KCl to treat K depletion is also important.

Alkalosis driven by alkali ingestion is best treated by discontinuation of oral alkali and/or adjustment of dialysate bicarbonate in dialysis-dependent patients.

When severe metabolic alkalosis develops and cannot be corrected (e.g., dialysis or continuous kidney replacement cannot be initiated), then HCl can be infused. The HCl solution is prepared at a concentration of 100 to 150 mmol/L and must be infused into a central vein to avoid hemolysis and vein damage/sclerosis. The volume of distribution of the HCl is about 50% of body weight.

Approach to the Diagnosis of Metabolic Alkalosis
[Total CO2] or [HCO3] > 30 mmol/L

Rule out chronic resp. acidosis

[HCO3] < 38 mmol/L, particularly with
[K+] ≤ 3.5 mmol/L

[HCO3] > 38 mmol/L or
? about the diagnosis

Vomiting, NG suction, loop or
thiazide diuretic use?

Measure arterial Pco2 and pH
to fully characterize disorder

Yes
Manage disorder

No
Assess BP, ECF volume, urine [Cl]

↑ BP, ECF volume replete or expanded
urine [CI] > 20 mmol/L

BP normal or low, ECF volume low
urine [CI] < 20 mmol/L

Consider mineralocorticoid excess
or apparent excess syndromes

Trial of NaCl repletion

Measure aldosterone and renin

Not easily corrected

Consider hereditary NaCl
wasting disorders

Easily corrected

Simple NaCl
depletion disorder

Fig. 14.6 Diagnostic approach to the causes of metabolic alkalosis. BP, Blood pressure; ECF, extracellular fluid; NG, nasogastric tube; Pco2, partial pressure of carbon dioxide.

SELF-ASSESSMENT QUESTIONS

1. A 56-year-old man with a history of hypertension and chronic kidney disease stage 3b has required nasogastric suction for 2 days following right hemicolectomy for colonic carcinoma. His blood pressure (BP) is 110/70 mm Hg and pulse is 105 beats/min. There is no jugular venous distention. There are no bowel sounds noted and no leg edema. Laboratory values are Na 138, K 2.9, Cl 92, and total CO2 36 (all mmol/L). Creatinine is 2.4 mg/dL, and venous pH is 7.52. Which of the following laboratory studies would most help define the mechanism of his alkalosis?

A. Low urine chloride concentration
B. Low urine potassium concentration
C. Low urine sodium concentration
D. Urine pH greater than 6.0

2. In addition to recommending intravenous 0.9% saline for correction of metabolic alkalosis in the patient in question 1, he will also require which one of the following?

A. Addition of a proton pump inhibitor
B. HCl infusion
C. KCl infusion
D. Kidney replacement therapy

3. A 26-year-old woman presents to the emergency department reporting weakness. She has no significant past medical history. Examination reveals BP 112/76 mm Hg, pulse 96 beats/min, and 3/5 strength in both legs. Laboratory values are Na 142, K 2.6, Cl 96, and total CO_2 34 (all mmol/L). Urine pH is 7, and urine electrolytes are Na 40, K 45, and Cl 10 (all mmol/L). The most likely cause of her illness is:

A. primary hyperaldosteronism.
B. Gitelman syndrome.
C. surreptitious vomiting.
D. diuretic use.

REFERENCES

1. Kraut JA, Lew V, Madias NE. Re-evaluation of total CO2 concentration in apparently healthy younger adults. Am J Nephrol. 2018;48:15–20.
2. Maehle K, Haug B, Flaatten H, Nielsen E. Metabolic alkalosis is the most common acid-base disorder in ICU patients. Crit Care. 2014;28(14):420. 420.
3. Javaheri S, Kazemi H. Metabolic alkalosis and hypoventilation in humans. Am Rev Respir Dis. 1987;136:1011–1016.
4. Feldman M, Alvarez NM, Trevino M, Weinstein GL. Respiratory compensation to a primary metabolic alkalosis in humans. Clin Nephrol. 2012;78:365–369.
5. Adrogue´ HJ, Madias NE. Secondary responses to altered acid-base status: the rules of engagement. J Am Soc Nephrol. 2010;21:920–923.
6. Hamm LL, DuBose TD. Chapter 16. In: Yu A, Chertow G, Luyckx V, Marsden P, Skorecki K, Taal M, eds. Brenner and Rector’s the Kidney. 11th ed. Philadelphia, PA: Elsevier; 2019:496–536.
7. Emmett M, Narins RG. Clinical use of the anion gap. Medicine (Baltim). 1977;56:38–54.
8. Emmett M, Seldin DW. Evaluation of acid-base disorders from plasma composition. In: Seldin DW, Giebisch G, eds. The Regulation of Acid-Base Balance. New York: Raven Press; 1989:213–263.
9. Madias NE, Ayus JC, Adrogue´ HJ. Increased anion gap in metabolic alkalosis: the role of plasma-protein equivalency. N Engl J Med. 1979;300:1421–1423.
10. Adrogue´ HJ, Brensilver J, Madias NE. Changes in the plasma anion gap during chronic metabolic acid-base disturbances. Am J Physiol. 1978;235:F291–F297.
11. Byrne AL, Bennett M, Chatterji R, Symons R, Pace NL, Thomas PS. Peripheral venous and arterial blood gas analysis in adults: are they comparable? a systematic review and meta-analysis. Respirology. 2014;19:168–175.
12. Seldin DW, Rector FC Jr. Symposium on acid-base homeostasis. the generation and maintenance of metabolic alkalosis. Kidney Int. 1972;1:306–321.
13. Luke RG, Galla JH. It is chloride depletion alkalosis, not contraction alkalosis. J Am Soc Nephrol. 2012;23:204–207.
14. Rosen RA, Julian BA, Dubovsky EV, Galla JH, Luke RG. On the mechanism by which chloride corrects metabolic alkalosis in man. Am J Med. 1988;84:449–458.
15. Galla JH, Bonduris DN, Luke RG. Effects of chloride and extracellular fluid volume on bicarbonate reabsorption along the nephron in metabolic alkalosis in the rat. reassessment of the classical hypothesis of the pathogenesis of metabolic alkalosis. J Clin Invest. 1987;80:41–50.
16. Galla JH, Bonduris DN, Luke RG. Correction of acute chloride depletion alkalosis in the rat without volume expansion. Am J Physiol. 1983;244:F217–F221.
17. Norris SH, Kurtzman NA. Does chloride play an independent role in the pathogenesis of metabolic alkalosis? Semin Nephrol. 1988;8:101–108.
18. Garella S, Cohen JJ, Northrup TE. Chloride-depletion metabolic alkalosis induces ECF volume depletion via internal fluid shifts in nephrectomized dogs. Eur J Clin Invest. 1991;21:273–279.
19. Stinebaugh B, Miller RB, Relman AS. The influence of non-reabsorbable anions on acid excretion. Clin Sci. 1969;36:53–65.
20. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol. 2009;5:193–202.
21. Halperin ML, Scheich A. Should we continue to recommend that a deficit of KCl be treated with NaCl? a fresh look at chloride depletion metabolic alkalosis. Nephron. 1994;67:263–269.
22. Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. J Am Soc Nephrol. 2011;22:1981–1989.
23. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. Kidney Int. 1975;5:279–283.
24. Van Goidsenhoven GM, Gray OV, Price AV, Sanderson PH. The effect of

prolonged administration of large doses of sodium bicarbonate in man. Clin Sci. 1954;13:383–401.

25. Roy A, Al-bataineh MM, Pastor-Soler NM. Collecting duct intercalated cell function and regulation. Clin J Am Soc Nephrol. 2015;10:305–324.
26. Gueutin V, Vallet M, Jayat M, et al. Renal b-intercalated cells maintain body fluid and electrolyte balance. J Clin Invest. 2013;123:4219–4231.
27. Wall SM. Recent advances in our understanding of intercalated cells. Curr Opin Nephrol Hypertens. 2005;14:480–484.
28. Soleimani M. SLC26 Cl-/HCO3- exchangers in the kidney: roles in health and disease. Kidney Int. 2013;84:657–666.
29. Wall SM, Weinstein AM. Cortical distal nephron Cl - transport in volume homeostasis and blood pressure regulation. Am J Physiol Renal Physiol. 2013;305:F427–F438.
30. Pham TD, Verlander JW, Wang Y, et al. Aldosterone regulates pendrin and epithelial sodium channel activity through intercalated cell mineralocorticoid receptor-dependent and -independent mechanisms over a wide range in serum potassium. J Am Soc Nephrol. 2020;31:483–499.
31. Wagner CA, Finberg KE, Stehberger PA, et al. Regulation of the expression of the Cl-/anion exchanger pendrin in mouse kidney by acid-base status. Kidney Int. 2002;62:2109–2117.
32. Kleyman TR, Satlin LM, Hallows KR. Opening lines of communication in the distal nephron. J Clin Invest. 2013;123:4139–4141.
33. Soleimani M. The multiple roles of pendrin in the kidney. Nephrol Dial Transplant. 2015;30:1257–1266.
34. Pela I, Bigozzi M, Bianchi B. Profound hypokalemia and hypochloremic metabolic alkalosis during thiazide therapy in a child with Pendred syndrome. Clin Nephrol. 2008;69:450–453.
35. Patel AM, Goldfarb S. Got calcium? Welcome to the calcium alkali syndrome. J Am Soc Nephrol. 2010;21:1440–1443.
36. Beall DP, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. Medicine (Baltim). 1995;74(2):89–96.
37. Huber L, Gennari FJ. Severe metabolic alkalosis in a hemodialysis patient. Am J Kidney Dis. 2011;58:144–149.
38. Riddel MJ, Strong JA, Cameron D. The electrolyte concentration of human gastric secretion. Q J Exp Physiol 65: 1–11, 196038. Wall SM: Mechanisms of NH41 and NH3 transport during hypokalemia. Acta Physiol Scand. 2003;179:325–330
39. Wall SM. Mechanisms of NH41 and NH3 transport during hypokalemia. Acta Physiol Scand. 2003;179:325–330.
40. DuBose TD Jr, Good DW. Effects of chronic Cl depletion alkalosis on proximal tubule transport and renal production of ammonium. Am J Physiol. 1995;269:F508–F514.
41. Kassirer JP, Schwartz WB. The response of normal man to selective depletion of hydrochloric acid. factors in the genesis of persistent gastric alkalosis. Am J Med. 1966;40:10–18.
42. Eiro M, Katoh T, Watanabe T. Use of a proton-pump inhibitor for metabolic disturbances associated with anorexia nervosa. N Engl J Med. 2002;346:140.
43. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both inside and outside the kidney. Physiol Rev. 2016;96:1327–1384.
44. Harrington JT, Hulter HN, Cohen JJ, Madias NE. Mineralocorticoidstimulated renal acidification: the critical role of dietary sodium. Kidney Int. 1986;30:43–48.
45. Ellison DH. Clinical pharmacology in Diuretic use. Clin J Am Soc Nephrol. 2019;14:1248–1257.
46. Seyberth HW, Weber S, Kömhoff M. Bartter’s and Gitelman’s syndrome. Curr Opin Pediatr. 2017;29:179–186.
47. Besouw MTP, Kleta R, Bockenhauer D. Bartter and Gitelman syndromes: questions of class. Pediatr Nephrol. 2020;35:1815–1824.

48. Huber L, Gennari FJ. Severe metabolic alkalosis in a hemodialysis patient. Am J Kidney Dis. 2011;58:144–149.
49. Schwartz WB, Hays RM, Polak A, et al. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. II. Recovery, with special reference to the influence of chloride intake. J Clin Invest. 1961;40:1238.

15

Respiratory Acidosis, Respiratory Alkalosis, and Mixed Acid-Base Disorders

Anip Bansal

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined by a decrease in arterial pH that is primarily because of an increase in whole body carbon dioxide (CO_2) stores, which are indirectly assessed by the partial pressure of CO_2 in arterial blood ($Paco_2$). The $Paco_2$ is the same as the Pco_2 in alveolar air but is usually lower than in the capillaries (which reflects the Pco_2 in both the interstitial fluid and in the cells surrounding these capillaries).1 At high altitude (i.e., above 4000 m or 13,000 feet), the underlying adaptation with chronic respiratory alkalosis usually causes a slight lowering of the $Paco_2$ at baseline so a respiratory acidosis may be present even with apparently normal $Paco_2$ levels.2 Pseudorespiratory alkalosis refers to the presence of arterial eucapnia (or hypocapnia) with severe venous hypercapnia in patients with profound circulatory failure with preserved respiratory function.3 4

PATHOPHYSIOLOGY OF RESPIRATORY ACIDOSIS

The quantity of CO_2 in the body remains constant if the lungs can excrete the amount of CO_2 produced from metabolism. This is reflected by the amount of dissolved CO_2 and in the partial pressure of CO_2 (Pco_2) in equilibrium with it. Although CO_2 is not an acid per se, it becomes a proton (H^+) donor when a portion of the dissolved CO_2 combines with water to form carbonic acid as follows:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + [HCO_3^-]$$

For any acid, the tendency to donate H^+ is defined by the following Henderson-Hasselbalch equation:

$$pH = pKa + \log_{10}(A^-/AH)$$

where pKa is the acid dissociation constant [A–] and [AH] are the concentrations of dissociated base and undissociated acid, respectively.

When simplified, the following relationship arises for carbonic acid:

$$pH \propto \frac{[HCO_3^-]}{[PaCO_2]}$$

The following relationship determines the $Paco_2$, which is a function of alveolar ventilation (VA) and CO_2 production (VCO_2)

$$PaCO_2 = (VCO_2 \times K)/VA$$

where K is a proportionality constant.

When the $Paco_2$ increases above its usual physiologic levels (i.e., above 40–45 mm Hg [5.33–6 kPa]), acidemia usually develops.

$$\frac{[HCO_3^-]}{\uparrow [PaCO_2]} \text{ results in } \downarrow pH$$

A decrease in VA or an increase in VCO_2 can increase $Paco_2$ and cause respiratory acidosis. CO_2 is the major end product of oxidative metabolism of carbohydrates and fatty acids. Normally, the amount of CO_2 produced metabolically is approximately 10 mmol/min, corresponding to an acid load of 13,000 to 16,000 mmol/day. Titration of HCO_3^- by nonvolatile acids leads to additional production of CO_2, which can be substantially increased in certain acidoses (e.g., lactic acidosis in septic shock). CO_2 production can also be increased by up to 30% to 100% of this basal production in conditions associated with increased metabolism (e.g., vigorous exercise, increased caloric intake with parenteral nutrition, or increased catabolism, such as in burns, trauma, and infection).5 Similarly, low metabolic states such as coma, anesthesia, paralysis, or a switch to nonoxidative metabolism (e.g., with ketogenesis) lead to decreased CO2 production.

Bicarbonate retention by the kidney in response to hypercapnia is slow; thus a sudden increase in Paco2 leads to a rapid lowering of the systemic pH. Total minute ventilation (MV) is the sum of VA and dead space ventilation; hence either a decrease in MV or an increase in dead space ventilation can decrease VA. Dead space can be either anatomic or alveolar (the latter refers to the fraction of alveolar ventilation ventilating unperfused alveoli). Dead space ventilation increases in the following situations6:

1. When the alveolar-capillary interface is destroyed (e.g., emphysema)
2. When blood flow is reduced (i.e., low cardiac output)
3. When alveoli are overdistended (e.g., during positive-pressure ventilation)

The maintenance of eucapnia depends on the ability of the ventilator system to match VCO2 by adjustment of the VA. Thus, respiratory acidosis (primary hypercapnia) results from an abnormality of either ventilatory effort (i.e., patients who will not breathe because of a lack of respiratory drive) and/or ventilatory output (i.e., patients who cannot breathe because of ventilator pump failure).1 The causes of respiratory acidosis (acute or chronic) are listed in Table 15.1.

RESPONSE TO RESPIRATORY ACIDOSIS

The timing of different responses to respiratory acidosis is shown in Fig. 15.1. This includes buffering by intracellular and extracellular buffers and renal compensation.

BICARBONATE BUFFERING SYSTEM

Of the 15,000 to 30,000 mmol of protons delivered daily to the extracellular fluid (ECF), only 40 to 60 nmol/L are found free in the blood.

The remainder are bound by the various buffer systems that are present in ECF and intracellular fluid (ICF), which can bind or release H+, thus preventing large changes in free H+ concentration. Quantitatively important buffers are the proteins present in the ECF (albumin and

TABLE 15.1

Causes of Respiratory Acidosis

Type of Defect

Mechanism or Type

Examples of Acute Etiologies

Examples of Chronic Etiologies

Depressed ventilatory drive

Congenital
Acquired

Drug overdose (opiates, sedatives, alcohol), general anesthesia, cerebrovascular accident, head trauma, acute meningoencephalitis, hypothermia

Primary hypoventilation (Ondine’s curse), obesity, hypoventilation syndrome, central sleep apnea, myxedema, brain tumor (primary or metastatic)

Neuromuscular disorders
Spinal cord
Peripheral nerves
Neuromuscular junction

Trauma
Vascular
Tumors
Demyelinating
Other
Phrenic nerve paralysis
Autoimmune
Iatrogenic
Infections/toxins

Cervical spinal cord injury, vascular accident, Guillain-Barré syndrome, traumatic cardiac surgery, myasthenia gravis, neuromuscular blocking agents, botulism, tetanus, tick paralysis

Vascular accident, primary or metastatic tumor, amyoltrophic lateral sclerosis, compression because of tumor, myasthenia gravis, multiple sclerosis, poliomyelitis

Ventilatory muscle weakness

Congenital
Autoimmune

Acquired

Hypokalemia, hypomagnesemia,
hypophosphatemia, ciguatera,
organophosphate and shellfish poisoning

Muscular dystrophy poliomyelitis,
dermatomyositis

Flail chest, right bandages, pneumothorax,
hemothorax

Kyphoscoliosis, morbid obesity, abdominal
distension from ascites/organomegaly,
pleural effusion, malignancy, fibrosis

Chest wall pleural diseases

Upper airways
Lower airways

Obstruction

Epiglottitis, foreign body, angioedema, acute
exacerbation of COPD, acute severe asthma

Tumor, tracheomalacia, goiter, COPD

Lung disease (parenchymal
or vascular)

High V/Q
Low V/Q (shunt)

Shock, pulmonary embolism, acute exacerbation
of COPD, pneumonia, pulmonary edema,
atelectasis

Emphysema, interstitial lung disease

Miscellaneous

Increased CO_2 production
Exogenous CO_2 inhalation

Fever, sepsis, burns, severe trauma, seizures,
accident, rebreathing

COPD, Chronic obstructive pulmonary disease; V/Q, ventilation/perfusion.

Timing of Response to Respiratory Acidosis
Generation of H^+ leading to
acidosis

accumulation of CO_2 occurs when there is a rise in tissue (e.g., muscle) metabolic rate without a reciprocal increase in blood flow to the tissue. It may also occur when there is a decrease in tissue blood flow without a reciprocal decrease in the metabolic rate of the tissue.

KIDNEY RESPONSE TO RESPIRATORY ACIDOSIS
- Buffering by
body proteins

Immediate

Minutes

- Respiratory removal of CO_2 after buffering by bicarbonate

- Renal adaptation

Days

Fig. 15.1 Timing of response to respiratory acidosis.

immunoglobulins); bone; and amino acid side groups such as carboxylates, amines, and the histidines.

The main buffer is the bicarbonate buffering system that forms carbonic acid and then CO_2, as follows:

$$H^+ + [HCO_3] \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

Eq.1

This process converts H^+ released from a nonvolatile acid anion to CO_2, allowing it to be expelled from the ECF by the respiratory actions of the lungs. If CO_2 is effectively eliminated, this reaction continues from left to right. In fact, acidemia stimulates ventilation, further lowering the $Paco_2$ and allowing more hydrogen ions to be buffered by bicarbonate. However, in some circumstances CO_2 accumulates at the tissue level, preventing the previous equation from going from left to right and may even drive the equation to the left. The

In respiratory acidosis, Equation 1 is driven to the left, leading to accumulation of H^+ and acidemia. The overall response is shown in Fig. 15.2. At first, when CO_2 levels in the extracellular fluid (ECF) become elevated, HCO_3 levels rise because of mass-action conversion of CO_2 to HCO_3 . This process is comparatively rapid (i.e., follows the onset of hypoventilation closely in time) and is not compensatory, but rather results in acidification of the plasma and the ECF because each mass action-produced HCO_3 is also accompanied by one H^+

After the induction of acidosis, the kidney responds via the increased expression of H^+ pumps in the apical membrane of tubular cells (largely in intercalated cells of the collecting duct). This process occurs over the course of several days, resulting in increased H^+ secretion. Because at this early stage all filtered HCO_3 has been reabsorbed proximally, these additional hydrogen ions are derived from CO_2 entering from the ECF (i.e., resulting in the synthesis of additional HCO_3). More importantly, this secreted H^+ is excreted in the urine. However, this mechanism of compensation is ultimately limited by the fact that for each compensating H^+ secreted, a HCO_3 is synthesized. Also adding to the HCO_3 pool is the bicarbonate formed by the original retention of CO_2, adding to the filtered load of HCO_3 . Thus, in the final phase of the renal response, most of the additional secreted H^+ now goes to reabsorb this newly added HCO_3 , and the H^+ excretion returns toward normal.

Renal Compensation in Respiratory Acidosis
Pulmonary insufficiency
↑pCO_2
↑H^+ in ECF
ACIDOSIS

↑ HCO_3^- by mass action

↑Apical H^+ pumps
Takes days…
Initially, ↑ H^+ secretion capacity
available for HCO_3^- synthesis

H^+ excreted

↑ HCO_3^- synthesized
↑ [HCO_3^-]
in plasma
Establishment of new steady state
Increased filtered load of HCO_3^-

↑ H^+ secretion capacity used for
HCO_3^- reabsorption

↓ H^+ secretion capacity available
for HCO_3^- synthesis

Maintenance of
constant but
ELEVATED [HCO_3^-]

Fig. 15.2 Renal compensation in respiratory acidosis.

In summary, the kidneys initially respond to a respiratory acidosis by increasing the excretion of H^+. Eventually, however, this compensation is limited by the increased filtered load of HCO_3 . Thus, in the case of a prolonged respiratory acidosis, one generally sees a partial renal compensation with elevated HCO_3 . Complete renal adaptation takes 3 to 5 days, and the expected change quantitatively is summarized in Table 15.2. The renal response to chronic hypercapnia is not altered by dietary sodium, chloride changes, or potassium changes, but in the presence of a chloride-deficient diet, recovery from chronic hypercapnia leads to a posthypercapnic metabolic alkalosis.7

Clinical Manifestations

Patients with acute failure of the ventilatory pump are usually dyspneic and tachypneic with overt respiratory distress, whereas patients with failure of ventilatory drive are usually hypoventilating or apneic. Hypercapnia has deleterious pulmonary and extrapulmonary consequences (Fig. 15.3). In the lungs, hypercapnia leads to pulmonary artery vasoconstriction, increases in right ventricular afterload, and right ventricular failure. In addition, hypercapnic acidosis may cause additional lung damage by increasing both nitric oxide production and inflammation and altering alveolar epithelial cells.8 Acute hypercapnia is associated with warm and flushed skin, sweating, and a bounding pulse because of increased cardiac output.9 This, however, can progress to shock because of depressed cardiac output and decreased systemic vascular resistance in severe hypercapnia.10

Hypercapnia increases cerebral blood flow and thus causes increased intracranial pressure. This is usually manifested by dyspnea, anxiety, disorientation, headache, and irritability, which can progress to somnolence, confusion, and coma (hypercapnic encephalopathy). Physical findings can include abnormal involuntary movements, including myoclonus, asterixis, tremors and, rarely, findings of increased intracranial pressure as evident by the finding of papilledema on retinal examination. Coma can occur in patients with acute exacerbations of conditions associated with chronic respiratory acidosis (e.g., chronic obstructive pulmonary disease [COPD]) because of treatment with high-flow oxygen.

Diagnosis

Whenever a respiratory acidosis is suspected, an arterial blood gas (ABG) should ideally be obtained to assess the overall acid-base status and pulmonary gas exchange. Appropriate compensatory responses should be assessed to rule out a component of respiratory acidosis in apparent metabolic disorders (see Table 15.2). However, an arterial puncture can be associated with complications, such as pain, infection, nerve injury, bleeding/hematoma, arterial aneurysm/pseudoaneurysm, dissection, thrombosis, and limb ischemia. Thus, there has been an increased use of venous blood gas (VBG) to replace frequent ABGs for diagnosis of

TABLE 15.2

Rules of Compensation in Acid-Base Disorders

Primary Acid-Base Disorder

Change in
Laboratory
Parameter

Expected Change in Laboratory Parameter with
Compensatory Response Compensatory Response

Metabolic acidosis

↓ HCO3

Respiratory alkalosis

↓ Paco2
1–1.5 mm Hg for each mEq/L decrease in HCO3
or
Expected Paco2 = 1.5 × [HCO3] + 8 ± 2

Metabolic alkalosis

↑ HCO3

Respiratory acidosis

↑ Paco2
0.6–0.7 mm Hg for each mEq/L increase in HCO3

Respiratory acidosis

↑ Paco2

Metabolic alkalosis

Respiratory alkalosis

↓ Paco2

↑ HCO3
Acute: 1 mEq/L for each 10 mm Hg ↑ in Paco2
Chronic: 4 mEq/L for each 10 mm Hg ↑ in Paco2

Metabolic acidosis

↓ HCO3
Acute: 2 mEq/L for each 10 mm Hg in ↓ Paco2
Chronic: 5 mEq/L for each 10 mm Hg in ↓ Paco2

Systemic Effects of Hypercapnia
Central Nervous System
Pulmonary Vascular
PVR
mPAP

Immunologic
Inflammatory
cytokines

Cerebral vasodilation
Cerebral blood flow

Cardiovascular
Contractility
HR
RVEF
RVSWI

Vascular

Renal
vasoconstriction

SVR

Fig. 15.3 Systemic effects of hypercapnia. HR, Heart rate; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction; RVSWI, right ventricular stroke work index; SVR, systemic vascular resistance. (From Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: A narrative review. Chest. 2018;154[1]:185–195.)

acid-base disorders in the emergency setting. Based on meta-analyses of studies looking at the correlation of results between ABG and VBG, venous and arterial pH and bicarbonate agree reasonably at all values, but the agreement is highest at normal values. However, peripheral venous CO2 (Pvco2) cannot be relied on as an absolute representation of Paco2. Despite this, a normal peripheral Pvco2 has a good negative predictive value for normal arterial Pco2, and a normal Pvco2 can be used as a screen to exclude hypercapnic respiratory disease.11

The overall assessment of the ABG helps differentiate between acute and chronic respiratory acidosis. Acute respiratory acidosis is usually caused by an abrupt decline in ventilation that causes the Paco2 to rise and pH to fall. In contrast, chronic respiratory acidosis is associated with elevated Paco2 values but only slight decreases in pH because of effective renal compensation. Sometimes an acute respiratory acidosis can be superimposed on a chronic respiratory

acidosis. In this case, the change in the pH is not as much as would be expected for a similar acute change in the Paco2 (in a person with baseline normal respiratory status). In this situation, the chronically elevated HCO3 reduces the fall in the pH and the kidney rapidly increases H+ secretion when an acute rise in Paco2 is superimposed on a chronic rise in Paco2 12

Hypercapnia is usually present along with hypoxemia because alveolar hypoventilation causes a proportional fall in alveolar oxygen pressure (PAO2), according to the alveolar gas equation:

$$PAO2 = PiO2 - [PaCO2 / R]$$

where arterial Pco2 is assumed to be nearly the same as alveolar Pco2, PiO2 is the inspired Po2 (i.e., the inspired oxygen fraction [Fio2] multiplied by the difference of barometric pressure and 47 [water vapor pressure at body temperature]), and R is the respiratory exchange ratio

(ratio between the amount of CO_2 produced in metabolism and O_2 used). At sea level with 21% FiO_2, this can be simplified to the following:

$$PAO_2 = 150 - [1.25 \times PaCO_2]$$

Calculating alveolar PO_2 using this relationship permits determination of the alveolar-arterial oxygen pressure difference (commonly called the “A–a gradient”). The normal A–a gradient is estimated by the following (Age + 10)/4 (i.e., ranges between 5 and 25 mm Hg). This calculation distinguishes between pure hypoventilation as an explanation for hypoxemia (in which case the A–a gradient is normal) and other mechanisms such as low ventilation-perfusion (V/Q) ratios and right-to-left shunt (in which case the A–a gradient is increased). The use of the alveolar gas equation is demonstrated in Box 15.1

Management

An overview of the management of acute respiratory acidosis is presented in Fig. 15.4. The management of respiratory acidosis is dependent on the cause of the acidosis, and treatment of the underlying cause can often reverse the respiratory acidosis in acute ventilatory failure. However, supportive treatment is often necessary, especially when the etiology is not rapidly or fully reversible. Immediate treatment involves restoring the patency of the airway (if compromised) and delivery of oxygen to maintain a PaO_2 of greater than 60 mm Hg and a peripheral oxygen saturation of greater than 90%. Several oxygen delivery devices are available (Table 15.3).

Examples Showing Use of the Alveolar Gas Equation

BOX 15.1

At sea level, $PAO_2 = 150 - [1.25 \times PaCO_2]$

Normal A–a gradient = 5 to 25 mm Hg

PaO_2	$PaCO_2$	PAO_2	A–a Gradient	Possible Cause
70	40	100	30	V/Q mismatch
70	60	75	5	Hypoventilation

If appropriate oxygenation cannot be achieved with these oxygen delivery devices or if increased work of breathing is leading to impending respiratory fatigue, either noninvasive ventilation (NIV) or invasive mechanical ventilation can be used. NIV is delivered via tight-fitting face masks and is used for patients with acute respiratory failure who will benefit from ventilatory support but may not need conventional mechanical ventilation (which requires endotracheal intubation). Ideally, NIV is reserved for patients without altered mentation and who are hemodynamically stable. There are three modes of ventilation available for NIV: (1) continuous positive airway pressure (CPAP), (2) bilevel positive airway pressure (BiPAP), and (3) pressure support ventilation (PSV). The latter two modes of ventilation (i.e., BiPAP and PSV) are also referred to as noninvasive positive pressure ventilation (NIPPV). Endotracheal intubation is necessary when airway protection is paramount or with failure of NIV.

In patients with inadequate ventilatory drive despite a presumably normal ventilatory pump, management focuses on restoring normal alveolar ventilation. In the setting of acute central hypoventilation, invasive mechanical ventilation is usually more rapid and protects the airway reliably versus NIV. In chronic neuromuscular disorders, NIV is often used (e.g., elective initiation of noninvasive ventilation is becoming a standard of care in motor neuron disease patients with progressive ventilatory impairment).5

In acute respiratory distress syndrome (ARDS), normal tidal volumes can cause regional overdistension (so-called volutrauma) and repetitive opening and closing of alveoli can cause lung injury (sometimes called atelectrauma). Lung-protective ventilation using lower tidal volumes (less than 6 mL/kg predicted body weight) to maintain a plateau pressure less than 30 mm Hg prevents barotrauma and has been shown to reduce mortality.13 Because of this, the respiratory rate is set at a higher rate on the ventilator to maintain minute
ventilation. This often requires a strategy of “permissive” hypercapnia, which

Treatment of Acute Respiratory Acidosis
Acute respiratory distress with hypercapnia
If airway not patent:
1. Remove foreign body
2. Heimlich maneuver
3. Consider early intubation or tracheostomy

Assess airway patency
Airway patent
Identify features of severe respiratory failure
(any of the following:)
1. Increased work of breathing
2. Severe hypoxia ($PaO_2/Fio_2<200$)
3. Severe hypercapnia ($PaCO_2>45$)

If yes, ventilatory support is indicated
Can NIV or HHFNC be considered?
Exclude the following:
1. Severe shock
2. Severely altered mentation, coma, seizures
3. Inability to protect airways
4. Hemetemesis or recurrent vomiting
5. Laryngeal edema, facial trauma, recent head
and neck surgery

Consider invasive mechanical
ventilation if:
1. Not a candidate for NIV
2. No improvement with NIV

Trial of NIV or HHFNC

Reassess response periodically

Worsening or lack of

improvement

No

Supportive treatment in all patients
1. Treat underlying cause, e.g., bronchodilators in COPD, antibiotics in pneumonia
2. Supplemental oxygen to maintain PaO2>60 mm Hg and O 2 saturation >90%

Wean from
ventilatory support

Improvement

Fig. 15.4 Treatment of acute respiratory acidosis. HHFNC, Humidified high-flow nasal cannula; NIV, noninvasive ventilation.

TABLE 15.3

Oxygen Delivery Devices

System or Device	Flow Rates (L/min)	Reservoir Volume (mL)	Fio_2 (%)
Low-flow nasal canula	1–6	None	Each L/min adds 4% Fio_2 above room air
Standard face mask	6–12	100–200	35–60
Venturi mask	Fixed flow based on adapter	600–1000	24–40
Nonrebreather mask	>10	600–1000	80–100
High-flow nasal canula	40–60	None	30–100

can lead to a persistent respiratory acidosis with a pH of less than 7.3. In this setting, if the kidneys are not able to generate a compensatory metabolic alkalosis, bicarbonate infusions or renal replacement therapy have been used to keep the pH at least greater than 7.15. Detailed protocols are available to guide this ventilatory strategy.[14] Although permissive hypercapnia was previously thought to be benign, it has several physiologic consequences, and alternative interventions, including prone ventilation, ultralow tidal volume ventilation, extracorporeal membrane oxygenation (ECMO), and extracorporeal CO_2 removal ($ECCO_2R$), are being used to minimize hypercapnia or even aim for normocapnia.[8] Permissive hypercapnia can be dangerous in patients with traumatic brain injury or in those with cerebrovascular disease because it can trigger increased cerebral blood with increased intracranial pressure.

ECMO is reserved for patients with refractory severe ARDS (Pao_2:Fio_2 ratio < 60 mm Hg) after adequate lung-protective ventilation and correction of volume overload have failed to improve oxygenation.[15]

$ECCO_2R$ is a novel extracorporeal technique whose objective is the decarboxylation of blood. This leads to correction of hypercapnia and resolution of respiratory acidosis. This therapy is being tested in clinical trials of acute severe exacerbations of COPD to prevent intubation, to minimize invasive mechanical ventilation, and to facilitate weaning from mechanical ventilation. Additional clinical scenarios where it may be useful are in ARDS and as a bridge to lung transplantation.[16]

It is often not possible to reverse the cause of chronic respiratory acidosis. Adequate airway drainage, relief of bronchospasm, treatment of pulmonary infections, and treatment of heart failure may lead to improvement in the hypercapnia. In some situations (e.g., in advanced COPD or chronic neuromuscular diseases causing ventilator pump failure), patients may require long-term use of NIV or invasive mechanical ventilation.[17,18]

RESPIRATORY ALKALOSIS

In respiratory alkalosis, the arterial pH increases primarily because of a decrease in whole body CO_2 stores, which are indirectly assessed by the $Paco_2$. Respiratory alkalosis is diagnosed by the finding of a $Paco_2$ less than 35 mm Hg (4.7 kPa) in patients with an increased arterial pH (>7.45). Respiratory alkalosis is commonly associated with a compensatory metabolic acidosis. This relationship, as reflected by the simplified Henderson Hasselbalch equation, is as follows:

$[HCO_3]$

results in ↑ pH

↓ $[PaCO_2]$

Failure to measure the systemic pH commonly leads to mislabeling of patients with respiratory alkalosis as having a primary metabolic acidosis when only the HCO_3 level as measured in the blood chemistries is reviewed. As discussed earlier, pseudorespiratory alkalosis refers to the presence of arterial eucapnia (or hypocapnia) with severe venous hypercapnia in patients with profound circulatory failure with preserved respiratory function. This can also be seen because of hyperventilation when such patients are placed on mechanical ventilation.

TABLE 15.4

Causes of Respiratory

Mechanism	Causes
Hypoxia	High altitude, cyanotic congenital heart disease, congestive heart failure, intrinsic lung disease, laryngospasm
Pulmonary receptor stimulation	Pneumonia, asthma, pulmonary edema, pulmonary

embolism, pulmonary fibrosis

Drugs

Salicylates, alkaloids, theophylline, progesterone, catecholamines

Central nervous system stimulation

Primary hyperventilation syndrome, subarachnoid hemorrhage, cerebrovascular accident, pain, trauma

Miscellaneous

Pregnancy, cirrhosis, sepsis, fever, anxietyhyperventilation syndrome

Alkalosis

Modified from Halperin, ML, Goldstein MB, Kamel KS. Fluid, Electrolyte, and Acid-Base Physiology: A Problem-Based Approach, 4th ed. Elsevier; 2010:222–239.

PATHOPHYSIOLOGY

Respiratory alkalosis is the most common acid-base disorder but often is not considered a serious clinical problem even though the mortality rate in patients with respiratory alkalosis is higher than the elderly general population.[19]

Paco2 is normally maintained in the normal range by control of the ventilatory drive. Chemoreceptors in the brain (central chemoreceptors) and in the carotid bodies (peripheral chemoreceptors) sense H+ in the blood and adjust the ventilation to regulate Paco2 and pH. Respiratory alkalosis is usually induced by a process involving hyperventilation. This leads to the shifting of Equation 1 to the right, effectively reducing the H+ concentration and causing an increase in the systemic pH. The causes of respiratory alkalosis include central causes, hypoxemic causes (leading to stimulation of peripheral chemoreceptors), pulmonary causes (leading to stimulation of peripheral afferent receptors), drugs, and some miscellaneous causes (Table 15.4). Common conditions associated with respiratory alkalosis include pregnancy (in which progesterone-induced hyperventilation leads to a mild respiratory alkalosis most evident in the third trimester)[20]; cirrhosis (characterized by both hypoxemia and stimulation of respiratory drive via progesterone, ammonia, vasoactive intestinal peptide, and glutamine); and iatrogenic hyperventilation in patients on mechanical ventilation.

Hyperventilation syndrome is a type of dysfunctional breathing in which an inappropriate increase in minute ventilation beyond metabolic needs leads to a respiratory alkalosis and is associated with a wide range of symptoms without a clear organic precipitant. It is caused by stress and anxiety, both of which act on the behavioral respiratory control system. The hyperventilation ceases during sleep, when the behavioral control system is inactive and only the metabolic system is controlling breathing. The diagnosis of hyperventilation syndrome should be a diagnosis of exclusion.

RESPONSE TO RESPIRATORY ALKALOSIS

An increase in the pH because of respiratory alkalosis can be acute or chronic. Excess HCO3 levels are initially buffered by release of H+ from intracellular sources to reduce HCO3 levels. This buffering is complete in minutes and persists for at least 2 hours.21 Within 2 to 3 days, there is progressive decrease in renal H+ secretion (which leads to reduced generation of new HCO3 to replace the amount used for buffering the daily acid load) and increased HCO3 secretion by reduced reclamation of filtered HCO3 , both of which lead to reductions in serum HCO3 aimed at restoring physiologic pH. Therefore, acute respiratory alkalosis is associated with high bicarbonate levels because there has not been sufficient time to lower the HCO3 levels, and chronic respiratory alkalosis is associated with low to normal HCO3 levels. The stimulus for renal compensation is not pH, but rather Pco2 22

Clinical Manifestations

Because the primary cause of all respiratory alkaloses is hyperventilation, most patients present with dyspnea. The specific clinical features depend on its duration, its severity, and the underlying disease process. Acute respiratory alkalosis can cause light-headedness, confusion, peripheral and circumoral paresthesias, cramps, and syncope. The mechanism of these symptoms is cerebral vasoconstriction causing decreased cerebral blood flow.23 Carpopedal spasm (which can often be elicited as the Trousseau sign or the Chvostek sign) may occur in severe cases because of decreased levels of ionized calcium in the blood (because of change in the degree of protein binding with change in the pH). Additional physical examination findings may include tachycardia, tachypnea, diaphoresis, hypertension or hypotension, and altered mental status. Chronic respiratory alkalosis is usually asymptomatic and has no distinctive signs.

Cardiovascular effects of hypocapnia in healthy and alert patients are minimal but can be significant in patients who are anesthetized, critically ill, or receiving mechanical ventilation. Cardiac output and systemic blood pressure may fall in these passively hyperventilated patients because of the effects of sedation and positive-pressure ventilation on venous return, systemic vascular resistance, and heart rate. Cardiac rhythm disturbances can also occur because of leftward shift of the hemoglobin-oxygen dissociation curve causing tissue hypoxia.

High altitude illness, which is usually associated with acute respiratory alkalosis, includes a spectrum of disorders that are important to recognize. Acute mountain sickness (AMS) is diagnosed clinically based on the appearance of typical symptoms in a person who ascends to a high altitude (generally >2000 m). Symptoms include headache, fatigue, lightheadedness, anorexia, nausea, vomiting, frequent awakening, and dyspnea with exertion. This can progress to high altitude cerebral edema (HACE), which is heralded by the onset of generalized neurologic symptoms.24

Diagnosis

A suspicion of respiratory alkalosis based on clinical features should lead to the measurement of an ABG. Failure to measure the systemic pH commonly leads to mislabeling of patients with respiratory alkalosis as having a primary normal anion gap metabolic acidosis when only the HCO3 level as measured in the blood chemistries is reviewed. This is very common in pregnancy and cirrhosis, which are usually associated with a respiratory alkalosis without overt respiratory distress.

Treatment

The treatment of respiratory alkalosis is primarily directed at correcting the underlying cause. Respiratory alkalosis itself is rarely life threatening and correcting significant hypoxemia (if present) is more critical.

If the $Paco_2$ is corrected rapidly in patients with chronic respiratory

alkalosis, metabolic acidosis may develop because of persistence of the renal compensatory drop in serum bicarbonate.

In mechanically ventilated patients who have respiratory alkalosis, the minute ventilation can be decreased by lowering the tidal volume and/or the respiratory rate. Inadequate sedation and pain control may contribute to respiratory alkalosis in patients breathing over the set ventilator rate.

Acute management of patients who are hyperventilating includes reassurance, removal of any stressors, and breathing retraining with a focus on abdominal (diaphragmatic) breathing. Rebreathing of carbon dioxide (CO_2) by breathing into a paper bag is not recommended because it can cause significant hypoxemia, especially in the presence of underlying respiratory or cardiovascular disease. If conservative treatment is not successful, small doses of short-acting benzodiazepines can be used to decrease hyperventilation. Long-term management requires identification and treatment of underlying conditions and precipitants and cognitive behavioral therapy.

MIXED ACID-BASE DISORDERS

Mixed acid-base disorders refer to the presence of more than one acidbase disorder concomitantly. Careful analysis of the ABG is essential to uncover the presence of a mixed acid-base disorder because they can be an important clue to the underlying etiology. An appropriate compensatory response to a primary acid-base disorder is not considered as indicative of a mixed acid-base disorder (see Table 15.2 for the expected compensatory response to the primary acid-base disorders). The effect of a mixed acid-base disorder on the systemic pH can either be additive or can help limit the change in pH (e.g., the presence of both a metabolic acidosis and respiratory acidosis leads to a more severe acidosis, whereas the presence of a concomitant metabolic acidosis and respiratory alkalosis could lead to a minimal change in systemic pH). Triple acid-base disorders can also be seen and involve a combination of two or more independent processes causing metabolic acidosis (leading to a combined high anion gap metabolic acidosis and normal anion gap metabolic acidosis) in the presence of a respiratory disorder.

Diagnosis

Using the following approach to acid-base analysis can help correctly identify mixed acid-base disorders:

Step 1: Look at the pH to classify if the person is acidemic or alkalemic.

Step 2: Determine whether the primary disorder is metabolic or respiratory.

Step 3: If the primary disorder is respiratory, is it chronic or acute? If the primary disorder is metabolic, is the anion gap elevated?

Step 4: Is the compensation for the primary disorder appropriate (using Table 15.2)? If not, a mixed acid-base disorder is present.

Step 5: In cases with a high anion gap metabolic acidosis, is there an additional metabolic disorder?

A simplified approach to the identification of mixed acid-base disorders is presented in Fig. 15.5, and the common mixed acid-base disorders are discussed later.

METABOLIC ACIDOSIS AND RESPIRATORY ACIDOSIS

In the presence of metabolic acidosis, the expected compensatory respiratory response is assessed using the Winters formula (Expected $Paco_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$). If the measured $Paco_2$ exceeds the expected $Paco_2$ by 5 mm Hg, this indicates a concomitant respiratory acidosis. Common clinical scenarios where this is seen include

Identification of Mixed Acid-Base Disorders

What’s the
systemic pH?

pH > 7.45
alkalosis

pH < 7.35
acidosis

Respiratory
(PaCO_2 high)

Metabolic
(HCO_3^- low)

Respiratory
(PaCO_2 low)

Metabolic
(HCO_3^- high)

Is the metabolic
compensation
appropriate?

Is the respiratory
compensation
appropriate?

Is the metabolic
compensation
appropriate?

Is the respiratory
compensation
appropriate?

Yes

Isolated
respiratory
acidosis

No

No

Combined metabolic
and respiratory
disorder*

Yes

Yes

Isolated
metabolic
acidosis*

Isolated
respiratory
alkalosis

No

No

Combined metabolic
and respiratory
disorder*

Yes

Isolated
metabolic
alkalosis

Fig. 15.5 Approach to identification of mixed acid-base disorders. *Evaluate for the presence of concomitant normal gap and high anion gap metabolic acidosis in every case of high anion gap metabolic acidosis.

cardiopulmonary arrest, severe kidney injury in patients with hypercapnic respiratory failure, shock with lactic acidosis in severe respiratory failure, respiratory muscle fatigue with septic shock, and in respiratory muscle weakness because of severe electrolyte disturbances (hypokalemia, hypophosphatemia) caused by prolonged diarrhea. The treatment should be focused on addressing the causes of the respiratory acidosis and the metabolic acidosis.

METABOLIC ACIDOSIS AND RESPIRATORY ALKALOSIS

In the presence of a metabolic acidosis, the expected compensatory respiratory response is assessed using the Winters formula (as above). If the measured Paco2 is lower than this expected Paco2 by 5 mm Hg, it indicates the presence of a concomitant respiratory alkalosis. Because of the opposing effects on systemic pH, the concomitant presence of these two disorders leads to a minimal change in pH. A classic condition associated with this pattern is salicylate intoxication, which leads to central stimulation of the ventilatory drive associated with a high anion gap metabolic acidosis because of a shift from oxidative phosphorylation to anerobic metabolism and increased production of lactic acid and ketoacids. Thus, salicylate toxicity should always be ruled out in patients who present to the hospital with this mixed acidbase disorder. This combination is also commonly seen in critically ill patients with metabolic acidosis caused by lactic acidosis or severe kidney injury in combination with hyperventilation caused by fever, sepsis, hypoxia, and/or mechanical hyperventilation. Another common scenario is hepatic failure in which situation hyperventilation leads to respiratory alkalosis and metabolic acidosis is caused by lactic acidosis or acute kidney injury (AKI) or both.

METABOLIC ALKALOSIS AND RESPIRATORY ALKALOSIS

Metabolic alkalosis is associated with a compensatory respiratory acidosis. The expected increase in Paco2 is 0.6 to 0.7 mm Hg for each mEq/L increase in HCO3 . If the measured Paco2 is less than this expected Paco2, a concomitant respiratory alkalosis is present. A marked rise in the pH may result in this mixed acid-base disorder. Common conditions associated with respiratory alkalosis like cirrhosis, pregnancy, and mechanically hyperventilated patients can often develop a metabolic alkalosis in the setting of vomiting, prolonged nasogastric suction, diuretic use, severe hypokalemia, or with alkali administration (e.g., citrate in blood products, exogenous bicarbonate supplements).

METABOLIC ALKALOSIS AND RESPIRATORY ACIDOSIS

Metabolic alkalosis is associated with a compensatory respiratory acidosis. The expected increase in Paco2 is 0.6 to 0.7 mm Hg for each mEq/L increase in HCO3 . If the measured Paco2 is higher than this expected Paco2, a concomitant respiratory acidosis is present. Common scenarios that present with this mixed disorder include acute exacerbations of COPD with cor pulmonale, or decompensated heart failure leading to acute respiratory acidosis and then metabolic alkalosis because of aggressive diuresis. Alternatively, metabolic alkalosis with prolonged vomiting or diuretic use can be complicated by respiratory muscle paralysis because of severe electrolyte disturbances (hypokalemia, hypophosphatemia).

nasogastric suction in patients with uremia or diabetic ketoacidosis can also present with the same problem.

MIXED METABOLIC ACIDOSIS

The approach to the evaluation of a metabolic acidosis begins with evaluation of the anion gap. In the setting of a high anion gap (AG) acidosis, further characterization of the metabolic acid-base disorder is important. For this, the relationship between the increment in the anion gap (delta AG) and the decrement in the serum bicarbonate concentration (delta HCO3) is reviewed. When the delta HCO3 is greater than the delta AG, it suggests that a mixed high AG and hyperchloremic normal gap metabolic acidosis is present. Common causes of a mixed high AG and normal gap acidosis include severe AKI or chronic kidney disease, ketoacidosis or lactic acidosis with concomitant diarrhea, and recovery phase of diabetic ketoacidosis.

METABOLIC ACIDOSIS AND METABOLIC ALKALOSIS

As discussed previously, in the setting of a high AG acidosis, the delta AG and the delta HCO3 are calculated to look for an additional metabolic disorder. When the delta HCO3 is less than the delta AG, a mixed metabolic alkalosis and high AG metabolic acidosis is likely to be present. Common causes for this mixed disorder include metabolic alkalosis induced by vomiting or diuretic use in patients with diabetic ketoacidosis or lactic acidosis because of liver cirrhosis. Prolonged

TRIPLE ACID-BASE DISORDERS

Typical triple acid-base disorders involve the presence of a mixed metabolic disorder along with either a respiratory acidosis or a respiratory alkalosis. In the example previously cited, vomiting or diuretic use in patients with diabetic ketoacidosis or lactic acidosis because of liver cirrhosis can lead to a mixed metabolic acidosis and metabolic alkalosis—if such patients then develop a hypercapnic ventilatory failure, this will lead to a triple disorder with additional respiratory acidosis. Another scenario involves the presence of an acute or chronic respiratory disorder in combination with a metabolic disorder (e.g., a COPD patient with chronic respiratory acidosis who gets intubated and mechanically ventilated then develops a sudden decrease in Paco2). In the presence of an underlying compensatory metabolic alkalosis, a new metabolic alkalosis caused by vomiting or nasogastric suction could lead to a rapid elevation in the pH.

Treatment of Mixed Acid-Base Disorders

The management of mixed acid-base disorders involves treating the underlying cause of the acid-base disorder and treating individual components (i.e., each simple acid-base disorder). Figs. 15.6 to 15.9

Treatment of Metabolic Acidosis and Respiratory Acidosis

Severe hypercapnic
encephalopathy or
hemodynamic instability

Metabolic acidosis
and respiratory acidosis

Implement causespecific measures

No

Yes

Administer O2 via nasal cannula or
Venturi mask; correct reversible causes
of pulmonary dysfunction with
antibiotics, bronchodilators, and
corticosteroids as needed

Consider use of noninvasive ventilation
through a nasal or full face mask

Consider intubation and use of standard
ventilator support if noninvasive ventilation
fails or is not applicable
PaO_2 <55 mm Hg (7.3 kPa), CO_2
retention worsens, mental status
deteriorates, or hemodynamic instability

Correct reversible causes of pulmonary
dysfunction with antibiotics, bronchodilators,
and corticosteroids as needed

Advanced renal failure, severe
fluid excess, congestive
heart failure
Yes
Dialysis or ultrafiltration with
alkali supplementation

No
Blood pH <7.10

No
$PaCO_2$ >50 mm Hg (6.7 kPa)

Yes
Alkali administration

Fig. 15.6 Treatment of metabolic acidosis and respiratory acidosis.

Treatment of Metabolic Alkalosis and Respiratory Alkalosis

Metabolic alkalosis
and respiratory alkalosis

Implement causespecific measures
Mechanical
hyperventilation

Hypoxemia

Extracellular
fluid volume
depletion

Administer
NaCl, withhold
diuretics

Congestive
heart
failure

K+
depletion

Administer
KCl

Acetazolamide,
ultrafiltration,
and NaCl
infusion

Severe
renal
failure

Low HCO3
dialysate,
ultrafiltration,
and NaCl
infusion

Vomiting,
gastric
drainage

Oxygen therapy

Addition of dead space or
change mode of ventilation
(e.g., assist-control to mandatory
ventilation)

HCl
secretion
inhibitors

If persistent,
sedation with
or without
skeletal muscle
paralysis

Blood pH
>7.55

Hemodynamic
instability,
altered mental
status, or cardiac
arrhythmias

Consider measures to correct blood
pH to 7.50 by:
1. Reducing [HCO3]: acetazolamide;
ultrafiltration and isotonic saline
replacement; hemodialysis using a
low HCO3 dialysate
2. Increasing PaCO2: rebreathing into
a closed system; control hypoventilation by ventilator with or without
skeletal muscle paralysis

Fig. 15.7 Treatment of metabolic alkalosis and respiratory alkalosis.

Treatment of Metabolic Alkalosis and Respiratory Acidosis
Severe hypercapnic
encephalopathy
or hemodynamic instability

Metabolic alkalosis
and respiratory acidosis

Implement cause-specific
measures

Yes

No
Administer O2 via nasal cannula or
Venturi mask; correct reversible
causes of pulmonary dysfunction
with antibiotics, bronchodilators,
and corticosteroids as needed

PaO2 <55 mm Hg (7.3 kPa),
CO2 retention worsens,
mental status deteriorates,
or hemodynamic instability

Consider use of noninvasive
ventilation through
a nasal or full face mask

Consider intubation and use
of standard ventilator support
if noninvasive ventilation
fails or is not applicable

Correct reversible causes of
pulmonary dysfunction with
antibiotics, bronchodilators,
and corticosteroids as needed

Extracellular fluid
volume depletion

K+
depletion

Congestive
heart failure

Severe renal
failure

Vomiting,
gastric drainage

Plasma
[HCO3–] >40 mmol/L

Administer
isotonic saline,
withhold diuretics

Administer
KCI

Acetazolamide,
ultrafiltration with
isotonic saline
replacement

Low
HCO3– dialysate,
ultrafiltration with
isotonic saline
replacement

HCI secretion
inhibitors

Consider
acetazolamide

Fig. 15.8 Treatment of metabolic alkalosis and respiratory acidosis.

Treatment of Metabolic Acidosis and Respiratory Alkalosis
Metabolic acidosis
and respiratory alkalosis

Implement causespecific measures

Salicylate
intoxication

Hypoxemia

Mechanical
hyperventilation

Yes

Yes
Consider:
Induced emesis
Gastric lavage
Activated charcoal
with sorbitol
Forced diuresis
Urinary alkalinization
Hemodialysis
(severe poisoning)

Oxygen
therapy

Sepsis,
circulatory
failure, hepatic
failure, other
causes

Yes

Yes

Addition of
dead space
or change
mode of
ventilation
(e.g., assistcontrol to
mandatory
ventilation)

Specific
measures
tailored to the
underlying
cause

Advanced renal failure,
severe fluid excess,
congestive heart failure
Yes
Dialysis or

ultrafiltration
with alkali
supplementation

No
Blood
pH <7.10
Yes
Administer
alkali

If persistent,
sedation with
or without
skeletal muscle
paralysis

Fig. 15.9 Treatment of metabolic acidosis and respiratory alkalosis.

provide algorithms for the management of some of the more common mixed disorders. Certain disorders (e.g., combined metabolic and respiratory acidosis) lead to a severe change in the pH, and treatment of just one of the simple acid-base disorders can restore the pH to an acceptable level. On the other hand, disorders that have components

with opposing effects on the pH should be approached with caution (e.g., although a mixed metabolic acidosis and respiratory alkalosis may have a minimal effect on the pH, complete correction of one of the simple acid-base disorders could lead to a severe acid-base disorder).

SELF-ASSESSMENT QUESTIONS

1. A 26-year-old woman with asthma was brought to the emergency department for severe shortness of breath and appeared to be struggling for air. Her examination was notable for tachypnea with very shallow breaths. She had extensive wheezing throughout both lung fields and audible stridor. Her lab results are as follows:

ARTERIAL

A. What acid-base disturbance is present?
B. Is compensation appropriate?
C. What is the underlying disorder that caused this problem?

2. A 77-year man is brought to the ICU after being found unresponsive. His initial lab results are as follows:

VENOUS

ARTERIAL

VENOUS

pH

Pco2

Pao2

Na

K

Cl

HCO 3

pH

K

Cl

61

55

138

4.5

104

26

Pao2

Na

7.24

Pco2

HCO 3–

7.07

28

59

135

2.5

100

8

What is the acid-base disturbance?

REFERENCES

1. Halperin ML, Goldstein MB, Kamel KS. Fluid, Electrolyte, and Acid-Base Physiology: A Problem-Based Approach. 4th ed. Philadelphia, PA: Saunders/ Elsevier; 2010:222–239.
2. Epstein SK, Singh N. Respiratory acidosis. Respir Care. 2001;46(4):366–383.
3. Adrogue HJ, et al. Arteriovenous acid-base disparity in circulatory failure: studies on mechanism. Am J Physiol. 1989;257(6 Pt 2):F1087–F1093.
4. Adrogue HJ, et al. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. N Engl J Med. 1989;320(20):1312–1316.
5. Hill N. Murray & Nadel’s Textbook of Respiratory Medicine, in Acute Ventilatory Failure. Philadelphia, PA: Elsevier Saunders; 2016:1723–1739.
6. Marino PL, Marino PL. Marino’s the ICU Book. 4th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1059.
7. Ferrara A, et al. [Physiopathological and clinical data on post-hypercapnic metabolic alkalosis. a case of severe hypercapnia treated with drugs and in an “iron lung”]. Minerva Med. 1979;70(1):67–73.
8. Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. Chest. 2018;154(1):185–195.
9. Rothe CF, Maass-Moreno R, Flanagan AD. Effects of hypercapnia and hypoxia on the cardiovascular system: vascular capacitance and aortic chemoreceptors. Am J Physiol. 1990;259(3 Pt 2):H932–H939.
10. Potkin RT, Swenson ER. Resuscitation from severe acute hypercapnia. determinants of tolerance and survival. Chest. 1992;102(6):1742–1745.
11. Bloom BM, et al. The role of venous blood gas in the emergency department: a systematic review and meta-analysis. Eur J Emerg Med. 2014;21(2):81–88.
12. Ingram Jr RH, Miller RB, Tate LA. Acid-base response to acute carbon dioxide changes in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1973;108(2):225–231.

13. Acute Respiratory Distress Syndrome N, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–1308.
14. NHLBI ARDS Network.http://www.ardsnet.org/tools.shtml. 2021.
15. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377(6):562–572.
16. Giraud R, et al. The use of extracorporeal CO2 removal in acute respiratory failure. Ann Intensive Care. 2021;11(1):43.
17. Struik FM, et al. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data metaanalysis. Respir Med. 2014;108(2):329–337.
18. Radunovic A, et al. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;10:CD004427.
19. Raphael KL, et al. Bicarbonate concentration, Acid-base status, and mortality in the health, Aging, and Body composition study. Clin J Am Soc Nephrol. 2016;11(2):308–316.
20. Beers K, Patel N. Kidney physiology in pregnancy. Adv Chronic Kidney Dis. 2020;27(6):449–454.
21. Arbus GS, et al. Characterization and clinical application of the “significance band” for acute respiratory alkalosis. N Engl J Med. 1969;280(3):117–123.
22. Schwartz WB, Cohen JJ. The nature of the renal response to chronic disorders of acid-base equilibrium. Am J Med. 1978;64(3):417–428.
23. Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest. 1948;27(4):484–492.
24. Bartsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. N Engl J Med. 2013;368(24):2294–2302.

16

Introduction to Glomerular Disease: Clinical Presentations

Jürgen Floege, Richard J. Johnson

DEFINITION

Glomerular disease has clinical presentations that vary from the asymptomatic individual who is found to have hypertension, edema, hematuria, or proteinuria at a routine medical assessment to a patient who has fulminant illness with acute kidney injury (AKI) possibly associated with life-threatening extrarenal disease (Fig. 16.1). The most dramatic symptomatic presentations are uncommon. Asymptomatic urine abnormalities are much more common but may also indicate a wide range of nonglomerular urinary tract diseases.

CLINICAL EVALUATION OF GLOMERULAR DISEASE

The history, physical examination, and diagnostic investigations are aimed at excluding nonglomerular disease, finding evidence of associated multisystem disease, and establishing kidney function.

History

The majority of glomerular diseases do not lead to symptoms that patients will report. However, specific questioning may reveal edema, hypertension, foamy urine, or urinary abnormalities noted during routine testing (e.g., during scheduled medical examinations). Multisystem diseases associated with glomerular disease include diabetes, hypertension, amyloid, lupus, and vasculitis. Classic genetic causes of kidney disease may include Alport syndrome, especially if associated with hearing loss (see Chapter 48); familial forms of immunoglobulin A (IgA) nephropathy (see Chapter 24); focal segmental glomerulosclerosis (FSGS) secondary to mutations in podocin or other molecules involved in glomerular permeability (see Chapters 19 and 20); complement-mediated glomerulonephritis (GN) (see Chapter 23); thrombotic microangiopathies (see Chapter 30); and other rare conditions (see Chapter 29). Morbid obesity can be associated with FSGS. Certain drugs and toxins may cause glomerular disease, including nonsteroidal antiinflammatory drugs (NSAIDs) and interferon in minimal change disease (MCD); penicillamine, NSAIDs, and mercury (e.g., skin-lightening creams) in membranous nephropathy; pamidronate and heroin in FSGS; smoking in nodular glomerulosclerosis; and cyclosporine, tacrolimus, mitomycin C, and oral contraceptives in hemolytic uremic syndrome (HUS). Recent or persistent infection, especially streptococcal or staphylococcal infection, endocarditis, and certain viral infections (see Chapters 22, 57, and 58) also may be associated with a variety of glomerular diseases.

Malignancies associated with glomerular disease include lung, breast, and gastrointestinal (GI) adenocarcinoma in membranous nephropathy; Hodgkin disease in MCD; non-Hodgkin lymphoma in membranoproliferative GN; and renal cell carcinoma in amyloid disease (see Chapter 28). Kidney disease is occasionally the first manifestation of a tumor.

Physical Examination

The presence of dependent pitting edema suggests nephrotic syndrome, heart failure, or cirrhosis. In the nephrotic patient, edema is often periorbital in the morning (Fig. 16.2), whereas the face is not affected overnight in edema associated with heart failure (edema distributes by gravity, and patients with heart failure often cannot lie flat due to orthopnea or cirrhosis (because of pressure on the diaphragm from ascites). Severe nephrosis can lead to edema of genitals and the abdominal wall, ascites, and pleural effusions. Edema is unpleasant, leading to feelings of tightness in the limbs and a bloated abdomen, with practical problems of clothes and shoes no longer fitting. Surprisingly, however, edema may become massive in nephrotic syndrome before patients seek medical help; fluid gains of 20 kg (44 lb) or more are not unusual (Fig. 16.3). The edema becomes firm and stops pitting only when it is long-standing. In children, fluid retention may be striking with acute GN (nephritic syndrome). Chronic hypoalbuminemia is also associated with white nails or white bands if nephrotic syndrome is transient (Muehrcke lines; Fig. 16.4). Xanthelasmas may be present as a result of the hyperlipidemia associated with long-standing nephrotic syndrome (Fig. 16.5).

Pulmonary signs suggest one of the so-called pulmonary-renal syndromes (see Boxes 25.3 and 25.4). Palpable purpura may be seen in vasculitis, systemic lupus, cryoglobulinemia, or endocarditis.

Laboratory Studies

Assessment of kidney function and careful examination of the urine are critical (see Chapters 3 and 4). The quantity of urine protein and the presence or absence of dysmorphic red cells and casts help classify the clinical presentation (see Fig. 16.1).

Useful serologic tests include antiphospholipase A2 receptor and other autoantibodies (see Chapter 21) for membranous GN, antinuclear and anti-DNA antibodies for lupus, cryoglobulins and rheumatoid factor suggesting cryoglobulinemia, anti–glomerular basement membrane (anti-GBM) antibodies for Goodpasture disease, antineutrophil cytoplasmic autoantibody (ANCA) for vasculitis, and

Clinical Presentations of
Glomerular Disease
Asymptomatic
Proteinuria 150 mg to 3 g per day
Hematuria >2 red blood cells
per high-power field in spun urine
or >10 × 106 cells/L
(red blood cells usually dysmorphic)

Macroscopic hematuria
Brown/red painless hematuria
(no clots); typically coincides with
intercurrent infection
Asymptomatic hematuria ± proteinuria
between attacks

Nephritic syndrome
Oliguria
Hematuria: red cell casts
Proteinuria: usually <3 g/day
Edema
Hypertension
Abrupt onset, usually
self-limiting

Nephrotic syndrome
Proteinuria: adult >3.5 g/day;
child >40 mg/h/m2
Hypoalbuminemia <3.5 g/dL
Edema
Hypercholesterolemia
Lipiduria

Fig. 16.3 Nephrotic Edema. Severe peripheral edema in nephrotic syndrome; note the blisters caused by intradermal fluid.

Rapidly progressive glomerulonephritis
Renal failure over days/weeks
Proteinuria: usually <3 g/day
Hematuria: red cell casts
Blood pressure often normal
May have other features of vasculitis

Chronic glomerulonephritis
Hypertension
Renal impairment
Proteinuria often >3 g/day
Shrunken, smooth kidneys

Fig. 16.1 Clinical presentation of various glomerular diseases.

Fig. 16.4 Muehrcke Lines (Bands) in Nephrotic Syndrome. The white line grew during a transient period of hypoalbuminemia caused by nephrotic syndrome.

Fig. 16.5 Xanthelasmas in Nephrotic Syndrome. These prominent xanthelasmas developed within 2 months in a patient with recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dL (14.2 mmol/L).

Fig. 16.2 Nephrotic Edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity.

antistreptolysin O titer or streptozyme test for poststreptococcal GN.
Serum and urine electrophoresis will detect monoclonal light chains or heavy chains, and assays for free light chains in serum or urine may aid in their quantification, as in myeloma-associated amyloid or lightchain deposition disease.
Blood cultures and testing for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection are also useful.
Measurement of systemic complement pathway activation by testing for serum C3, C4, and CH50 (50% hemolyzing dose of complement) is often helpful in limiting the differential diagnosis (Table 16.1).
The importance of genetic evaluation in patients with GN is discussed in Chapters 20 and 23

TABLE 16.1

Hypocomplementemia in Glomerular Disease

Pathways Affected

Complement Changes

Glomerular Disease

Classical pathway activation

C3 ↓, C4 ↓, CH50 ↓

Lupus nephritis (especially class IV)
Cryoglobulinemia
Membranoproliferative GN type 1

Alternative pathway activation

C3 ↓, C4 normal, CH50 ↓

Poststreptococcal GN
GN associated with other infectiona (e.g., endocarditis, shunt nephritis)
HUS

plus C3 nephritic factor

Dense deposit disease

Reduced complement synthesis

Acquired
Hereditary C2 or C4 deficiency
Factor H deficiency

Nonglomerular Disease

Atheroembolic renal disease

Hepatic disease
Malnutrition
Lupus nephritis
Familial HUS
Dense deposit disease

aGN

with visceral abscesses is generally associated with normal or increased complement (elevations occur because complement components are acute-phase reactants).
CH50, 50% hemolyzing dose of complement; GN, glomerulonephritis; HUS, hemolytic uremic syndrome.

Imaging
A kidney ultrasound is recommended in the workup to ensure the presence of two kidneys, to rule out obstruction or anatomic abnormalities, and to assess kidney size. Kidney size is often normal in GN, although large kidneys (>14 cm) are sometimes seen in nephrotic syndrome associated with

diabetes, amyloid disease, or HIV infection. Large kidneys also can occasionally be seen with any acute severe GN and acute interstitial nephritis. Small kidneys (<9 cm) and/or severe cortical thinning suggests advanced chronic kidney disease (CKD) and should limit enthusiasm for kidney biopsy or aggressive immunosuppressive therapies.

Kidney Biopsy

Kidney biopsy is generally required to establish the type of glomerular disease and to guide treatment decisions (see Chapter 7). In some patients, however, kidney biopsy is not performed. If nephrotic children (ages 2–12) have no unusual clinical features, the probability of MCD is so high that corticosteroids can be initiated without biopsy (see Chapter 18). In patients with acute nephritic syndrome, if all features point to poststreptococcal GN, especially in an epidemic, biopsy can be reserved for those without early spontaneous improvement (see Chapter 57).

In Goodpasture disease (see Chapter 25), the presence of lung hemorrhage and rapidly progressive kidney failure with urinary red cell casts and high levels of circulating anti-GBM antibody establishes the diagnosis without the need for a biopsy. In patients with systemic features of vasculitis, a positive ANCA titer, negative blood cultures, and a biopsy specimen from another site showing vasculitis are sufficient to secure a diagnosis of renal vasculitis. However, even when kidney biopsy is not needed for diagnosis, it may provide important clues to disease activity and chronicity. Biopsy is also not generally performed in patients with long-standing diabetes with characteristic findings suggestive of diabetic nephropathy and other evidence of microvascular complications of diabetes (see Chapter 31). Biopsy may not be indicated in many patients with glomerular disease presenting with minor, asymptomatic urine abnormalities and well-preserved kidney function because the prognosis is excellent and histologic findings will not alter management.

countries, symptomless individuals may have a urine test only if they require medical approval for some key life event, such as obtaining life insurance, joining the armed forces, or sometimes for employment purposes. In other countries, such as Japan, urinalysis is performed routinely in school or for employment. These different practices may partly account for the apparently variable incidence of certain diseases, such as IgA nephropathy, which often manifests as asymptomatic proteinuria and microhematuria. Asymptomatic low-grade proteinuria and microhematuria and the combination of the two also increase in prevalence with age1 (Fig. 16.6). Nevertheless, there is no evidence to justify routine population-wide screening for asymptomatic urine abnormalities as kidney biopsy and therapeutic intervention are rarely required when kidney function is preserved. For certain high-risk populations, such as patients with diabetes or hypertension, searching for albuminuria (“case-finding”) may be useful as it carries increased risk for cardiovascular disease.

Asymptomatic Microhematuria

Microhematuria is defined as the presence of more than two red blood cells (RBCs) per high-power field in a spun urine sediment (3000 rpm for 5 minutes) or more than 10 × 106 RBCs/L. Microhematuria is common in many glomerular diseases, especially IgA nephropathy and thin basement membrane nephropathy, although there are many other causes of hematuria (see Chapters 48 and 63). A glomerular origin should be assumed if more than 5% of RBCs are acanthocytes or dysmorphic (see Chapter 4) or if the hematuria is accompanied by RBC casts or proteinuria (Fig. 16.7).

Pathogenesis

Glomerular hematuria results from small breaks in the GBM that allow extravasation of RBCs into the urinary space. This may occur in the peripheral capillary wall but more often occurs in the paramesangial basement membrane, particularly in diseases involving injury to the mesangium (mesangiolysis). As long as the kidney tubules are intact, low amounts of serum proteins lost together with RBCs in damaged glomeruli can be fully reabsorbed, resulting in “isolated” microhematuria.

ASYMPTOMATIC URINE ABNORMALITIES

Evaluation

The random nature of urine testing in most communities inevitably means that much mild glomerular disease remains undetected. In some

The evaluation of microhematuria, discussed further in Chapters 48 and 63, begins with a thorough history. Urine culture should

16
14
12

Hematuria
Proteinuria
Both

10
8
6
4
2
0
18-29 30-39 40-49 50-59 60-69 70-79

A

Urinary Abnormalities in
Women of Different Ages
Incidence of abnormal urinalysis (%)

Incidence of abnormal urinalysis (%)

Urinary Abnormalities in
Men of Different Ages

80+

Age (years)

16
14
12

Hematuria
Proteinuria
Both

10
8
6
4
2
0
18-29 30-39 40-49 50-59 60-69 70-79

B

80+

Age (years)

Fig. 16.6 Prevalence of Asymptomatic Proteinuria and Hematuria With Age. Mass screening of a population of 107,192 adult men (A) and women (B) in Okinawa, Japan. Hematuria is more common in women.
(Modified from Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49:800–805.)

Asymptomatic Nonnephrotic Proteinuria

Fig. 16.7 A red blood cell cast typical of glomerular hematuria.

exclude urinary or prostatic infection. Phase contrast microscopy should follow in cases of persistent microhematuria to search for dysmorphic RBCs and RBC casts. In the absence of urine infection or a bladder catheter, any detectable albuminuria (>0.3 g/24 h) in the patient with microhematuria virtually excludes “urologic” bleeding and strongly suggests a glomerular origin. If this evaluation is nondiagnostic, kidney imaging is performed to exclude anatomic lesions such as stones, tumors, polycystic kidneys, or arteriovenous malformations.

In individuals older than 40 years with persistent isolated microhematuria without evidence of a glomerular origin (see previous discussion), cystoscopy is mandatory to exclude uroepithelial malignant disease. In people younger than 40 years, malignancy is so rare that cystoscopy is not recommended. If all the prior study results are normal, a glomerular cause is likely.2 The glomerular cause can be determined only by kidney biopsy, but this is rarely done because the prognosis is excellent in patients with normal kidney function, normal blood pressure, and low-grade proteinuria (<0.5 g/day). However, repeated evaluation and prolonged follow-up are mandatory for as long as the urinary abnormality persists.

The hallmark of glomerular disease is the excretion of protein in the urine. Normal urine protein excretion is less than 150 mg/24 h, consisting of 20 to 30 mg of albumin, 10 to 20 mg of low-molecularweight proteins that undergo glomerular filtration, and 40 to 60 mg of secreted proteins (e.g., Tamm-Horsfall, IgA). Proteinuria is identified and quantified by dipstick testing or by assay in timed urine collections (see Chapter 4).

An albumin excretion rate of 30 to 300 mg of albumin per day (previously termed microalbuminuria), equivalent to a urine albumin-tocreatinine (gram/gram) ratio of 0.03 to 0.3, is detected by quantitative immunoassay or by special urine dipsticks because this is below the sensitivity of the normal dipstick (see Chapter 31). This measurement is primarily used to identify diabetic individuals at risk for development of nephropathy and to assess cardiovascular risk, for example, in patients with hypertension.

Nonnephrotic proteinuria is usually defined as a urine protein excretion of less than 3.5 g/24 h or a urine protein/creatinine ratio of less than 3 g/g. Whereas nephrotic-range proteinuria is absolutely characteristic of glomerular disease, lower levels of proteinuria (<3.5 g/24 h) are much less specific and may occur with a wide range of nonglomerular parenchymal diseases as well as other conditions that must be excluded by clinical evaluation and investigation.

Increased urine protein excretion may result from alterations in glomerular permeability or tubulointerstitial disease, although only in glomerular disease will it be in the nephrotic range. Protein excretion also can increase if there is greater filtration through normal glomeruli (overflow proteinuria).

Overflow Proteinuria

Overflow proteinuria is typical of urinary light chain excretion. It is seen in myeloma but can occur in other settings (e.g., release of lysozyme by leukemic cells) and should be suspected when the urine dipstick is negative for albumin despite detection of large amounts of proteinuria by other tests.

Tubular Proteinuria

Tubulointerstitial disease can be associated with low-grade proteinuria (usually <2 g/day). In addition to the loss of tubular proteins such

as α1- or β2-microglobulin, there will also be some albuminuria secondary to impaired tubular reabsorption of filtered albumin. Tubular proteinuria accompanying glomerular proteinuria is an adverse prognostic sign in various glomerular diseases because it usually indicates advanced tubulointerstitial damage.

Evaluation of Isolated Asymptomatic Proteinuria

Asymptomatic
proteinuria

Glomerular Proteinuria

Glomerular proteinuria is further classified into transient or hemodynamic (functional) proteinuria, proteinuria that is present only during the day (orthostatic), and persistent or fixed proteinuria.

Functional proteinuria. Functional proteinuria refers to the transient nonnephrotic proteinuria that can occur with fever, exercise, heart failure, and hyperadrenergic or hyperreninemic states. Functional proteinuria is benign, usually assumed to be hemodynamic in origin, and the result of increases in single-nephron flow or pressure.

Orthostatic proteinuria. In children and young adults, lowgrade glomerular proteinuria may be orthostatic, meaning that proteinuria is absent when urine is generated in the recumbent position. If there is no proteinuria in early-morning urine, the diagnosis of orthostatic proteinuria can be made. In patients with fixed orthostatic proteinuria, renal plasma flow and glomerular filtration rate (GFR) decrease in the upright position because of a lower systemic blood pressure. As recently proposed, the decreased GFR translates into a lower streaming potential across the filtration barrier, which under physiologic conditions retains albumin within the blood. When GFR and filtration pressure are reduced beyond a certain threshold, albumin is no longer excluded efficiently from the filter by electrophoresis and consequently leaks through the filter, explaining reversible low-grade proteinuria in the upright position in these patients.3

Total urine protein in the patient with orthostatic proteinuria is usually less than 1 g/24 h; hematuria and hypertension are absent. Kidney biopsy usually shows normal morphology or occasionally mild glomerular change. The prognosis is uniformly good, and kidney biopsy is not indicated.4

Fixed nonnephrotic proteinuria. Fixed nonnephrotic proteinuria is usually caused by glomerular disease. If GFR is preserved and proteinuria is less than 0.5 to 1 g/day, biopsy is not indicated but prolonged follow-up is necessary if significant proteinuria persists, to rule out the possibility of disease progression. Previous studies indicate that the biopsy findings in these patients can be similar to those seen in nephrotic syndrome (most commonly FSGS or membranous nephropathy), although milder lesions are more common, particularly mesangial proliferative GN or IgA nephropathy. In general, other than regular monitoring and blood pressure control as needed, no treatment is necessary.

While controversial, some nephrologists perform a kidney biopsy in patients with normal GFR if nonnephrotic proteinuria exceeds 1 g/day, in particular if it persists after initiation of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

Fig. 16.8 summarizes the evaluation of isolated asymptomatic proteinuria.

Asymptomatic Proteinuria With Hematuria

Patients with coincident asymptomatic hematuria and proteinuria have a much greater risk for significant glomerular injury, hypertension, and progressive kidney dysfunction. Minor histologic changes are less common. Kidney biopsy is often performed even if urine protein is only 0.5 to 1 g/24 h if there is also persistent microhematuria with casts and/or declining kidney function.

Quantitate protein excretion
Measure glomerular filtration rate (GFR)

Normal GFR
Non-nephrotic proteinuria
Recumbent
overnight

Reduced GFR
Dipstick
negative
Orthostatic
proteinuria
No further
action

Persistent fixed
proteinuria

Reassess at
6–12 months
Urine protein
GFR
Blood pressure

Serologic
tests
Ultrasound

Consider renal
biopsy
If GFR or blood
pressure (BP)
abnormal,
if proteinuria
increases

If normal GFR and BP
persist: reassess annually

Fig. 16.8 Evaluation of patients with isolated asymptomatic proteinuria.

MACROHEMATURIA

Episodic painless macrohematuria associated with glomerular disease is often brown or “smoky” rather than red, and clots are unusual. Macrohematuria must be distinguished from other causes of red or brown urine, including hemoglobinuria, myoglobinuria, porphyrias, consumption of food dyes (particularly beetroot), and intake of drugs (especially rifampin/rifampicin).

Macrohematuria caused by glomerular disease is seen mainly in children and young adults and is rare after age 40 years. Most cases are caused by IgA nephropathy, but hematuria may occur with other glomerular and nonglomerular kidney diseases, including acute interstitial nephritis. Although macrohematuria is typically painless, the patient may have an accompanying dull loin ache that suggests other diagnoses, such as nephrolithiasis or loin-pain hematuria syndrome (see Chapter 60). In IgA nephropathy, the frank hematuria is usually episodic, occurring within a day of an upper respiratory tract infection. There is a clear distinction between this history and the 2- to 3-week latency between an upper respiratory tract infection and hematuria that is highly suggestive of postinfectious (usually poststreptococcal) GN; furthermore, patients with poststreptococcal disease usually will have other features of nephritic syndrome.

Macrohematuria requires urologic evaluation, including cystoscopy, at any age unless the history is characteristic of glomerular hematuria.

TABLE 16.2

Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults

Disease

Associations

MCD

Allergy, atopy, NSAIDs, Hodgkin disease

None*

FSGS

African American race

—

HIV infection

HIV antibody

Heroin, pamidronate

—

MN

Serologic Tests

Idiopathic drugs: gold, penicillamine, NSAIDs

Antibodies to PLA2R and other new autoantigens (see Chapter 21)

Infections: hepatitis B and C; malaria

Hepatitis B surface antigen, anti–hepatitis C virus antibody

Lupus nephritis

Anti-DNA antibody

Malignancy: breast, lung, gastrointestinal tract

—

MPGN type I

C4 nephritic factor

C3 ↓, C4 ↓

Dense deposit disease

C3 nephritic factor

Cryoglobulinemic MPGN

Hepatitis C

Anti–hepatitis C virus antibody, rheumatoid factor, C3↓,
C4 ↓, CH50 ↓

Amyloid disease

Myeloma
Rheumatoid arthritis, bronchiectasis, Crohn disease (and other chronic inflammatory conditions), familial Mediterranean fever

Plasma free light chains
Serum protein electrophoresis, urine immunoelectrophoresis
C-reactive protein

Other diabetic microangiopathy

None

Diabetic nephropathy

C3 ↓, C4 normal

*Possibly

anti-nephrin antibodies in the future.
CH50, 50% Hemolyzing dose of complement; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; NSAIDs, nonsteroidal antiinflammatory drugs; PLA2R, phospholipase A2 receptor.

TABLE 16.3

Age-Related Variations in the Prevalence (%) of Nephrotic Syndrome
YOUNG ADULT
Child (<15 yr)

Whites

Blacks

MIDDLE AND OLD AGE
Whites

Blacks

Minimal change disease

78

23

15

21

16

Focal segmental glomerulosclerosis

8

19

55

13

35

Membranous nephropathy

2

24

26

37

24

Membranoproliferative glomerulonephritis

6

13

0

4

2

Other glomerulonephritides

6

14

2

12

12

Amyloid

0

5

2

13

11

Data from Cameron JS. Nephrotic syndrome in the elderly. Semin Nephrol. 1996;16:319–329; and Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: A comparison of renal biopsy findings from 1976–1979 and 1995–1997. Am J Kidney Dis. 1997;30:621–631.

NEPHROTIC SYNDROME

Definition

Nephrotic syndrome is pathognomonic of glomerular disease. It is a clinical syndrome with a characteristic pentad5 (see Fig. 16.1). Patients may be nephrotic with preserved renal function, but in many, progressive kidney failure will become superimposed when nephrotic syndrome is prolonged. Independent of the risk for progressive loss of kidney function, the nephrotic syndrome has far-reaching effects on the general health of the patient. Some episodes of nephrotic syndrome are self-limited, and a few patients respond completely to specific treatment (e.g., corticosteroids in MCD), but for most patients it is a relapsing or chronic condition. Not all patients with proteinuria above 3.5 g/24 h will have full nephrotic syndrome; some have a normal serum albumin concentration and no edema. This difference presumably reflects the varied response of protein metabolism; some patients sustain an increase in

albumin synthesis in response to heavy proteinuria that may even normalize serum albumin.

Etiology

Table 16.2 shows the major causes of nephrotic syndrome. Proteinuria in the nephrotic range in the absence of edema and hypoalbuminemia has similar causes. The relative frequency of the different glomerular diseases varies with age (Table 16.3). Although it is predominant in childhood, MCD remains common at all ages.6 The prevalence of FSGS in African Americans is increased, which may explain why FSGS is becoming more common in US adults but not in European adults.7 8

Hypoalbuminemia

Hypoalbuminemia is mainly a consequence of urinary losses. The liver responds by increasing albumin synthesis, but this compensatory mechanism appears to be blunted in nephrotic syndrome.9 The end result is that serum albumin falls further. White bands in the nails

Mechanisms of Nephrotic Edema
Underfill

Overfill

Proteinuria

Primary tubular
defect causing
sodium retention

Hypoalbuminemia

Plasma colloid
oncotic pressure ↓
Starling forces
Normal/raised
plasma volume

Reduced
plasma volume

Vasopressin ↑

Atrial natriuretic
peptide (ANP)
normal/low

Renin-angiotensin
system activated
Aldosterone ↑

Vasopressin
normal

ANP ↑

Aldosterone ↓

*
Sodium
retention

Water retention

Edema

Fig. 16.9 Mechanisms of Nephrotic Edema. *The kidney is relatively resistant to ANP in this setting, so ANP has little effect in countering sodium retention.

(Muehrcke lines) are a characteristic clinical sign of hypoalbuminemia (see Fig. 16.4). The increase in protein synthesis in response to proteinuria is not discriminating; as a result, proteins not being lost in the urine may actually increase in concentration in plasma. This is chiefly determined by molecular weight; large molecules are not lost in urine and will increase in plasma, whereas smaller proteins will enter urine and will decrease in plasma. These variations in plasma proteins are clinically important in two areas: hypercoagulability and hyperlipidemia (see later discussion).

a tendency to hypertension rather than to hypotension. The kidney is also relatively resistant to the actions of atrial natriuretic peptide. An elevated blood volume results (overfill), which, in association with the low plasma oncotic pressure, provokes transudation of fluid into the extracellular space and edema. In addition to activation of the ENaC (see earlier discussion), it has been hypothesized that inflammatory leukocytes in the interstitium, which are found in many glomerular diseases, may impair sodium excretion by producing angiotensin II and oxidants (oxidants inactivate local nitric oxide, which is natriuretic).[12]

Edema

Metabolic Consequences of Nephrotic Syndrome

At least two major mechanisms are involved in the formation of nephrotic edema: underfill and overfill[10] (Fig. 16.9; see Chapter 8).

In the first, the edema appears to result from the low serum albumin, producing a decrease in plasma oncotic pressure, which allows increased transudation of fluid from capillary beds into the extracellular space. The consequent decrease in circulating blood volume (underfill) results in a secondary stimulation of the renin-angiotensin system (RAS), resulting in aldosterone-induced sodium retention in the distal tubule. This attempt to compensate for hypovolemia merely aggravates edema because the low oncotic pressure alters the balance of forces across the capillary wall in favor of hydrostatic pressure, forcing more fluid into the interstitial space rather than retaining it within the vascular compartment.

However, a much more common mechanism for edema, occurring in most nephrotic patients, is a primary defect in the ability of the distal nephron to excrete sodium, possibly related to activation of the epithelial sodium channel (ENaC) by proteolytic enzymes that enter the tubular lumen in heavy proteinuria.[11] As a result, there is an increased blood volume; suppression of renin, angiotensin, and vasopressin; and

Negative Nitrogen Balance

The heavy proteinuria leads to marked negative nitrogen balance, usually measured in clinical practice by serum albumin. Nephrotic syndrome is a wasting illness, but the degree of muscle loss is masked by edema and not fully apparent until the patient is rendered edema free. Loss of 10% to 20% of lean body mass can occur. Albumin turnover is increased in response to the tubular catabolism of filtered protein rather than merely to urinary protein loss. Increasing protein intake does not improve albumin metabolism because the hemodynamic response to an increased intake is a rise in glomerular pressure, increasing urine protein losses. A low-protein diet will reduce proteinuria, but it also reduces the albumin synthesis rate and in the longer term may increase the risk for a worsening negative nitrogen balance.

Hypercoagulability

Multiple proteins of the coagulation cascade have altered levels in nephrotic syndrome; in addition, platelet aggregation is enhanced.[13] The net effect is a hypercoagulable state that is enhanced further by immobility, coincidental infection, and hemoconcentration if the

Coagulation Abnormalities
in Nephrotic Syndrome

Lipid Abnormalities in Nephrotic Syndrome
Circulating lipids

Hepatic
synthesis ↑

Hyperlipidemia

Coagulation proteins
Raised:
fibrinogen; factors V, VII,
von Willebrand factor;
protein C;
α1-macroglobulin

Urine
clearance ↑

Unchanged/reduced:
prothrombin;
factors IX, X, XI, XII;
antithrombin III
Platelet aggregability ↑

VLDL ↑

VLDL deposition in
vascular tissues ↑

Hepatic
synthesis ↑

IDL ↑

Liver- or
kidney-derived
PCSK9 ↑

Catabolism ↓
Endothelial
lipoprotein lipase ↓

LDL ↑

Oxidized LDL ↑

Hepatic
secretion HDL ↑

HDL

Lecithin
cholesterol
acyltransferase
(LCAT) activity ↓

HDL3↓

Urine clearance
of smaller HDL3

HDL2↓

Cholesterol removal
from tissue to
liver impaired

Fig. 16.10 Coagulation abnormalities in nephrotic syndrome.

Lipoprotein (a)
↑

Atherogenicity ↑

patient has a contracted plasma volume (Fig. 16.10). Not only is venous thromboembolism common at any site, but spontaneous arterial thrombosis may rarely occur. Arterial thrombosis may occur in adults, promoting coronary and cerebrovascular events in particular, but it also occurs in nephrotic children, in whom spontaneous thrombosis of major limb arteries can rarely occur. Up to 10% of nephrotic adults and 2% of children will have a clinical episode of thromboembolism. For unexplained reasons, the risk appears particularly high in those with membranous nephropathy.14 Individual levels of coagulation proteins are not helpful in assessing the risk for thromboembolism, and serum albumin is mostly used as a surrogate marker. Thromboembolic events increase greatly if the serum albumin concentration decreases to less than 2 g/dL.

The hypoproteinemia and dysproteinemia produce a marked increase in erythrocyte sedimentation rate (ESR), which is not a useful marker of an acute phase response in nephrotic patients.

Renal vein thrombosis is an important complication of nephrotic syndrome (see Chapter 43) and presents clinically in up to 8% of nephrotic patients; when sought systematically by ultrasound or contrast venography, the frequency increases to 10% to 50%. Symptoms when the thrombosis is acute may include flank pain and hematuria; rarely, AKI can occur if the thrombosis is bilateral. However, the thrombosis often develops insidiously with minimal symptoms or signs because of the development of collateral blood supply. Pulmonary embolism is an important complication.

Fig. 16.11 Lipid Abnormalities in Nephrotic Syndrome. Changes in high-density lipoprotein (HDL) are more controversial than those in very-lowdensity lipoprotein (VLDL). IDL, Intermediate-density lipoprotein; LDL, lowdensity lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

Accelerated
atherogenesis

Volume contraction
Hemoconcentration

Immobility

Arterial thrombosis

Venous thromboembolism

Hyperlipidemia and Lipiduria

Hyperlipidemia is so frequently associated with heavy proteinuria that it is regarded as an integral feature of nephrotic syndrome.15 Clinical stigmata of hyperlipidemia, such as xanthelasmas, may have a rapid onset (see Fig. 16.5). Serum cholesterol concentration can be above 500 mg/dL (13 mmol/L), although serum triglyceride levels are highly variable. The lipid profile in nephrotic syndrome is known to be highly atherogenic in other populations (Fig. 16.11). Many patients who are nephrotic for more than 5 to 10 years will develop additional cardiovascular risk factors, including hypertension and uremia, so it is difficult to separate these influences. However, it is now generally accepted that nephrotic patients have about a fivefold increased risk for coronary death, except for those with MCD, presumably because the nephrotic state is transient before remission with corticosteroid treatment and does not subject the patient with MCD to prolonged hyperlipidemia. Experimental evidence shows that hyperlipidemia contributes to progressive kidney disease by various mechanisms, with protection afforded by lipid-lowering agents. However, clinical evidence to support a role of statins in slowing CKD progression is inconclusive,[16] so lipid-lowering drugs are indicated in nephrotic syndrome primarily to prevent cardiovascular disease.

Atherogenicity ↑

Several mechanisms account for the lipid abnormalities in nephrotic syndrome. These include increased hepatic synthesis of lowdensity lipoprotein (LDL), very-low-density lipoprotein (VLDL), and lipoprotein(a) secondary to the hypoalbuminemia; defective peripheral lipoprotein lipase activity resulting in increased VLDL; and urinary losses of high-density lipoprotein (HDL; see Fig. 16.11). More recently, kidney and hepatic overexpression of proprotein convertase subtilisin/kexin type 9 (PCSK9) has been identified in nephrotic syndrome, which is the basis for a possible new therapeutic intervention using PCSK9 antibodies.[17]

Lipiduria, the fifth component of the nephrotic syndrome, is manifested by the presence of refractile accumulations of lipid in cellular debris and casts (oval fat bodies and fatty casts; Fig. 16.12). However, the lipiduria appears to be a result of the proteinuria and not the plasma lipid abnormalities.

Other Metabolic Effects of Nephrotic Syndrome

Vitamin D–binding protein is lost in the urine, resulting in low plasma 25-hydroxyvitamin D levels, but plasma free vitamin D is usually normal, and overt osteomalacia or uncontrolled hyperparathyroidism is

Causes of Acute Kidney Injury in Nephrotic Syndrome

BOX 16.1

-
-
-
-
-

very unusual in nephrotic syndrome in the absence of kidney impairment. Thyroid-binding globulin is lost in the urine and total circulating thyroxine reduced, but again free thyroxine and thyroid-stimulating hormone are normal, and there are no clinical alterations in thyroid status. Occasional patients have been described with copper, iron, or zinc deficiency caused by the loss of binding proteins in the urine. Drug binding may be altered by the decrease in serum albumin, but most drugs do not require dose modifications. Reduced protein binding also may reduce the dose of vitamin-K antagonists (e.g., warfarin [Coumadin]) required to achieve adequate anticoagulation or the dose of furosemide required to achieve adequate fluid loss (see later discussion).

Infection

Nephrotic patients are prone to bacterial infection. Before corticosteroids were shown to be effective in childhood nephrotic syndrome, sepsis was the most common cause of death, and it remains a major problem in the developing world. Primary peritonitis, especially that caused by pneumococci, is particularly characteristic of nephrotic children. It is less common with increasing age; by 20 years of age, most adults have antibodies against pneumococcal capsular antigens. Peritonitis caused by both β-hemolytic streptococci and gram-negative organisms occurs, but staphylococcal peritonitis is not reported. Cellulitis, especially in areas of severe edema, is also common, most frequently caused by β-hemolytic streptococci.

The increased risk for infection has several explanations. Large fluid collections are sites for bacteria to grow easily; nephrotic skin is fragile, creating sites of entry; and edema may dilute local humoral immune factors. Loss of immunoglobulin G (IgG) and complement factor B (of the alternative pathway) in the urine impairs host ability to eliminate encapsulated organisms such as pneumococci. Zinc and transferrin are lost in the urine, and both are required for normal lymphocyte function. Neutrophil phagocytic function is impaired in patients with nephrotic syndrome, and several forms of in vitro T cell dysfunction are described, although their clinical significance is unclear.

Acute and Chronic Changes in Kidney Function

Acute Kidney Injury

Patients with nephrotic syndrome are at risk for AKI[18] through a variety of mechanisms (Box 16.1). These include volume depletion or sepsis, resulting in prerenal AKI or acute tubular necrosis[19]; transformation of the underlying disease, such as crescentic nephritis in a patient with membranous nephropathy; bilateral renal vein thrombosis; increased disposition to prerenal AKI from NSAIDs and ACE inhibitors or ARBs; and increased risk for allergic interstitial nephritis secondary to drugs, including diuretics. AKI may rarely result from intrarenal edema with compression of tubules and, as with nephrotic

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal antiinflammatory drugs.

Proteinuria and Prognosis
in Glomerular Disease
Uprot <5 g/d

100
Renal survival (%)

Fig. 16.12 Fat in the Urine. This hyaline cast contains oval fat bodies, which are tubular epithelial cells full of fat. Oval fat bodies often appear brown.

Prerenal failure caused by volume depletion
Acute tubular necrosis caused by volume depletion and/or sepsis
Intrarenal edema
Renal vein thrombosis
Transformation of underlying glomerular disease (e.g., crescentic nephritis superimposed on membranous nephropathy)
- Adverse effects of drug therapy
- Acute allergic interstitial nephritis secondary to various drugs, including diuretics
- Hemodynamic response to NSAIDs and ACE inhibitors or ARBs

Uprot ≥5 g/d

75

Nephrotic
syndrome

50
Proteinuria never exceeds 5 g/day (n = 33)

25

Nephrotic syndrome at onset (n = 200)
Proteinuria exceeds 5 g/day during illness,
never nephrotic (n = 20)

0
0

40

80

120 160 200
Months

Fig. 16.13 Proteinuria and Prognosis in Glomerular Disease. The influence of heavy proteinuria (Uprot) on long-term renal function in 253 patients with primary glomerular disease at Manchester Royal Infirmary, United Kingdom. Heavy proteinuria at any time during longterm follow-up substantially worsens the prognosis even without frank nephrotic syndrome. (Courtesy Dr. C.D. Short.)

patients with prerenal azotemia, may respond with diuresis to albumin infusions combined with a loop diuretic.

Chronic Kidney Disease

With the exception of MCD, most causes of nephrotic syndrome are associated with progressive kidney failure. A major risk factor for progression is the degree of proteinuria (see Chapters 81 and 82). Progression is uncommon if there is sustained proteinuria of less than 2 g/day. The risk increases in proportion to the severity of the proteinuria, with marked risk for progression when protein excretion is more than 5 g/day (Fig. 16.13). Proteinuria identifies patients with severe glomerular injury; however, experimental and clinical evidence also suggests that proteinuria itself may be toxic, especially to the tubulointerstitium.20 In experimental models, measures that reduce proteinuria (e.g., ACE inhibitors) also prevent tubulointerstitial disease and progressive kidney failure.

NEPHRITIC SYNDROME

In nephrotic syndrome, the glomerular injury is manifested primarily as an increase in permeability of the capillary wall to protein. By contrast,

TABLE 16.4 Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

TABLE 16.5
Disease

Associations

Serologic Tests

Typical Features

Nephrotic

Pharyngitis, impetigo

Onset

Insidious

Abrupt

Poststreptococcal glomerulonephritis

Antistreptolysin titer, streptozyme antibody

Edema

++++

++

Nephritic

Blood pressure

Normal

Raised

Jugular venous pressure

Normal/low

Raised

Proteinuria

++++

++

Hematuria

May/may not occur

+++

Red blood cell casts

Absent

Present

Serum albumin

Low

Normal/slightly reduced

in nephritic syndrome, there is evidence of glomerular inflammation resulting in a reduction in GFR, nonnephrotic proteinuria, edema and hypertension (secondary to sodium retention), and hematuria with RBC casts.

The classic nephritic syndrome presentation is seen with acute poststreptococcal GN in children, but this complication has become rare. These children usually present with rapid onset of oliguria, weight gain, and generalized edema over a few days. The hematuria results in brown rather than red urine, and clots are not seen. The urine contains protein, RBCs, and RBC casts. Because proteinuria is rarely in the nephrotic range, serum albumin concentration is usually normal. Circulating volume increases with hypertension, and pulmonary edema follows without evidence of primary cardiac disease.

The distinction between typical nephrotic syndrome and nephritic syndrome is usually straightforward on clinical and laboratory grounds (Table 16.4). The use of these clinical descriptions for patients with suspected GN at first presentation helps narrow the differential diagnosis. However, the classification systems are imperfect, and patients with certain glomerular disease patterns, such as a membranoproliferative GN pattern on biopsy, may present with nephrotic syndrome, nephritic syndrome, or a combination of both syndromes.

Etiology

Table 16.5 lists the primary glomerular diseases associated with nephritic syndrome and the serologic tests helpful in diagnosis. The classification is even more challenging than for nephrotic syndrome, because some diseases are identified by histology (IgA nephropathy), some by serology and histology (ANCA-associated vasculitis and lupus nephritis), and others by etiology (postinfectious GN).

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

In rapidly progressive glomerulonephritis (RPGN), glomerular injury is so acute and severe that kidney function deteriorates markedly over days or weeks. The patient may present as a uremic emergency, with nephritic syndrome that rapidly progresses to kidney failure, or with rapidly deteriorating kidney function when being investigated for extrarenal disease (many of the GN associated with RPGN occur as part of a systemic immune illness).

The histologic counterpart of RPGN is crescentic GN. The proliferative cellular response seen outside the glomerular tuft but within Bowman’s space is known as a “crescent” because of its shape on histologic cross section (see Fig. 17.8). Typically, the glomerular tuft also

Common Glomerular Diseases Presenting as Nephritic Syndrome

Other postinfectious disease

Endocarditis

Cardiac murmur

Blood cultures, C3 ↓

Abscess

—

Blood cultures, C3, C4
normal or increased

Shunt

Treated hydrocephalus

Blood cultures, C3 ↓

IgA nephropathy

Upper respiratory or
gastrointestinal
infection

Serum IgA ↑

Lupus nephritis

Other multisystem
features of lupus

Antinuclear antibody,
anti–double-stranded
DNA antibody,
C3 ↓, C4 ↓

IgA, Immunoglobulin A.

shows segmental necrosis or focal segmental necrotizing GN, especially in the vasculitis syndromes.

The term rapidly progressive GN is therefore often used to describe acute deterioration in kidney function in association with crescentic nephritis. Unfortunately, not all patients with a nephritic urine sediment and AKI will fit this syndrome. For example, AKI may also occur in milder glomerular disease if it is complicated by accelerated hypertension, renal vein thrombosis, or acute tubular necrosis. This emphasizes the need to obtain histologic confirmation of the clinical diagnosis.

Etiology

Table 16.6 shows the primary glomerular diseases associated with RPGN and helpful serologic tests. As with nephritic syndrome, different assessment methods are useful for different diseases causing RPGN.

PROGRESSIVE CHRONIC KIDNEY DISEASE

In most types of chronic GN, between 25% and 50% of patients will have slowly progressive kidney impairment. Patients may present late with established hypertension, proteinuria, and kidney impairment. In long-standing GN, the kidneys shrink but remain smooth and symmetric. Kidney biopsy at this stage is more hazardous and less likely to provide diagnostic material. Light microscopy often shows nonspecific features of end-stage kidney disease (ESKD), consisting of focal or global glomerulosclerosis and dense tubulointerstitial fibrosis, and it may not be possible to confirm that a glomerular disease was responsible, let alone define the glomerular pattern more precisely. Immunofluorescence may be more helpful; in particular, mesangial IgA may be present in adequate amounts to diagnose IgA nephropathy. However, when kidney imaging shows small kidneys, only rarely will biopsy be appropriate, and so chronic GN often has been a presumptive diagnosis in patients presenting late with shrunken kidneys, proteinuria, and kidney impairment. This in turn may have led to an overestimate of the frequency of GN as a cause of ESKD in registry data. GN should be diagnosed only if there is confirmatory histologic evidence.

TABLE 16.6

Glomerular Diseases Presenting as Rapidly Progressive Glomerulonephritis

Disease

Associations

Serologic Tests

Lung hemorrhage

Anti–glomerular basement membrane antibody (occasionally ANCA present)

Upper and lower respiratory tract involvement

Mostly PR3 ANCA

Microscopic polyangiitis

Multisystem involvement

Mostly MPO ANCA

Pauci-immune crescentic glomerulonephritis

Renal involvement only

MPO or PR3 ANCA

Immune Complex Disease
Systemic lupus erythematosus

Other multisystem features of lupus

Antinuclear antibody, anti–double-stranded DNA antibody, C3↓, C4 ↓

Poststreptococcal glomerulonephritis

Pharyngitis, impetigo

Antistreptolysin titer, streptozyme antibody
C3 ↓, C4 normal

IgA nephropathy; IgA vasculitis (HSP)

Characteristic rash ± abdominal pain in IgA vasculitis

Serum IgA ↑ (30%)
C3 and C4 normal

Cardiac murmur; other systemic features of bacteremia

Blood cultures
ANCA (occasionally)
C3 ↓, C4 normal

Goodpasture Syndrome

Vasculitis
Granulomatosis with polyangiitis

Endocarditis

Note the overlap between these diseases and those in Table 16.5. A number of glomerular diseases may present with either nephritic syndrome or RPGN.
ANCA, Antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; IgA, immunoglobulin A; MPO, myeloperoxidase; PR3, proteinase 3; RPGN, rapidly progressive glomerulonephritis.

TREATMENT OF GLOMERULAR DISEASE

General Principles

Before any therapeutic decisions, it should always be ascertained that glomerular disease is primary and that no specific therapy is indicated. For example, treatment of an underlying infection or tumor may result in remission of GN. In the remaining cases, both general supportive treatment (see Chapter 82) and disease-specific therapy should be considered. Supportive treatment includes treatment of hypertension, proteinuria, edema, and other metabolic consequences of nephrotic syndrome. If successful, these relatively nontoxic therapies can prevent the need for immunosuppressive drugs, which have multiple potential side effects. Supportive therapy is usually not necessary in corticosteroid-sensitive MCD with rapid remission or in patients with IgA nephropathy, Alport syndrome, or thin basement membrane nephropathy, provided the patient exhibits no proteinuria above 0.5 g/day, loss of GFR, or hypertension.

Hypertension

Hypertension is very common in GN; it is virtually universal as chronic GN progresses toward kidney failure and is the key modifiable factor in preserving kidney function. Sodium and water overload is an important part of the pathogenetic process, and high-dose diuretics with moderate dietary sodium restriction are usually an essential part of the treatment. As in other chronic kidney diseases, the blood pressure control reduces cardiovascular risk and also delays progressive kidney function loss. In the Modification of Diet in Renal Disease (MDRD) study, patients with proteinuria (>1 g/day) had a better outcome if their blood pressure was reduced to 125/75 mm Hg rather than to the previous standard of 140/90 mm Hg.21 22 The recent Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline recommends a blood pressure target of 130/80 mm Hg in proteinuric patients,23 but the SPRINT trial and some other studies suggest that a systolic blood pressure target in the 120s may reduce

cardiovascular complications in nondiabetic subjects compared with a higher target (140 mm Hg; see Chapters 35 and 82). Clinical trial data strongly supports the use of ACE inhibitors and ARBs as the first-choice therapy.24-26 Nondihydropyridine calcium channel blockers may also have a beneficial effect on proteinuria as well as on blood pressure. In contrast, dihydropyridine calcium channel blockers may exacerbate proteinuria because of their ability to dilate the afferent arteriole, but these agents are considered relatively safe to use if the patient is receiving either an ACE inhibitor or an ARB. As in primary hypertension, lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation) should be an integral part of the therapy.23 If target blood pressure cannot be achieved with these measures, antihypertensive therapy should be stepped up according to current guidelines (see Chapter 37).

Treatment of Proteinuria

Besides hypertension, proteinuria represents the second key modifiable factor to preserve GFR in patients with glomerular disease (see

Chapters 81 and 82). Most studies suggest that progressive loss of kidney function can be minimized if proteinuria can be reduced to levels below 0.5 g/d. This may be because many of the measures to reduce protein excretion (e.g., ACE inhibitors, ARBs) also reduce glomerular hypertension, which contributes to progressive kidney failure. However, there is also increasing evidence that proteinuria or factors present in proteinuric urine may be toxic to the tubulointerstitium.23 In nephrotic patients, a reduction of proteinuria to a nonnephrotic range can induce serum proteins to rise, with alleviation of many of the metabolic complications of nephrotic syndrome.

Most of the agents used to reduce urinary protein excretion do so by blocking efferent arteriolar constriction (ACE inhibitors or ARBs) or reducing preglomerular pressure (most other classes of antihypertensive drugs). As mentioned, dihydropyridine calcium antagonists are the exception because they preferentially dilate the afferent arteriole and thereby can increase intraglomerular pressure and thus exacerbate

Fig. 16.14 Treatment of Nephrotic Edema before the Availability of Diuretics. Edema in nephrotic syndrome was very difficult to treat. In 1953 this child with anasarca stands in a bowl while edema fluid drips out through small tubes placed through needles in the skin of the feet. Nevertheless, this was effective treatment. The two pictures of the same child were taken 4 days apart, during which time the child lost 4.5 kg (10 lb), or 18% of body weight. (Courtesy Dr. Robert Vernier.)

proteinuria. Some of the agents, such as ACE inhibitors and ARBs, also may directly reduce the increased glomerular capillary wall permeability. A consequence of this type of therapy is a reduction in GFR; in general, however, the decrease in GFR is of a lower magnitude than the decrease in protein excretion. ACE inhibitors and ARB reduce proteinuria by an average of 40% to 50%, particularly if the patient is on dietary salt restriction. There is little clinical evidence to suggest that ACE inhibitors differ from ARBs in this respect. The combination of ACE inhibitors and ARBs does not appear to provide additional benefit and increases the risk for AKI and hyperkalemia, in particular when used in older people with vascular disease and diabetes.27 28 Similar concerns relate to the combination of an ACE inhibitor or ARB with a direct renin inhibitor.29

In addition, whereas other classes of antihypertensive agents will reduce proteinuria coincident with a decrease in systemic blood pressure, particularly the nondihydropyridine calcium channel blockers such as diltiazem, both ACE inhibitors and ARBs usually reduce proteinuria independent of blood pressure. If doses are increased slowly to minimize symptomatic hypotension, treatment with ACE inhibitors and ARBs is usually possible in the normotensive proteinuric patient. Common side effects include hyperkalemia in patients with advanced CKD, which may necessitate a loop diuretic but rarely should lead to cessation of ACE inhibitors and ARBs, and cough with ACE inhibitors, in which case ARBs should be used instead. Because both agents lower GFR, a 10% to 30% increase in serum creatinine concentration may be observed. Unless serum creatinine continues to increase, this moderate increase reflects the therapeutic effect of ACE inhibitors and ARBs and should not prompt their withdrawal.

Finally, if proteinuria persists despite maximum allowed or tolerated doses of ACE inhibitors or ARBs, a low dose of an aldosterone antagonist may overcome so-called aldosterone breakthrough and further reduce proteinuria (see Chapter 82). Hyperkalemia is an important safety aspect, similar to the ACE inhibitor and ARB combination mentioned earlier.

The NSAIDs lessen proteinuria by reducing intrarenal prostaglandin production and dipyridamole through adenosine-mediated afferent arteriolar vasoconstriction. However, they are generally contraindicated as their use can cause profound decreases in GFR, salt retention, and diuretic resistance.

A low-protein diet will lessen proteinuria but must be advised with great care because of the risk for malnutrition.23 Adequate compensation must be made for urine protein losses,30 and the patient must be carefully monitored for evidence of malnutrition (see Chapter 90). Whether a low-protein diet is still antiproteinuric in patients treated with a full dose of ACE inhibitor or ARB is not established.

Treatment of Hyperlipidemia

Treatment of hyperlipidemia (or hypercholesterolemia) in patients with glomerular disease should usually follow the guidelines that apply to the general population to prevent cardiovascular disease. A statin or statin/ezetimibe combination is recommended in adults older than 50 years with CKD stage 3 to 5. Statins alone are also recommended in adults over 50 years with earlier-stage CKD. In younger adults, statins should be considered if the patient has significant comorbidity (coronary disease, diabetes mellitus, stroke; see Chapter 85). Statins may protect from a decrease in GFR, although this is not firmly established. Dietary restriction alone has only modest effects on hyperlipidemia in glomerular disease, particularly nephrotic syndrome. Side effects of some medications, such as rhabdomyolysis provoked by fibrates, occur more frequently in patients with kidney failure.

Avoidance of Nephrotoxic Substances

Apart from NSAIDs, which may induce AKI, particularly in patients with preexisting kidney impairment and dehydration, other nephrotoxic substances, such as radiocontrast agents, some cytotoxic drugs, and antibiotics (e.g., aminoglycosides), also should be used with caution in patients with glomerular disease and kidney impairment or nephrotic syndrome. There is also increasing concern that proton pump inhibitors may be associated with increased risk for both acute interstitial nephritis and CKD, and thus their use should be restricted to documented indications when histamine-2 blockers are not effective.

Special Therapeutic Issues in Patients With Nephrotic Syndrome

Treatment of Nephrotic Edema

In contrast to the lack of therapies in the past (Fig. 16.14), the mainstay of current treatment of nephrotic edema is diuretic therapy accompanied by moderate dietary sodium restriction (60–80 mmol/24 h).

Nephrotic patients are diuretic resistant even if GFR is normal. Loop diuretics must reach the kidney tubule to be effective, and transport from the peritubular capillary requires protein binding, which is reduced in hypoalbuminemia. When the drug reaches the kidney tubule, it will become 70% bound to protein present in the urine and therefore be less effective. Oral diuretics with twice-daily administration are usually preferred, given the longer therapeutic effect compared with intravenous diuretics. However, in severe nephrosis, GI absorption of the diuretic may be uncertain because of intestinal wall edema, and intravenous diuretic by bolus injection or infusion may be necessary to provoke an effective diuresis. Alternatively, combining a loop diuretic with a thiazide diuretic or with metolazone may overcome diuretic resistance (see Chapter 8). A third alternative is adding amiloride to loop diuretics because nephrotic syndrome is associated with activation of the ENaC channel. Significant hypovolemia is not often a clinical problem, provided fluid removal is controlled and gradual. Daily weight should decrease by no more than 1 to 2 kg/day. Nephrotic children are much more prone to hypovolemic shock than adults. A stepwise approach to diuretic use is required, aiming at fluid removal in adults of no more than 2 kg daily, moving on to the next drug level if this is not achieved (Fig. 16.15).

Management of Edema
in Nephrotic Syndrome
Oral loop diuretic
(e.g., furosemide 40 mg bid,
bumetanide 1 mg bid,
torsemide 20 mg qd)
No response

Response

Reduce stepwise
to maintenance
dose as diuresis
continues

Double dose until diuresis
or
Ceiling dose reached
Furosemide 250 mg daily
Bumetanide 5 mg daily
Torsemide 200 mg daily
No response

Treatment of Hypercoagulability

The risk for thrombotic events increases as serum albumin values decrease to less than 2.5 g/dL. Immobility as a consequence of edema or intercurrent illness further aggravates the risk. Prophylactic low-dose anticoagulation (e.g., heparin 5000 U subcutaneously twice daily) is indicated at times of high risk, such as relative immobilization in the hospital and albumin levels between 2 and 2.5 g/dL. Full-dose anticoagulation with low-molecular-weight heparin or warfarin should be considered if serum albumin decreases to less than 2 g/dL,13 31 and this is mandatory if a thrombosis or pulmonary embolism is documented. Heparin is used for initial anticoagulation, but an increased dose may be needed because part of the action of heparin depends on circulating antithrombin III, which is often reduced in nephrotic patients. Warfarin (target international normalized ratio [INR] 2 to 3) is the long-term treatment of choice but should be adjusted with special care because of altered protein binding, which may require dose reductions. Newer oral anticoagulants have not been systematically tested so far in this situation.

Management of Infection

A high degree of clinical suspicion for infection is vital in nephrotic patients. Especially in nephrotic children, ascitic fluid should be

Monitor serum K+
If hypokalemic:
Add K supplements
or amiloride
5–20 mg daily
or spironolactone
50–200 mg daily*

Add: oral thiazide
(e.g., hydrochlorothiazide
25–50 mg daily, metolazone
2.5–5 mg daily)
or add amiloride (start with
5 mg once daily)

No response

Correction of Hypoproteinemia

Adequate dietary protein should be ensured in nephrotic patients (0.8–1 g/kg/day) with a high carbohydrate intake to maximize use of that protein. In patients with heavy proteinuria, the amount of urinary protein loss should be added to dietary protein intake.

In the very rare setting of proteinuria so severe that the patient is dying of the complications of nephrotic syndrome, the physician may need to resort to medical nephrectomy to prevent continued protein losses: the deliberate use of NSAIDs combined with ACE inhibitors and diuretic to lessen proteinuria by provoking AKI. If medical nephrectomy alone does not adequately reduce proteinuria, bilateral renal artery embolization can be considered. It is a painful procedure and is not always as successful (perhaps because of collateral arterial supply to the kidneys, which is not blocked by embolization). A final alternative is bilateral nephrectomy, which can be performed by laparoscopic surgery with reduced morbidity compared with classical surgical removal.

Bilateral nephrectomy is commonly used in the management of infants with congenital nephrotic syndrome.

Change loop diuretic to IV bolus
(max. furosemide 80 mg tid)
or infusion (max. furosemide
500 mg per day)
No response
Add: 20% human albumin
50–100 mL IV followed by
IV bolus diuretic
No response
Mechanical ultrafiltration

Fig. 16.15 Management of Edema in the Patient With Nephrotic Syndrome. Edema is often diuretic resistant, but the response is not predictable. Therefore, stepwise escalation of therapy is appropriate until diuresis occurs. Even when there is anasarca, diuresis should not proceed faster than 2 kg/day in adults to minimize the risk for clinically significant hypovolemia. Mechanical ultrafiltration is rarely required for nephrotic edema unless there is associated renal impairment. *Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects. Spironolactone should be used with great caution if the glomerular filtration rate is very low. bid, Twice daily; IV, intravenous.

examined microscopically and cultured if there is any suspicion of systemic infection. Bacteremia is common even if clinical signs are localized. ESR is unhelpful, but an elevated C-reactive protein level may be informative. Parenteral antibiotics should be started once culture specimens are taken, and the regimen should include coverage for pneumococci. If repeated infections occur, serum immunoglobulins should be measured. If serum IgG is less than 600 mg/dL, an uncontrolled study suggested that infection risk is reduced by monthly administration of intravenous immune globulin (10–15 g) to keep the IgG levels above 600 mg/dL.[32]

Disease-Specific Therapies

Specific treatments for glomerular diseases are discussed in the subsequent chapters; the general principles are discussed here. Most glomerular diseases have an immune pathogenesis, and treatment has generally consisted of immunosuppressive therapy. In the patient with glomerular disease resulting from ineffectual elimination of a foreign antigen, treatment aims at eliminating this antigen, such as antibiotics in endocarditis-associated GN or antiviral therapy for cryoglobulinemia resulting from hepatitis C viral infection.

In general, the more severe and acute the presentation of GN, the more successful is immunosuppressive treatment. Immunosuppression in chronic GN has had minimal success. When kidney function is declining rapidly, as in RPGN, the toxicity of intensive regimens becomes acceptable for a short period, although it would be unacceptable if prolonged. Furthermore, the nonspecific nature of most immunosuppressive treatments results in widespread interruption of immune and inflammatory events at multiple levels. Despite great increases in the understanding of immune mechanisms in glomerular disease since the 1970s, most immunosuppressive therapies are not yet much more specific or precise. The mainstays of treatment include corticosteroids, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil, and/or rituximab. Novel agents, including some that modify inflammation (e.g., complement antagonists) or B cell immunity (e.g., inhibitors of B cell activation factor), are now being studied in clinical trials in glomerular disease but as yet have no proven indications.

The use of immunosuppressive therapies to treat patients with GN has drawbacks. In many diseases, good prospective controlled trials are often lacking. If sufficient glomerular damage is present, proteinuria and progressive deterioration of kidney function may occur by nonimmune pathways that may not be responsive to immunosuppressive therapies. This is particularly relevant in patients in whom the GN has already resulted in advanced CKD. Unfortunately, good noninvasive markers to assess disease activity are missing in most clinical circumstances. Given the frequent uncertainty of the response to immunosuppressive therapy, it becomes mandatory to weigh the potential benefits against the risks of therapy.

Immunosuppression may be associated with reactivation of tuberculosis and hepatitis B infection and also can lead to a hyperinfection syndrome in patients with Strongyloides infection. Therefore, highrisk patients should be tested for these diseases before embarking on therapy.

Alkylating agents such as cyclophosphamide have considerable toxicity. In the short term, leukopenia is common, as is alopecia, although hair will regrow within a few months with discontinuation of therapy. These agents can cause infertility (observed in adults with cumulative doses of cyclophosphamide >200 mg/kg). There is also an increased incidence of leukemias (observed with total doses of cyclophosphamide >80 g). Cyclophosphamide is also a bladder irritant, and treatment can result in hemorrhagic cystitis and bladder carcinoma, particularly after therapy lasting more than 6 months.33 Irritation of the bladder is caused by a metabolite, acrolein. The effect can be minimized in patients receiving intravenous cyclophosphamide by enforcing a good diuresis and administering mesna. The dose of mesna (milligrams) should equal the dose of cyclophosphamide (milligrams); 20% is given intravenously with the intravenous cyclophosphamide, and the remaining 80% should be given in two equal oral doses at 2 and 6 hours. Cyclophosphamide also requires dose reduction in the setting of impaired kidney function. Given all these concerns, oral treatment with cyclophosphamide should ideally be limited to 12 weeks.

The modes of action and potential adverse effects of corticosteroids, azathioprine, and other immunosuppressive agents occasionally used in glomerular disease are discussed further in Chapter 106

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding proteinuria is correct?

A. Tubular proteinuria is characterized by equal amounts of α1 microglobulin and immunoglobulins.
B. Proteinuria exceeding 3.5 g/day (i.e., “nephrotic” proteinuria) inevitably results in hypoalbuminemia.
C. In orthostatic proteinuria, urinary protein is typically increased with the patient lying down.
D. Overflow proteinuria is typical of urinary light chain excretion.
E. Functional proteinuria typically occurs after heavy meals with high protein intake.

2. Which of the following statements regarding general treatment of glomerular disease is incorrect?

A. The KDIGO CKD guideline recommends a blood pressure target below 130/80 mm Hg in proteinuric patients.
B. ACE inhibitors and ARBs may directly reduce the increased glomerular capillary wall permeability.
C. Common side effects of ACE inhibitors and ARBs in patients with advanced CKD include hyperkalemia, which may necessitate a loop diuretic.

D. A statin or a statin-ezetimibe combination is recommended in all adults younger than 50 years with CKD.
E. A low-protein diet will lessen proteinuria but must be advised with great care because of the risk of malnutrition.

3. Which statement regarding the treatment of nephrotic syndrome is correct?

A. Nephrotic patients are diuretic resistant only if GFR is greatly impaired.
B. Patients with heavy proteinuria should be advised to consume a high-protein diet of about 2 to 3 g/kg/day.
C. Full-dose anticoagulation with low-molecular-weight heparin or warfarin should be considered if serum albumin decreases to less than 2 g/dL.
D. Ascitic fluid should be examined regularly by microscopy and culture independently of a suspicion of systemic infection.
E. Nephrotic children are no more prone to hypovolemic shock than are adults.

REFERENCES

1. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49(3):800–805.
2. Topham PS, Harper SJ, Furness PN, Harris KP, Walls J, Feehally J. Glomerular disease as a cause of isolated microscopic haematuria. Q J Med. 1994;87(6):329–335.
3. Saritas T, Kuppe C, Moeller MJ. Progress and controversies in unraveling the glomerular filtration mechanism. Curr Opin Nephrol Hypertens. 2015;24(3):208–216.
4. Springberg PD, Garrett Jr LE, Thompson Jr AL, Collins NF, Lordon RE, Robinson RR. Fixed and reproducible orthostatic proteinuria: results of a 20-year follow-up study. Ann Intern Med. 1982;97(4):516–519.
5. Orth SR, Ritz E. The nephrotic syndrome. N Engl J Med. 1998;338(17):1202–1211.
6. Cameron JS. Nephrotic syndrome in the elderly. Semin Nephrol. 1996;16(4):319–329.
7. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. Am J Kidney Dis. 1997;30(5):621–631.
8. Hanko JB, Mullan RN, O’Rourke DM, McNamee PT, Maxwell AP, Courtney AE. The changing pattern of adult primary glomerular disease. Nephrol Dial Transplant. 2009;24(10):3050–3054.
9. Kaysen GA, Gambertoglio J, Felts J, Hutchison FN. Albumin synthesis, albuminuria and hyperlipemia in nephrotic patients. Kidney Int. 1987;31(6):1368–1376.
10. Humphreys MH. Mechanisms and management of nephrotic edema. Kidney Int. 1994;45(1):266–281.
11. Svenningsen P, Friis UG, Versland JB, et al. Mechanisms of renal NaCl retention in proteinuric disease. Acta Physiol. 2013;207(3):536–545.
12. Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Interstitial inflammation, sodium retention, and the pathogenesis of nephrotic edema: a unifying hypothesis. Kidney Int. 2002;62(4):1379–1384.
13. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. J Am Soc Nephrol. 2007;18(8):2221–2225.
14. Barbour SJ, Greenwald A, Djurdjev O, et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012;81(2):190–195.
15. Wheeler DC, Bernard DB. Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. Am J Kidney Dis. 1994;23(3):331–346.
16. Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009;(2):CD007784.
17. Molina-Jijon E, Gambut S, Mace C, Avila-Casado C, Clement LC. Secretion of the epithelial sodium channel chaperone PCSK9 from the cortical collecting duct links sodium retention with hypercholesterolemia in nephrotic syndrome. Kidney Int. 2020;98(6):1449–1460.
18. Smith JD, Hayslett JP. Reversible renal failure in the nephrotic syndrome. Am J Kidney Dis. 1992;19(3):201–213.

19. Jennette JC, Falk RJ. Adult minimal change glomerulopathy with acute renal failure. Am J Kidney Dis. 1990;16(5):432–437.
20. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest. 2006;116(2):288–296.
21. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330(13):877–884.
22. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of

high blood pressure: the JNC 7 report. JAMA. 2003;289(19):2560–2572.

23. Stevens PE, Levin A. Kidney Disease: Improving global outcomes chronic kidney disease guideline development work group m. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825–830.

24. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensinconverting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in progressive renal insufficiency study group. N Engl J Med. 1996;334(15):939–945.

25. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;135(2):73–87.

26. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349(9069):1857–1863.

27. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372(9638):547–553.

28. Lennartz DP, Seikrit C, Wied S, et al. Single versus dual blockade of the renin-angiotensin system in patients with IgA nephropathy. J Nephrol. 2020;33(6):1231–1239.

29. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204–2213.

30. Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K. Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein-restricted diet. J Clin Invest. 1997;99(10):2479–2487.

31. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int. 2014;85(6):1412–1420.

32. Ogi M, Yokoyama H, Tomosugi N, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. Am J Kidney Dis. 1994;24(3):427–436.

33. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamideinduced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med. 1996;124(5):477–484.

17

Introduction to Glomerular Disease: Histologic Classification and Pathogenesis

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HISTOLOGIC CLASSIFICATION

Glomerular disease has a wide variety of etiologies and clinical presentations (see Chapter 16). Some glomerular diseases are given the generic title of glomerulonephritis (GN), which implies an immune or inflammatory pathogenesis. Although a specific diagnosis is sometimes possible based on clinical presentation and laboratory tests, in most patients a kidney biopsy is useful for both classification and prognosis. Ideally, the kidney biopsy should be examined by light microscopy, immunohistology or immunofluorescence, and electron microscopy (EM), which allows description of the underlying histopathological pattern. Using this approach, an etiologic classification or specific diagnosis can often be made, particularly when integrating the biopsy results with clinical features and other laboratory tests. One useful example of an etiologic classification is the Mayo/Renal Pathology Society consensus report on the classification of GN,1 distinguishing five major disease etiologies: immune-complex GNs, pauci-immune GNs, anti–glomerular basement membrane (GBM) antibody GNs, monoclonal gammopathy–associated GNs, and complement-related GNs. In some cases the exact condition might remain idiopathic, but in the vast majority of cases one of these GN classes can be assigned. However, because treatments are often developed for specific histologic patterns, a histology-based approach is currently favored in the management of most patients with glomerular disorders.

HISTOPATHOLOGY

The full assessment of a kidney biopsy requires light microscopy, EM, and examination for deposits of complement and immunoglobulin by immunofluorescence (IF) or immunoperoxidase (IP) techniques.

Light Microscopy

In GN the dominant, but not the only, histologic lesions are in glomeruli (Fig. 17.1). GN is described as focal (<50% of glomeruli are involved) or diffuse (>50% of glomeruli are involved). In any individual glomerulus, injury may be segmental (affecting <50% of any glomerulus) or global (>50%). Sampling error is possible in a kidney biopsy; the extent of a focal lesion may be misjudged in a small biopsy specimen, and sections through glomeruli may miss segmental lesions. Therefore, the number of glomeruli in a biopsy is an essential quality parameter, and serial sections may be necessary for the biopsy workup. In general and for most lesions and pathologies, 10 to 15 glomeruli are considered optimal and 8 to 10 necessary, albeit in a few cases a diagnosis can be made even on a single glomerulus. Lesions may be hypercellular (termed proliferative) because of an increase in endogenous cells or infiltration of inflammatory leukocytes, and based on localization (extracapillary, endocapillary, mesangial or combinations thereof). Severe acute inflammation may produce glomerular necrosis, which is often segmental. Multiple processes can cause thickening of the walls of the glomerular capillaries, including an increase in GBM material and immune deposits. Segmental sclerosis (scarring) may occur and is characterized by segmental capillary collapse with the accumulation of hyaline material and extracellular matrix, often with attachment of the capillary wall to Bowman’s capsule (synechiae or adhesion formation). The classic stains used in light microscopy include hematoxylineosin (HE) and the periodic acid–Schiff (PAS) reaction, the latter being particularly effective for evaluating the overall histological pattern. More specific stains include methenamine silver, which stains GBM and other matrix black and which is particularly helpful in revealing GBM abnormalities (such as double contours or spikes of the GBM), which are not easily detected with other techniques. Trichrome staining is also useful to show areas of scarring (blue) and immune deposits or thrombi (red).

Extracapillary proliferations, or crescents, are defined as increased number of cells in Bowman's space. Crescents develop when severe glomerular injury results in local rupture of the capillary wall or Bowman's capsule, allowing plasma proteins and inflammatory material to enter into Bowman's space. Crescents mainly consist of proliferating parietal cells, probably some visceral epithelial cells, and infiltrating fibroblasts; lymphocytes and monocytes/macrophages might be also involved, often with local fibrin deposition. They are called crescents because of their appearance when the glomerulus is cut in one plane for histology. Crescents are destructive, may rapidly increase in size, and may lead to glomerular tuft occlusion (see Fig. 17.1). If the acute injury is stopped, the crescents may probably either resolve with restitution of normal morphology or, more likely, heal via fibrosis (i.e., via transformation to fibrocellular and later fibrous crescents, which in turn may contribute to irreversible loss of renal function). Crescents are most frequently observed in vasculitis and in Goodpasture disease but also in severe acute GN of any cause.

Tubulointerstitial injury, inflammation, and tubular atrophy and fibrosis can accompany GN, particularly the latter, which is usually strongly correlated with prognosis (see Chapter 81).

Immunofluorescence and Immunoperoxidase Microscopy

Indirect IF and IP staining are both used to identify immune reactants (Fig. 17.2 and Table 17.1), particularly for immunoglobulins (IgG, IgA, and IgM), for components of the complement system (usually C3 and C1q in native and C4d in transplant biopsies), and for the presence of fibrin, which is typically observed in crescents and in capillaries in thrombotic disorders such as hemolytic uremic syndrome (HUS) and antiphospholipid syndrome. For diagnostic purposes, not only the composition of the deposits is important but also their localization; that is, in the mesangium or along capillary loops (distinguishing subepithelial, subendothelial, or combined localization) and in the staining pattern (i.e., continuous [linear] or discontinuous [granular]).

A

B

C

D

E

F

Fig. 17.1 Pathology of Glomerular Disease: Light Microscopy. Characteristic patterns of glomerular disease illustrating the range of histologic appearances and the descriptive terms used. (A) Normal glomerulus: minimal change disease. (B) Segmental sclerosis: focal segmental glomerulosclerosis. (C) Diffuse mesangial hypercellularity: immunoglobulin A nephropathy. (D) Diffuse endocapillary hypercellularity: poststreptococcal glomerulonephritis. (E) Segmental necrosis: renal vasculitis. (F) Crescent formation: anti–glomerular basement membrane disease. (A–B, hematoxylin-eosin; C–D and F, periodic acid–Schiff; E, trichrome.)

Electron Microscopy

Electron microscopy (EM) is valuable for defining the morphology of the GBM, which is abnormal in some forms of hereditary nephropathy (e.g., Alport syndrome and thin basement membrane nephropathy; see Chapter 48) and for identifying fibrils (e.g., in amyloidosis) or tubuloreticular intracellular structures (e.g., in lupus nephritis). EM is also useful for localizing the site of immune deposits, which are usually homogeneous and electron dense (Fig. 17.3). Electron-dense deposits are seen in the mesangium or along the capillary wall on the subepithelial or subendothelial side of the GBM. Infrequently, the electrondense material follows a linear pattern within the GBM. The sites of immune deposits are helpful in the classification of the types of GN.

GENERAL MECHANISMS OF GLOMERULAR INJURY

Proteinuria

Proteinuria, accompanied by variable degrees of hematuria, is the hallmark of glomerular disease. The endothelial glycocalyx and the GBM may repel proteins in part through their highly negative charge (proteins are mostly negatively charged as well) and prevent them from entering Bowman’s space. The key barrier for protein is the slit diaphragm between the podocyte foot processes[2,3] (Fig. 17.4). The slit diaphragm consists of several transmembrane proteins that extend from adjacent interdigitating foot processes to form a zipper-like scaffold on the outer side of the GBM (Fig. 20.1 and Chapter 1).

A

B

C

D

Fig. 17.2 Pathology of Glomerular Disease: Immunofluorescence Microscopy. Common patterns of glomerular staining found by immunofluorescence. (A) Linear capillary wall immunoglobulin (Ig) G: anti–glomerular basement membrane disease. (B) Fine granular capillary wall IgG: membranous nephropathy. (C) Coarse granular capillary wall IgG: membranoproliferative glomerulonephritis type I. (D) Granular mesangial IgA: IgA nephropathy.

The importance of the slit diaphragm in proteinuric states has been documented in numerous hereditary types of nephrotic syndrome in which the mutations involve various slit diaphragm proteins (see Chapter 20). These diseases usually manifest as a type of steroid-resistant minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). Whereas most recessive mutations of slit diaphragm or podocyte proteins manifest in childhood or even prenatally, dominant mutations tend to manifest in early adult life.3 An exception is steroid-resistant autosomal recessive nephrotic syndrome, in which the homozygous mutation in podocin (NPHS2) presents in childhood, but the heterozygous mutation, when it coexists with the p.R229Q variant polymorphism, may manifest clinically in young adulthood (age 20–35 years).4

Although it may result from injury or mutation of slit diaphragm proteins, proteinuria may be caused by nonspecific injury to the podocyte in many cases. When the podocyte is injured, it may undergo shape changes with swelling and loss or fusion of the foot processes. Filtration is reduced at sites where the foot processes fuse (possibly accounting for the reduction of the filtration coefficient Kf seen in nephrotic syndrome), but there are gaps where the podocytes are detached from the GBM. Massive protein filtration may occur at these sites; structurally, the capillary wall defects are likely to correspond to the large pores noted in functional studies5 (Fig. 17.5). Podocyte immaturity also can result in nephrotic syndrome, perhaps from incomplete differentiation and slit diaphragm development. Congenital nephrotic syndrome with mesangial sclerosis has been linked with mutations in the phospholipase C epsilon gene (PLCE1), which is important in podocyte development.6

In addition to podocyte damage, and in particular slit diaphragm defects, proteinuria also can result from changes in the glomerular endothelium, especially its glycocalyx, as well as from changes in the GBM and altered electrical forces across the GBM.

Severe albuminuria reflects a glomerular defect, but some albumin is normally filtered but then endocytosed and metabolized in the proximal tubule or is transcytosed intact through the tubular cell. Proximal tubular dysfunction can therefore result in albuminuria if endocytosis is impaired, although this is generally in the nonnephrotic range.

Antibody and Antigen

Many glomerular diseases are associated with deposition or glomerular trapping of immunoglobulins, often with components of the complement system, and with the presence of electron-dense deposits by EM. These findings likely represent immune complexes. Experimentally, immune complexes can localize in glomeruli by two major mechanisms. In some conditions, such as mesangial proliferative GN, diseases associated with a membranoproliferative GN (MPGN) pattern, or lupus nephritis, the immune complexes are thought to originate in the circulation and to be passively trapped in the mesangium or subendothelial areas. However, circulating immune complexes cannot readily pass across the GBM. Therefore, the presence of immunoglobulin G (IgG) on the subepithelial aspect of the basement membrane, such as occurs in membranous nephropathy (MN), either results from the direct binding of podocyte antigens by an antibody (e.g., phospholipase A2 receptor antibody) or represents binding of an antibody to an antigen that was temporarily “trapped” or bound at this site (in situ complex formation).7 GN also may occur only with complement activation in the glomeruli in the absence of IgG, as occurs in dense deposit disease (DDD), in which ribbon-like deposits replace the basement membrane (see Chapter 23). Some antigens may deposit in

TABLE 17.1 Antibodies Used in Nephropathology Diagnostics

Immunostaining	Example of Diagnostic Use
Standard	
IgG	Diseases with IgG deposits (e.g., MPGN, anti-GBM GN)
IgA	IgA nephropathy and vasculitis
IgM	Mixed cryoglobulinemia or Waldenstrom macroglobulinemia
C3	C3 glomerulopathies
C1q	Lupus nephritis
Kappa and light chain	Renal involvement in monoclonal light chain diseases
Fibrinogen	Necrosis, thrombotic microangiopathies
Specific	
Phospholipase A2 receptor	Primary membranous nephropathy
THSD7A, exostosin 1 and 2	PLA2R negative membranous nephropathy
IgG1, IgG2, IgG3	Monoclonal IgG deposits
IgG4	Membranous nephropathy, IgG4associated interstitial nephritis
DNAJB9	Fibrillary GN
Collagen type 4 alpha 3 and 5 chains	

Alport syndrome

Specific amyloid antibodies
(e.g., amyloid A,
transthyretin)

Subtyping amyloidosis

Each nephropathology laboratory uses a different set of antibodies as a standard panel; the five mentioned in this table are considered a “minimal” standard for nontransplant kidney biopsies.
In kidney transplant biopsies, C4d and eventually stains for polyomavirus are used as a standard set, additionally, staining for adenovirus or cytomegalovirus can be used.
DNAJB9, DnaJ homolog subfamily B member 9; GBM, glomerular basement membrane; GN, glomerulonephritis; Ig, immunoglobulin; MPGN, membranoproliferative GN pattern; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing protein 7A.

glomeruli and directly activate the alternative pathway of complement in the absence of IgG, as may occur in poststreptococcal GN (PSGN). Immunoglobulin with aberrant characteristics may also aggregate in glomeruli and activate complement in the absence of antigen, as occurs in IgA nephropathy with aberrantly glycosylated IgA (see Chapter 24) and glomerular diseases associated with monoclonal immunoglobulins (see Chapters 22 and 28).8
Normally, immune complexes are removed from the circulation by binding of the complex to the C3b receptors on erythrocytes. The immune complexes are then removed and degraded during transit of the erythrocytes in the liver and spleen. If antigenemia persists or clearance of complexes is impaired (e.g., chronic liver disease), immune complexes may deposit in the glomerulus by binding to Fc receptors on mesangial cells or by passive deposition in the mesangium or subendothelial space. Physical characteristics of the complexes also may favor deposition, including avidity, charge, and size. However, quantification of circulating immune complexes in patients with GN does not correlate reliably with glomerular events and thus is not typically measured.
In some glomerular diseases, the target antigen has been identified (Table 17.2). In other patients, glomerular disease develops as a result

of infection with organisms that release superantigens that cause a polyclonal activation of B cells. The classic organism responsible for superantigen-associated GN is Staphylococcus aureus, and the pattern of immune deposits often includes the presence of both IgG and IgA.
Some infections initiate an immune response that cross-reacts with endogenous antigens. This type of molecular mimicry may be responsible for Goodpasture disease and certain types of vasculitis9 (see Table 17.2). Once an immune response is initiated, local injury may lead to the release of additional antigens that extend the immune response (epitope spreading). In Goodpasture disease, in which the antigen is an α3 chain of type IV collagen, the antigen is present in the lung alveolar basement membrane but is normally sequestered. In tobacco smokers, however, the inhalation results in oxidative injury with exposure of the α3 chain, allowing the binding of antibodies.10 This may explain why lung involvement rarely occurs in nonsmokers with Goodpasture disease.

Complement

The complement system is often activated in glomerular disease (Fig. 17.6). Complement can be activated through three pathways. Classic pathway activation involves the binding of C1q to the Fc region of antibody in IgG- and IgM-containing immune complexes and can result in reduced serum C4 and C3. This is common in lupus nephritis, immune complex–induced GN, and cryoglobulinemic MPGN. Complement may be activated by the alternative pathway, which is activated independently of immune complexes and can be triggered by polysaccharide antigens, polymeric IgA, injured cells, bacterial products (e.g., streptococcal antigens), and antibodies to complement pathway components (C3 convertase). The alternative pathway appears to be activated in IgA nephropathy, DDD, and PSGN. Serum complement levels are generally normal in IgA nephropathy; in DDD and PSGN, however, the C3 is typically low but C4 is normal. In DDD as well as in C3-glomerulonephritis (C3GN) (see Chapter 23), the activation of the alternative pathway may not involve an antigen but rather results from continuous activation of the pathway through altered factor H or an IgG autoantibody (nephritic factor) that stabilizes the C3 convertase (see Chapter 23). Complement also can be activated through the mannose-binding lectin (MBL) pathway initiated by MBL, which has a structure similar to that of C1q. The role of the MBL pathway in GN is emerging in IgA nephropathy and idiopathic MN. However, despite evidence for intraglomerular complement activation in these conditions, serum complement components such as C3 and C4 generally remain in the normal range.

Activation of the complement pathway has several consequences. Leukocyte recruitment is facilitated by the chemotactic factor C5a, and C3b binding is important in the binding and opsonization of the immune complexes by the infiltrating leukocytes. The terminal membrane attack complex of the cascade, C5b-9, inserts into cell membranes, where it can kill cells or more commonly activate them to secrete cytokines, oxidants, and extracellular matrix. C5b-9 likely has a role in mediating injury to the glomerular epithelial cell in MN, in which immune deposits and complement activation occur in the subepithelial space. Complement also can be activated in proteinuric urine because of amidation of C3 by ammonia, which may have a role in mediating tubulointerstitial injury even in conditions not associated with immune complex formation. Experimental studies have emphasized the importance of local synthesis of complement components by the tubular cells as a mechanism that may augment this process.[11]

Activation of complement is controlled by complement regulatory proteins (see Fig. 17.6). A genetic absence or malfunction of factor H or other regulatory proteins can result in increased susceptibility to glomerular endothelial injury, resulting in thrombotic microangiopathy (Chapter 30) or less often hereditary forms of GN (see Chapter 23).

B

A

CL

BS

C

D

E

F

Fig. 17.3 Ultrastructural Pathology of Glomerular Disease. Some characteristic patterns of electrondense deposits and glomerular basement membrane (GBM) abnormalities seen in glomerular disease. (A) Normal. (B) Foot process effacement: minimal change disease (arrows). (C) GBM thickening and splitting: Alport syndrome. (D) Subendothelial electron-dense deposits (arrows): membranoproliferative glomerulonephritis type I. (E) Subepithelial electron-dense deposits (arrows): membranous nephropathy. (F) Mesangial electron-dense deposits (arrows): IgA nephropathy. BS, Bowman’s space; CL, capillary lumen.

Antigens Identified in Glomerulonephritis

TABLE 17.2

Mechanisms of Proteinuria
Normal epithelium
Urinary space

Epithelial cell defects

Visceral epithelium

Disease

Antigens

Poststreptococcal GN

Streptococcal pyrogenic exotoxin B (SPEB), plasmin receptor
α3 type IV collagen (likely induced by molecular mimicry)
Possibly no antigen but rather polymeric polyclonal IgA (? superantigen driven)
Phospholipase A2 receptor
Thrombospondin type-1 domain-containing 7A
Neutral endopeptidase in podocyte (congenital)
HBeAg (hepatitis B virus associated)
Staphylococcus superantigens induce polyclonal response; not necessarily antigen in glomeruli
HCV and HBsAg in hepatitis-associated MPGN

Anti-GBM disease
IgA nephropathy

Endothelium

MNa

Albumin

Albumin
Capillary lumen

Fig. 17.4 Mechanisms of Proteinuria. Normally, negatively charged proteins such as albumin (blue circles) are repelled by the negatively charged proteins in the endothelium (sialoglycoproteins) and basement membrane (heparan sulfate proteoglycans), as well as by a size barrier in the glomerular basement membrane (GBM) and at the slit diaphragm so that only small amounts of albumin pass into the urinary space. In most proteinuric states, the podocytes are injured, leading to foot process swelling and injury to the slit diaphragm; in these situations, large amounts of protein (albumin) can pass through the GBM and the gaps between the fused foot processes (red arrows).

Glomerular Permeability in Nephrotic Syndrome
1

Fractional dextran clearance

Controls
Nephrotic syndrome
0.1

0.01

0.001
24

28

32

36 40 44 48 52 56 60
Dextran radius (Å)

Fig. 17.5 Glomerular Permeability in Nephrotic Syndrome. Dextran sieving curve shows the relative glomerular permeability of differentsized dextrans in normal individuals and nephrotic patients with membranous nephropathy and minimal change disease. Nephrotic patients actually have a lower fractional dextran clearance for small dextrans (26–48 Å [2.6–4.8 nm]) but have an increased clearance for dextrans of larger molecular weight (52–60 Å [5.2–6.0 nm]). This is consistent with large pores appearing in the glomerular basement membrane. (Modified from Machuca E, Hummel A, Nevo F, et al. Clinical and epidemiological assessment of steroid-resistant nephrotic syndrome associated with the NPHS2 R229Q variant. Kidney Int. 2009;75:727–735.)

Staphylococcus aureus–
associated GN
MPGN

aSee Chapter 21 for less common newer autoantigens.
GBM, Glomerular basement membrane; GN, glomerulonephritis; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IgA, immunoglobulin A; MPGN, membranoproliferative GN pattern; MN, membranous nephropathy; SPEB, streptococcal pyrogenic exotoxin B.

Mechanisms of Immune Glomerular Injury

Two major mechanisms account for the presence of immune complexes in glomerular diseases. There may be ineffectual clearance of an antigen from an impaired immune response, as in chronic viral infections caused by hepatitis B or hepatitis C virus (HBV or HCV). Despite a strong humoral response, viral infection persists because the cell-mediated response required for elimination of these viruses is impaired. The consequence is a state of persistent antigenemia with circulating antigen-antibody complexes, which predisposes to glomerular injury. Eradication of the virus with antiviral therapy can be associated with remission of the glomerular disease.

More often, glomerular disease results from autoimmunity. In health, a tension exists between the normal immune response to foreign antigen and tolerance, which is the cellular process that prevents an immune response to self-antigen. Tolerance develops because selfreactive T and B cells are clonally deleted during fetal and neonatal life, although small numbers survive outside the thymus or bone marrow, respectively. Under certain conditions, these peripheral self-reactive cells can be stimulated to generate a cellular and humoral response to a self-antigen. Infection or toxins may play a role in initiating the response by releasing antigens from sequestered sites so they have access to dendritic cells, which carry the antigen to lymph nodes for presentation to T cells, by altering host proteins to make them more immunogenic, or by molecular mimicry, in which antibodies to an exogenous antigen (e.g., those present in infecting organism) crossreact with a native protein.[12] Activation of T cells may be further enhanced by the release of cytokines or endogenous danger-associated molecular patterns, such as toll-like receptor ligands or inflammasome activators, and the conversion of normally innocuous endogenous renal cells into antigen-presenting cells through the upregulated or de novo expression of human leukocyte antigen (HLA) class II molecules and cytokines.

Regulatory T cells (CD4+, CD25+) have a key role in controlling T cell responses and preventing the development of autoimmunity. However, their role is not well understood, and the local regulation of these cells in the kidney by a subset of dendritic cells (CD103+) may be more important than systemic numbers of regulatory T cells.[13]

Complement System
Mannose-binding lectin (MBL) pathway Alternative pathway
Classical pathway
Circulating autoactivated C3b
MBL (similar structure to C1q)
C1q binds to Fc portion of IgG
binds to activating surface
binds to bacterial cell wall
or IgM in an immune complex
MBL
Immune complex

Bacterial polysaccharides
Injured cells
Aggregated IgA
Endotoxins

C3b
MASP-1

C1q

C4

MASP-2
B
Properdin

C2

Classical
C3 convertase
C4b2b

D

Alternate
C3 convertase
C3bBb

C3a Anaphylatoxin

C3

Properdin

C3b Immune adherence
H
C3b

I
iC3bC3d

Classical C5
convertase
C4b2b3b

Alternate
C5 convertase

C3bBbP*C3b
C5

C5a Chemotactic factor:
attracts inflammatory cells

C6
C7
C8
C9
C5b-9: membrane
attack complex

Fig. 17.6 Complement System. The complement system is a self-amplifying cascade of proteins that generates a membrane attack complex, which is cytolytic; the cascade promotes inflammation by the activity of the fragments it produces. The amplifying cascades result from activated fragments of the components combining to make convertase enzymes that degrade C3 and C5. The complement cascade is controlled in part by the short active life of many of its components. There are also inhibitory regulatory proteins, most notably factors H and I inhibiting C3b. Activated fragments of any component are designated b (e.g., C3b); anaphylatoxic fragments are designated a (e.g., C5a). Inflammatory functions of complement components are shown in green. IgA, Immunoglobulin A; MASP, MBL-associated serine protease.

Variations in HLA molecules and the T cell receptor are under strong genetic influence. Close immunogenetic associations, particularly between HLA expression and various patterns of GN, have been described in IgA nephropathy, MN, and other glomerular diseases. For example, whereas HLA-DR2 identifies a powerful relative risk for the development of Goodpasture disease, some individuals can develop the disease without HLA-DR2, and the vast majority with HLA-DR2 never develop this rare disease. HLA associations also differ among various ethnic groups. To date, HLA associations have no practical diagnostic or therapeutic implications, and HLA typing is not needed in the clinical management of patients with GN.

Inflammation

The presence of glomerular inflammation is largely determined by the site of immune deposits. Immune deposits with direct access to the circulation (subendothelial and intrabasement membrane locations) are usually associated with leukocyte accumulation. Mesangial deposits elicit an intermediate response, whereas immune deposits in the subepithelial space generally are not associated with inflammatory cells.

In GN associated with subendothelial deposits, such as class III or IV lupus nephritis or MPGN, leukocyte infiltration is common. With acute injury, the predominant infiltrating cells are platelets and monocytes, and occasional neutrophils, and in chronic injury the predominant cells are monocyte/macrophages and T cells. The primary mechanism for attracting these cells is the secretion of chemokines and the expression of leukocyte adhesion molecules by local endothelial and resident cells; local release of complement activation fragments (C5a) is also important.

Although neutrophils are common with immune complex disease, cell-mediated immunity is important in some glomerular diseases. For example, T cells likely have a role in crescentic nephritis, becoming

Crescent Formation
Normal

GBM rupture

- Podocyte
- Glomerular endothelial cell
- Parietal epithelial cell
- Interstitial fibroblast
- Monocyte-macrophage
- Fibrin-clot
- Interstitial collagenfibrils

Fibrous crescent
Cellular crescent
Restitution

Fig. 17.7 Crescent Formation. In early crescent formation, cytokines and growth factors cross the glomerular basement membrane (GBM) to initiate proliferation of the parietal epithelial cells. Small breaks in the GBM occur secondary to injury from oxidants and proteases from neutrophils and macrophages, thus allowing the macrophage to enter Bowman's space, where it can proliferate. Breaks in Bowman's capsule secondary to the periglomerular inflammation also occur, allowing the entrance of more inflammatory cells, as well as fibroblasts. The proliferation of parietal and visceral epithelial cells and macrophages is associated with fibrin deposition, slowly choking the glomerular tuft until filtration becomes impossible. In the late stages, the crescent becomes fibrotic and the glomerulus end stage. Alternatively, in less severe cases, complete restitution of the glomerular tuft can occur.

sensitized to endogenous or exogenous antigen and then recruiting macrophages that mediate crescent formation.

Proliferation, Apoptosis, and Fibrosis

Intrinsic glomerular cells (epithelial, mesangial, and endothelial) are also activated in various glomerular diseases. Mesangial cells can become myofibroblast-like cells that proliferate and produce excessive extracellular matrix. Endothelial cells produce nitric oxide and other antiinflammatory proteins, and injury to this cell population can result in the expression of leukocyte adhesion molecules and activation of the coagulation system. Podocytes are differentiated epithelial cells that when injured undergo shape change (reorganization of the actin filaments) that can lead to disruption of the slit diaphragm, resulting in proteinuria. Interestingly, podocytes also can be induced to express receptors involved in antigen presentation that are similar to those expressed by dendritic cells. Progressive loss of podocytes by apoptosis is associated with the development of glomerulosclerosis. Important growth factors associated with glomerular injury include transforming growth factor β (TGF-β), which mediates matrix deposition; platelet-derived growth factor (PDGF), which mediates mesangial cell proliferation; and vascular endothelial growth factor (VEGF), required for endothelial health.

Crescent formation represents a severe cellular response and is initiated by cytokine-driven proliferation, particularly of the parietal epithelial cells. Local breaks in the GBM or Bowman's capsule, mediated by activated leukocytes, are followed by macrophage infiltration, proliferation of parietal epithelial cells and podocytes, and local fibrin deposition (Fig. 17.7).

Glomerular scarring (i.e., sclerosis) is characterized by proliferation of mesangial cells with loss (apoptosis) of endothelial cells and podocytes and deposition of extracellular matrix. Tubulointerstitial fibrosis also accompanies progressive glomerular disease and correlates with both renal function and prognosis. Proteinuria has been shown to activate tubular cells and induce toxicity, either directly or through the generation of oxidants (from iron proteins excreted in urine) or from complement activation, which can be shown in proteinuric urine. Tubulointerstitial ischemia after loss of glomerular and peritubular capillaries also may drive fibrosis. Finally, loss of renal function may result from leakage of plasma ultrafiltrate into the peritubular space, resulting in a scarring response (misdirected filtration) or stenosis/occlusion of the opening of the proximal tubule from Bowman’s space, resulting in nonfunctional (atubular) glomeruli. A detailed discussion of current mechanisms involved in glomerulosclerosis is presented in Chapter 81. Specific pathogenic mechanisms in the different patterns of glomerular disease are discussed in subsequent chapters in Section IV.

PATHOGENESIS OF SPECIFIC GLOMERULAR SYNDROMES

Minimal Change Disease

Minimal change disease (MCD) is a steroid-sensitive nephrotic syndrome in which the only structural abnormality is podocyte swelling and fusion of foot processes on EM (see Chapter 18). For many years, the podocyte injury in MCD was thought to be caused by a cytokine released from T cells. T cells are activated in MCD, and T cell hybridomas from these patients were reported to secrete a factor that provokes heavy proteinuria in rats.[14] One candidate cytokine is interleukin-13 (IL-13), which is expressed by T cells in patients with MCD; overexpression of IL-13 causes nephrotic syndrome and histologic changes consistent with MCD in rats. However, proteinuria can be induced in immunodeficient mice using CD34-positive hematopoietic bone marrow cells of patients with MCD and recurrent FSGS but not by their T cells.15 Thus, the role of T cells in this disorder remains to be clarified.

Evidence also suggests that the podocyte injury is associated with overexpression of angiopoietin-like-4, which is associated with a proteinuric response.16 This overexpression can be reduced with corticosteroids and N-acetyl-d-mannosamine. In addition, patients with MCD show high levels of CD80 (also known as B7.1) in urine and in podocytes, and the level of urinary CD80 correlates with disease activity. CD80 is an antigen that is normally expressed by dendritic cells and B cells.

Finally, two additional discoveries have been recently made. The first is the observation that a subset of patients with MCD have antibodies to nephrin despite IF showing minimal IgG deposition in glomeruli. The other observation is that the majority of individuals with MCD have evidence for mild glomerular endothelial injury with circulating endothelial biomarkers. This has suggested that MCD is not a strict “podocytopathy” as originally proposed.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a generic term to describe a pattern of glomerular scarring and is therefore nonspecific. Focal segmental sclerosing lesions in the absence of nephrotic syndrome, often termed secondary FSGS, can occur in a range of contexts, including GN, chronic hypertension, obesity, and progressive renal disease of any etiology. These lesions are particularly common in African Americans; recent findings suggest this susceptibility relates to increased frequency of a genetic polymorphism in APOL1, a gene coding for a circulating lipoprotein.

When the histologic pattern of FSGS is seen in association with the nephrotic syndrome (a podocytopathy often termed primary FSGS if there is no associated condition), immune deposits are absent, but as with MCD, there is a generalized foot process fusion (also termed effacement) on EM (see Chapter 19). However, unlike MCD, there is segmental scarring (sclerosis) in some glomeruli with FSGS. Some forms of FSGS result from mutations of podocyte proteins (see Chapter 20), whereas others are believed to originate from a circulating factor; cardiotrophin-like cytokine 1 is one candidate molecule, but others are also being investigated as potential circulating factors that may mediate FSGS (see Chapter 19). Although it is unproven, some consider that MCD and FSGS share similar pathogenic mechanisms and are part of a “podocytopathy” spectrum in which MCD has lower levels of the circulating factor and is therefore more sensitive to corticosteroids. These forms of FSGS may be particularly prone to rapid recurrence, sometimes within hours, after renal transplantation.

A variant of FSGS is collapsing FSGS, in which there is proliferation of the normally quiescent podocyte, leading to collapse of the glomerular tuft, often in association with massive proteinuria. The pathogenesis may involve production by the podocyte of growth factors such as VEGF or local inhibition of cell cycle proteins that normally maintain the podocyte in a nonproliferative state.17

Membranous Nephropathy

In membranous nephropathy (MN), immune deposits are localized to the subepithelial space, representing autoantibody binding to an intrinsic podocyte antigen (see Chapter 21). The major antigen is the M-type phospholipase A2 receptor (PLA2R), accounting for as many as 70% of cases of idiopathic MN.18 Antibodies to PLA2R are specific for MN. Circulating anti-PLA2R reflects the immunologic activity of the disease and may be useful to monitor the clinical course, including patient response to treatment. Other autoantibodies have been found, albeit much less frequently, including those against thrombospondin type-1 domain-containing 7A,[19] exostosin-1 and exostosin-2,[20] neutral

endopeptidase (in the very rare neonatal MN), or against bovine serum albumin (BSA).[21] Some cases of MN may be caused by low-avidity immune complexes, which may dissociate and then reform at the subepithelial space; this may be a mechanism for some MN caused by viruses such as HBV.

Most cases of idiopathic MN caused by anti-PLA2 antibodies are associated with IgG4 deposition, which is an isoform of IgG that does not activate the classic complement pathway. However, there is evidence that the IgG4-PLA2 complex can activate complement through the MBL complement pathway, resulting in local generation of the membrane attack complex (C5b-9), which may insert into the podocyte to cause activation, injury, and proteinuria.

Glomerulonephritis With a Membranoproliferative Pattern on Histology

The term MPGN describes a histologic pattern rather than a single disease entity. The pattern may result from localization of immune deposits to both the mesangium and the subendothelial space (see Chapter 22).

One of the diseases causing an MPGN pattern is cryoglobulinemic GN, in which the immune complexes contain a monoclonal IgM or polyclonal IgM that acts as a rheumatoid factor by binding to the IgG in the immune complex. Whether due to cryoglobulinemia or another cause, the MPGN pattern and its clinical consequences are thought to occur by passive deposition from the circulation, and the antigen is often a component of the HCV virus, especially in adults. When this pattern is seen in lupus nephritis, it may be facilitated by the binding of extracellular nucleosomes to the complexes. Nucleosomes are cationic nuclear proteins that can interact with the negatively charged proteins within the glomerulus.

Studies in experimental models suggest that the intraglomerular immune complexes cause local complement activation with the generation of chemotactic factors, including C5a, chemokines, and leukotrienes. Leukocyte adhesion molecules on endothelial cells are upregulated (intracellular adhesion molecule 1) or expressed de novo (E- and P-selectin). Proinflammatory cytokines (IL-1 and tumor necrosis factor-α) are generated locally and augment the inflammatory response. Neutrophils, platelets, and monocytes/macrophages then localize in the glomerulus and release oxidants, particularly hypohalous acids generated by neutrophil myeloperoxidase, and proteases (elastase, cathepsin G, metalloproteinases) that cause local cellular injury and GBM degradation.

Dense Deposit Disease and C3 Glomerulonephritis

In contrast to the MPGN forms described above, immune complexes are absent in glomeruli of patients with DDD and C3-GN. Initiation results from spontaneous intraglomerular activation of the alternative complement pathway. The most common cause is nephritic factor, an autoantibody that activates the alternative pathway. Some cases may be caused by mutations of the complement regulatory factor H, in which case the location of the mutation within the gene determines whether the disease manifests as DDD or atypical HUS.[22]

Mesangial Proliferative Glomerulonephritis

IgA nephropathy is the most common type of GN (see Chapter 24). Production of an abnormally glycosylated IgA, possibly by a bacterial superantigen,[23] or perhaps from an altered mucosal immune system, may lead to IgA polymers that deposit in the mesangium; the glomerular capillary wall is relatively spared. Marked yet usually nonnephrotic proteinuria is a common feature of the clinical presentation. Mesangial cell injury may be mediated by binding of the IgA-containing immune complexes to Fcα or other IgA receptors on the mesangial cell, resulting in the release of chemokines and growth factors that provokes leukocyte infiltration as well as mesangial cell proliferation and mesangial matrix production.

Poststreptococcal Glomerulonephritis

Poststreptococcal GN (PSGN) has long been considered the human equivalent of acute serum sickness in rabbits (see Chapter 57). It is observed only in patients infected with specific (nephritogenic strains) of group A streptococci. One antigen responsible for some cases of PSGN, streptococcal pyrogenic exotoxin B, enters the circulation and localizes to glomeruli, resulting in a brisk inflammatory reaction with local endothelial and mesangial cell proliferation and manifestations of nephritic syndrome. Complement activation occurs through the alternative pathway and may result from direct activation of the pathway by streptococcal antigens. Some deposits ("humps") also form in the subepithelial space and may represent the translocation of immune complexes across the GBM or in situ immune complex formation.

Goodpasture Disease

Goodpasture disease (anti-GBM disease) is caused by an autoantibody to the α3 chain of type IV collagen present in the GBM and alveolar basement membrane (see Chapter 25). The autoantibody develops in genetically susceptible individuals because of molecular mimicry between the type IV collagen antigens and certain bacterial antigens.9 Binding of antibody results in complement activation with the infiltration of inflammatory cells, causing local capillary wall damage and proteinuria. Crescent formation also usually occurs and may be mediated by both T cells and macrophages.

Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A severe form of segmental necrotizing glomerular injury, often in association with crescents, can be observed with vasculitis (see Chapter 26). The two most common types of vasculitis causing this type of injury are granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Both are associated with circulating antibodies against neutrophil cytoplasmic antigens (ANCAs), with antibodies to endopeptidase (proteinase) 3, which give a cytoplasmic pattern by staining (c-ANCA) in most patients with GPA granulomatosis, and antibodies to myeloperoxidase, which give a perinuclear staining pattern (p-ANCA) in subjects with MPA. Experimental evidence suggests that ANCAs are pathogenic by activating neutrophils within the vasculature. The mechanism responsible for triggering autoantibodies to neutrophil antigens remains unclear, although geographic and temporal clustering suggest a role for infection or antigen exposure that may induce an autoimmune response.12

Further discussion of specific pathogenic mechanisms in the different patterns of glomerular disease can be found in Chapters 18 to 30

SELF-ASSESSMENT QUESTIONS

1. MN may result from all of the following except:

A. Anti–phospholipase A2 receptor antibodies
B. Thrombospondin type-1 domain-containing 7A antibodies
C. Antibodies to cationic bovine serum albumin
D. Factor H deficiency
E. Deposition of hepatitis B virus antigens and antibody

2. A low serum C3 level would suggest all the following diseases except:

A. Membranoproliferative glomerulonephritis secondary to hepatitis C virus
B. Cryoglobulinemic glomerulonephritis accompanying bacterial endocarditis
C. Class IV lupus nephritis
D. Goodpasture disease
E. Class III lupus nephritis

3. Marked proteinuria typically results from damage to which structures?
A. Mesangial cells
B. Parietal epithelial cells
C. Podocytes
D. Preglomerular arterioles
E. Loops of Henle
4. Which statement best describes FSGS?
A. It is typically a disease of the mesangium.
B. It usually results in nephrotic syndrome.
C. It can result from a circulating factor.
D. It is an autoimmune disease.
E. Most cases result from mutations.

REFERENCES

1. Sethi S, Haas M, Markowitz GS, et al. Mayo clinic/renal pathology society consensus report on pathologic classification, diagnosis, and reporting of GN. J Am Soc Nephrol. 2016;27:1278–1287.
2. Mundel P, Shankland SJ. Podocyte biology and response to injury. J Am Soc Nephrol. 2002;13:3005–3015.
3. Hildebrandt F, Heeringa SF. Specific podocin mutations determine age of onset of nephrotic syndrome all the way into adult life. Kidney Int. 2009;75:669–671.
4. Machuca E, Hummel A, Nevo F, et al. Clinical and epidemiological assessment of steroid-resistant nephrotic syndrome associated with the NPHS2 R229Q variant. Kidney Int. 2009;75:727–735.
5. Myers BD, Guasch A. Mechanisms of proteinuria in nephrotic humans. Pediatr Nephrol. 1994;8:107–112.
6. Hinkes B, Wiggins RC, Gbadegesin R, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nat Genet. 2006;38:1397–1405.
7. Couser WG. Pathogenesis of glomerular damage in glomerulonephritis. Nephrol Dial Transplant. 1998;13(suppl 1):10–15.
8. Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis. 2011;58:992–1004.
9. Arends J, Wu J, Borillo J, et al. T cell epitope mimicry in anti–glomerular basement membrane disease. J Immunol. 2006;176:1252–1258.
10. Kalluri R, Cantley LG, Kerjaschki D, Neilson EG. Reactive oxygen species expose cryptic epitopes associated with autoimmune Goodpasture syndrome. J Biol Chem. 2000;275:20027–20032.
11. Sheerin NS, Risley P, Abe K, et al. Synthesis of complement protein C3 in the kidney is an important mediator of local tissue injury. FASEB J. 2008;22:1065–1072.
12. Couser WG, Johnson RJ. The etiology of glomerulonephritis: roles of infection and autoimmunity. Kidney Int. 2014;86(5):905–914.

13. Evers BDG, Engel DR, Böhner A, et al. CD103+ kidney dendritic cells protect against crescentic glomerulonephritis by maintaining IL-10–producing regulatory T cells. J Am Soc Nephrol. 2016;27(11):3368–3382.
14. Koyama A, Fujisaki M, Kobayashi M, et al. A glomerular permeability factor produced by human T cell hybridomas. Kidney Int. 1991;40:453–460.
15. Sellier-Leclerc AL, Duval A, Riveron S, et al. A humanized mouse model of idiopathic nephrotic syndrome suggests a pathogenic role for immature cells. J Am Soc Nephrol. 2007;18:2732–2739.
16. Clement LC, Avila-Casado C, Macé C, et al. Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. Nat Med. 2011;17:117–122.
17. Barisoni L, Kriz W, Mundel P, D’Agati V. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 1999;10:51–61.
18. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361:11–21.
19. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371:2277–2287.
20. Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/exostosin 2-associated membranous nephropathy. J Am Soc Nephrol. 2019;30:1123–1136.
21. Debiec H, Lefeu F, Kemper MJ, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med. 2011;364:2101–2110.
22. Pickering MC, de Jorge EG, Martinez-Barricarte R, et al. Spontaneous hemolytic uremic syndrome triggered by complement factor H lacking surface recognition domains. J Exp Med. 2007;204:1249–1256.
23. Koyama A, Sharmin S, Sakurai H, et al. Staphylococcus aureus cell envelope antigen is a new candidate for the induction of IgA nephropathy.

Kidney Int. 2004;66:121–132.

18

Minimal Change Disease

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INTRODUCTION

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children (approximately 80%) and accounts for 10% to 20% of cases in adults. MCD is so called because on kidney biopsy, glomeruli are normal or near normal on light microscopy, with podocyte foot process fusion or effacement found on electron microscopy. Compared to other causes of nephrotic syndrome, MCD has a higher rate of remission after steroid treatment, with better long-term kidney outcomes.

However, MCD still causes significant morbidity, especially in older patients, due to complications such as acute kidney injury (AKI) and thrombosis. A high proportion of patients with MCD relapse, resulting in the need for multiple courses of steroids or alternative immunosuppressive therapy and significant associated side effects.1

EPIDEMIOLOGY

The International Study of Kidney Disease in Children (ISKDC) study found that 363 of 471 (77%) children presenting with nephrotic syndrome had MCD as the underlying histologic diagnosis,2 and MCD accounted for 94% of cases in patients younger than 6 years who responded to an 8-week course of oral steroids. In older children with nephrotic syndrome, the proportion with MCD decreases steadily, reaching about 50% of all cases between ages 8 and 16 years, with a rising proportion secondary to focal segmental glomerulosclerosis (FSGS) relative to MCD.

The incidence of MCD in children ranges from 1.2 to 7 new cases per 100,000 population. It has a higher incidence during winter and shows variability among different populations. The incidence of MCD is reported to be as low as 1 per million population in the United Kingdom and up to 27 per million in the United States. It is less common in Blacks, in whom nephrotic syndrome is much more likely to be caused by FSGS.3 In adults, MCD is generally rarer than in children, although incidence is less well defined.

ETIOLOGY

Most patients have idiopathic MCD. Secondary MCD is usually clinically indistinguishable from idiopathic MCD1; causes include Hodgkin disease and nonsteroidal antiinflammatory drugs (NSAIDs) (see Table 18.1 for full list).

Stimulation of the immune system (e.g., by infections or atopic reactions) has been linked with both onset and relapses of MCD. In children, most exacerbations occur with an upper respiratory infection,1 and recent reports show an association with SARS-CoV-2.

Atopic individuals have a higher risk of MCD, and atopic reactions, such as to pollen, bee stings, and food allergens, have been reported as triggers of MCD relapses. This clinical association led to the introduction of allergen-free diets for patients with MCD, and a gluten-free diet, elemental diets, or skin desensitization may result in a decrease in proteinuria.4 A link between vaccinations and presentations and relapses of MCD has also been suggested.

Rare cases of familial MCD have been reported but likely represent an underlying mutation in genes encoding for slit diaphragm proteins instead of primary or idiopathic MCD.5 Certain human leukocyte antigen alleles and other genes have been suggested to lead to an increased risk of MCD.6

PATHOGENESIS

Traditionally, MCD has been considered an immune disorder in which circulating T cells release factors that increase the permeability of the glomerular filtration barrier to plasma proteins by altering podocyte shape. However, the pathogenesis remains poorly understood.

Fig. 18.1 summarizes proposed pathways involved in MCD.

Circulating Factors as Mediator of Disease

In 1974, Shalhoub postulated that MCD was a T cell–mediated disorder based on the lack of immune deposits in the glomerulus, the rapid response to steroids, the association with Hodgkin disease, and the observation that remission often occurred during resolution of measles infection.7 This hypothesis was supported by the observations that (1) supernatants from T cell hybridomas from a patient with MCD induced podocyte injury and proteinuria in rats,8 and (2) proteinuria remitted when kidneys from a patient with active MCD were transplanted into patients without nephrotic syndrome.9 Several candidate molecules have been considered as possible circulating factors.

Cytokines

Certain T cell cytokines have been proposed as circulating factors, including interleukins IL-4 and IL-13. Some animal studies have shown that IL13 or IL-4 can lead to increased proteinuria and foot process effacement, although how this translates to human MCD is unclear.10 Levels of IL-4 and IL-13 are higher in children with nephrotic relapse compared with healthy controls or those in remission, although this is not true for all patients. IL4 and IL-13 are both produced as part of a Th2 immune response, which underlies atopy. Cytokines from other T cells may also be implicated. IL17 and IL-23 from proinflammatory Th17 cells are higher in MCD than controls, whereas IL-10 and TGFβ from opposing T-regulatory (Treg) cells are higher in controls. An increased Th17:Treg ratio was found in MCD patients compared with a control group. This ratio normalized with therapy, leading to the hypothesis that MCD may be due to an imbalance of proinflammatory Th17 cells and immune-modulatory Tregs.11 Other proinflammatory cytokines of the innate immune system may also have a role in MCD. IL-8 has also been shown to increase urine protein creatinine ratio after its infusion into rats.12 Tumor necrosis factor-α (TNF-α) has also been shown to act directly on podocytes, where it causes nephrin

Secondary Causes of Minimal Change Disease

TABLE 18.1

Causes	Examples
Drugs	NSAIDs, interferon-α, lithium (rare: usually causes chronic interstitial nephritis), tamoxifen, antimicrobials (ampicillin, rifampicin, cefixime), gold (rare: usually causes membranous nephropathy), mercury in skin-lightening products
Allergy	Pollen, house dust, insect stings, poison oak
Hematologic conditions	Hodgkin disease, non-Hodgkin lymphoma, leukemia, hemophagocytic syndrome, myelodysplastic syndrome
Solid organ tumors	Most commonly lung, colorectal, renal cell carcinoma, thymoma (rare: pancreatic, breast, bladder, ovarian)
Other	Immunizations

NSAIDs, Nonsteroidal antiinflammatory drugs.

downregulation, restructuring of the actin cytoskeleton, and altered focal adhesions.13 However, case studies show that TNF-α blockade with etanercept can also lead to MCD.

Hemopexin

Hemopexin is synthesized in the liver and is present in human plasma of patients with MCD. Mechanistically, hemopexin is thought to mediate podocyte injury in a nephrin-dependent manner, but the role of hemopexin in MCD remains unproven.

Microbial Products

A role for microbial products as circulating factors is attractive because of the association between upper respiratory infections and relapses. Two toll-like receptor (TLR) ligands, lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, and polyinosinicpolycytidylic acid (polyIC), a viral-like particle, bind to TLR-4 and TLR-3 on podocytes, respectively, and cause proteinuria in animals.14 However, the relevance of these findings for human MCD remains unknown.

Glomerular Filtration Barrier in Healthy State and Minimal Change Disease During Relapse

Fig. 18.1 Glomerular Filtration Barrier in Healthy State (left) and in Minimal

Change Disease (MCD) During Relapse (right). In MCD, microbial products, circulating interleukins, hemopexin, and/or antinephrin antibodies (Ab) may target podocytes leading to foot process effacement and proteinuria. Circulating products may target and activate endothelial cells during relapse. Upregulation of CD80, c-mip, and angiopoietin-like 4 (Angptl4) seem to play a role in experimental models of MCD-like injury. ARP 2/3, Actin-related protein 2/3 complex; CD80, cluster of differentiation 80; CD2AP, CD2-associated protein; c-mip, c-maf inducing protein; DG, dystroglycans; IL, interleukin receptor; SMPDL3b, sphingomyelin phosphodiesterase acid like 3B; TLR, toll-like receptor;TRPC6, Transient receptor potential cation channel subfamily C member 6; WASP, Wiskott-Aldrich syndrome protein.
(Figure created using biorender.com.)

Loss of Anionic Charges in the Glomerular Filtration Barrier

Heparan sulfate proteoglycans (HSPs) represent the major source of anionic sites in the glomerular basement membrane (GBM), and loss of HSP is observed in some MCD patients. Although HSP loss was thought to facilitate the passage of albumin through the GBM, subsequent experimental studies do not support this hypothesis driving proteinuria in MCD.15 An “electrokinetic model” has been proposed in that the endothelial glycocalyx represents a major site for the generation of a streaming potential that would repel albumin before passing through endothelial fenestration.16 Scattered reports showed increased circulating markers of endothelial injury in MCD, but their significance is unknown.

Podocyte Dysfunction as a Cause of Minimal Change Disease

In patients with MCD during relapse, podocytes display several molecular changes. An increase in podocyte focal adhesion kinase phosphorylation has been reported in MCD but not in FSGS.17 Likewise, changes in nephrin expression, phosphorylation, and localization have been reported by several groups.18 In experimental models, few molecules have been thought to mediate podocyte injury (Fig. 18.1).

CD80. In cultured podocytes, CD80 mediates actin reorganization and podocyte migration by targeting Neph 1 and β1 integrins. In some patients with active MCD, CD80 can be upregulated in glomerular cells, primarily glomerular endothelial cells but also podocytes.19 In addition, most patients with MCD have higher urinary CD80 levels than patients with other glomerular disease,20 but the relevance of this finding remains unknown. Anti-CD80 therapy has been associated with remission in two patients with MCD and high urinary CD80, whereas results in patients with FSGS have been contradictory.

Angptl4. This is a glycoprotein that has been proposed as a mediator of proteinuria in MCD. In a transgenic rat model characterized by glomerular overexpression of Angptl4 and podocin, rats had a marked loss of GBM heparan sulfate proteoglycans, podocyte foot process effacement, and albuminuria.21 However, data on Angptl4 in MCD are scarce and conflicting. A larger study did not confirm that MCD is associated with glomerular overexpression of Angptl4. In addition, urinary Angptl4 levels do not differ between different glomerular diseases.22

C-mip. Experimental studies provide evidence for a pathogenic role of podocyte c-mip in proteinuria and podocyte injury. Mechanistically, c-mip impairs nephrin phosphorylation, which is a molecular feature of MCD. C-mip is upregulated in podocytes from patients with MCD but also in patients with other glomerular diseases,23 so the exact role of c-mip in MCD is yet to be determined.

Role of B cells

The anti-CD20 monoclonal antibody rituximab has been effective for treating some patients with MCD, suggesting that B cells could be implicated in MCD. Recently, some patients with MCD were found to have antinephrin antibodies in circulation and in glomeruli.23b Still, the role of B cells in MCD, either secreting antibodies or modulating T cell activation, remains poorly understood. It has been postulated that rituximab exerts a direct protective role in podocytes by binding to sphingomyelin phosphodiesterase acid-like 3 b (SMPDL3B),24 but this remains controversial.10

In summary, the mechanisms of podocyte injury in MCD remain unknown. How findings from experimental studies may translate to human disease remain a matter of debate and clearly require further investigations. It also highlights the need to develop novel animal models of MCD. The observation that glomerular endothelial cells are activated during relapse warrants further investigation, as well as the role of B cells and B cell–T cell interactions in MCD.

Fig. 18.2 Podocyte Toot Process Fusion and Effacement in Minimal Change Disease. The epithelial cells (arrows) are completely effaced along the glomerular basement membranes. (Electron micrograph; magnification ×6000.) The normal appearance of epithelial cell foot processes is shown in Chapter 1, Figs. 1.6 and 1.7.

PATHOLOGY

MCD received its name because of the minimal, if any, glomerular abnormalities present by light microscopy. Mild changes such as a slight increase in mesangial matrix and hypercellularity may occasionally be observed. A small percentage (<10%) of glomeruli may display global, but not segmental, glomerulosclerosis, which may reflect the natural senescence of glomeruli observed in young adults. In a few cases, minor focal tubular atrophy with segmental interstitial fibrosis may be present. Fat and hyaline droplets also may be found in the proximal tubule.

By immunofluorescence, immunoglobulins or complement deposits are rarely found. If present, deposits are limited to the mesangium.

There is a small subset of patients who have IgM deposits, which have been considered by some clinicians to represent an entity distinct from MCD known as IgM nephropathy and characterized by a poorer clinical outcome. Although mesangial IgM had been considered due to “passive trapping” and of no pathogenic significance, subsequent studies suggested IgM may be directed against mesangial antigens and contribute to proteinuria.25 Some case series have found mesangial C1q deposits, which may be associated with worse outcomes, leading to the concept of C1q nephropathy (see Chapter 29). However, it remains controversial whether the long-term prognosis is dictated by the presence of C1q deposits or, most likely, by the presence or lack of glomerulosclerosis on light microscopy.

Electron microscopy demonstrates diffuse podocyte foot process effacement or fusion (Fig. 18.2). Although fusion of foot processes is observed in other nephrotic conditions, in the absence of light microscopy glomerular changes, the finding is pathognomonic for MCD. The GBM is normal, and no electron-dense deposits are observed.

CLINICAL MANIFESTATIONS

Rapid onset of pitting edema, worse in the lower extremities, is often the first sign of MCD. Some patients present with bilateral periorbital edema, often misinterpreted as an allergic process. Edema may be mild or severe, presenting as anasarca with pleural effusions and ascites. Bowel edema may manifest as diarrhea. The mechanism(s) of edema formation in MCD is not fully understood but may be due to both a decrease in oncotic pressure and an increase in sodium and water reabsorption in the distal tubule (see Chapter 16).

Abdominal pain and nausea are common manifestations in MCD. Pain is usually dull due to massive ascites and bowel hypoperfusion. This pain resolves after albumin is administered. Severe pain may be due to peritonitis or acute pancreatitis.

MCD usually presents with a normal blood pressure. However, approximately 20% of adult patients are hypertensive on presentation. Some patients may develop transient renin-mediated hypertension during relapse from hypovolemia and renal hypoperfusion. Urinary changes may also be noted. Patients may describe “frothiness” of the urine. Macroscopic hematuria is concerning for renal vein thrombosis. Less commonly, patients with MCD may develop “white nails,” sometimes in bands (Muehrcke lines) correlating with periods of clinical relapse (see Fig. 16.4). Adults may develop xanthomas and xanthelasmas, especially on the eyelids (see Fig. 16.5).

LABORATORY TESTS

Nephrotic syndrome is the combination of nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia, and edema. In children, nephroticrange proteinuria is defined as greater than 50 mg/kg/24 h, greater than 40 mg/h/m2 (urinary specimens collected overnight), 200 mg protein/ mmol urine creatinine, or a ratio of urinary protein to creatinine (uPCR) greater than 3 mg/mg.2 In adolescents and adults, nephrotic-range proteinuria is defined as greater than 3.5 g/24 h or an uPCR greater than 3 mg/mg. In MCD, proteinuria is not only massive but also selectively albuminuria (see Chapter 16). Urine microscopy shows hyaline casts and fat bodies, as well as microscopic hematuria in 20% of patients. Hypoalbuminemia is defined by a serum level of albumin below 2.5 g/dL, and it is the result of the increased glomerular filtration permeability to plasma proteins. The liver production of albumin is increased in MCD patients, and gastrointestinal losses are minimal. In MCD, massive edema usually develops with serum albumin levels below 2 g/dL. Hyperlipidemia (elevated total cholesterol and low-density lipoprotein [LDL] cholesterol) is a universal feature of patients with MCD in relapse, and if massive proteinuria is persistent, triglycerides and verylow-density lipoprotein (VLDL) are also elevated. Hyperlipidemia results from increased hepatic synthesis of cholesterol and triglycerides, decreased activity of lipoprotein lipase, and altered expression of proprotein convertase subtilisin/kexin type 9 (PCSK9; see Chapter 16). In addition, urinary losses of lecithin cholesterol acyltransferase lead to a reduction of chylomicrons and VLDL clearance. The hyperlipidemia resolves after resolution of proteinuria.

Kidney function is commonly normal, but acute kidney injury is seen in up to 25% of adults. Oliguria can occur, and some patients may require dialysis, which can be prolonged in some cases. Risk factors for AKI include older age, history of hypertension, and more severe nephrotic syndrome. AKI is also seen in children hospitalized with MCD. AKI in MCD can be due to intravascular depletion, but without excessive diuretic therapy, intravascular volume is not reduced.

Despite this, up to 60% of kidney biopsies in MCD patients with AKI show acute tubular injury, suggesting ischemia, the mechanism for which is not understood. One theory is that the nephrotic state in MCD causes local release of the potent vasoconstrictor endothelin-1.26

Mild hyponatremia is common during relapse and may represent pseudohyponatremia due to hyperlipidemia. Total serum calcium may be low, as hypoalbuminemia leads to decreased protein-bound calcium. Ionized calcium is usually normal, and no treatment is indicated. Urinary losses of vitamin D–binding proteins can cause low vitamin D levels, and supplementation should be considered, especially if treatment with steroids is being considered.

Other Presentations (Complications)

Infection

Infections are a common complication of MCD, causing 19% of all hospital admissions for pediatric patients and a significant proportion of pediatric deaths. Mechanisms for increased susceptibility to

infection are diverse, including disruption of complement, especially in the alternative pathway where urinary losses reduce levels of factors B and I, persistent hypogammaglobulinemia, and immunosuppressive burden. Pneumonia, urinary tract infection, bacteremia, and peritonitis have all been reported. The predominant infective agents are Streptococcus pneumoniae, Haemophilus species, and Escherichia coli.27

Thrombosis

The combination of hypercoagulability (decreased anti–thrombin III and proteins C and S and increased fibrinogen; coagulation factors V, VII, VIII, X, and XII; increased platelet aggregability) with hypovolemia (and resulting thrombocytosis) puts MCD patients at high risk for thrombosis. However, the risk is lower than in membranous glomerulonephritis (see Chapter 16). Thromboses are more common in adults than in children. Predisposing factors for development of thromboembolism include increased severity of the nephrotic syndrome at presentation, concurrent infection, male sex, and central venous catheterization. Presentations include pulmonary emboli, sagittal venous thrombosis, renal vein thrombosis, peripheral venous thrombosis, and less frequently, arterial thrombosis.27 Children with nephrotic syndrome have a 2.8% chance of thromboembolism, whereas in adults that risk is 26.7%.28

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Kidney Biopsy

MCD is the most common type of idiopathic nephrotic syndrome in children, and therefore kidney biopsy is not routinely done in children younger than 10 years. However, if there are features that are not characteristic for MCD, such as hypertension, red cell casts, gross hematuria, kidney dysfunction, or lack of response to steroids (4- to 6-week course), a kidney biopsy should be considered at presentation.

In adults, a kidney biopsy is required to establish the diagnosis. Clinical and pathologic findings must be carefully interpreted. A patient with normal-appearing glomeruli who does not respond to immunosuppression could have a hereditary disease associated with a podocyte mutation (e.g., congenital nephrotic syndrome; see Chapter 20). Some patients with FSGS may only have a small percentage of glomeruli affected, which may not be evident on initial kidney biopsy sample due to sampling error. Indeed, there is ongoing debate about whether MCD and FSGS represent different diseases or whether they are the same disease at different stages.1 MCD patients with steroid resistance often have findings consistent with FSGS in subsequent kidney biopsies.

NATURAL HISTORY OF MINIMAL CHANGE DISEASE

Children and adults with MCD classically present with nephrotic syndrome with normal kidney function, and spontaneous remission is uncommon in the absence of steroid treatment. Steroid treatment is usually effective in inducing remission, and time to remit with steroid therapy is longer with adults than children. In children, 50% of patients remit within 8 days of starting therapy, whereas adults have a median time to remission of over 2 months.

Up to 75% patients with both pediatric- and adult-onset MCD will have one or more relapses. Among children with MCD, 25% never relapse, 25% relapse infrequently, and 50% have numerous relapses. The last group are classified as frequent relapsers if they have at least four relapses per year and steroid dependent if relapse occurs during the steroid taper or soon after it is stopped. In adults, approximately 45% of patients have more than one relapse, a proportion of whom develop steroid dependence.29 Relapses may occur at any point after

Suggested Treatment Algorithm in Children With MCD
Child with biopsy-proven or suspected MCD
Corticosteroid therapy

Responder (~95%)

Occasional relapses (~25%)

Frequent relapses (~50%)

CNI
Remission

No steroid toxicity
Steroid dependent

Frequent relapser

Second-line
therapy

Continuing
relapses

Consider
corticosteroidsparing therapy

Remission

Still relapsing
Consider repeat
biopsy

CNI or rituximab

CNI/cyclophosphamide

Still relapsing

CNI
dependency/toxicity
or nonresponse

Remission

CNI dependency/toxicity

Second-line therapy

Repeat corticosteroid
therapy

Second-line therapy

No relapses (~25%)

Nonresponder (~5%)

Symptomatic
therapy

Consider repeat biopsy

Rituximab or MMF or levamisole
after remission is induced

Symptomatic therapy

Fig. 18.3 Algorithm for Treatment of Childhood Minimal Change Disease. For definitions, see Table 18.2.
The patient or parents should be involved in the decision after the potential side effects of the second-line treatment are considered in the rare patient who is a nonresponder to standard corticosteroid therapy and by definition is corticosteroid resistant. CNI, Calcineurin inhibitor; MMF, mycophenolate mofetil.

diagnosis, including at more than 15 years after initial presentation. However, patients in remission for more than 5 years may be less likely to relapse. There is no evidence that disease resolves during puberty, and it is not unusual to see children with MCD undergoing relapses during adulthood.

In contrast to FSGS, long-term kidney function in MCD is usually good. However, there is significant morbidity, mortality, and reduced quality of life, from both relapse and treatment, especially in older adults.

TREATMENT

General Considerations

Management of nephrotic syndrome is discussed in Chapter 16, including a low-sodium diet to control edema. Diuretics are infrequently used in children because of potential further volume depletion but are often used to control extracellular fluid volume in adults, in whom hypovolemia before treatment is less common. For patients who are diuretic resistant, intravenous albumin is frequently given, although there is scarce evidence for benefit.30 Prophylactic anticoagulation should be considered for patients with pronounced hypoalbuminemia (i.e., serum albumin <2 g/dL), particularly in adults whose nephrotic syndrome is likely to be more prolonged. One reported regimen uses daily low-molecular-weight heparin or warfarin if serum albumin is below 2 g/dL, switching to aspirin once serum albumin rises to over 2 g/dL and the thrombosis risk is reduced.31 There is little data on the use of newer direct oral anticoagulants, such as apixaban and rivaroxaban, in nephrotic syndrome, but these agents are highly protein bound, leading to increased urinary losses that may reduce efficacy.32

Management of AKI in MCD is supportive. Patients with persistent AKI should be considered for repeat kidney biopsy.

Treatments for hyperlipidemia are more commonly given in adults than children due to the increased time to remission. Statins are the mainstay of cholesterol-lowering therapy, although these have little effect on triglyceride or lipoprotein levels.

Treatment in Children

A summary of suggested treatment for children with MCD is shown in Fig. 18.3

Initial Treatment

Steroids are the first-line therapy to induce remission in children with idiopathic nephrotic syndrome and biopsy-proven MCD, because 95% of MCD patients respond to this therapy. The ISKDC recommended

TABLE 18.2

Terms Used in Nephrotic Syndrome in Adults and Children

Classification	Definition
Nephrotic syndrome	Nephrotic-range proteinuria (uPCR ≥2 mg/mg or ≥200 mg/mmol or 3+ protein on urine dipstick for children, or ≥3.5 g/day proteinuria for adults) and either hypoalbuminemia ≤3 g/dL (≤30 g/L) or edema when albumin level is not available
Complete remission	uPCR <0.2 mg/mg or <20 mg/mmol or negative or trace dipstick on three or more consecutive occasions (children) Reduction of proteinuria to ≤0.20 g/day and serum albumin >3.5 g/dL (adults)
Partial remission	uPCR >0.2 but <2 mg/mg or >20 and <200 mg/mmol, and, if available, serum albumin ≥3 (children) Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline (adults)
Relapse	Recurrence of nephrotic-range proteinuria. In children, relapse is commonly assessed by urine dipstick, defined as dipstick≥3+ for 3 consecutive days or ≥1+ for 7 days. In adults, relapse is defined as proteinuria ≥3.5 g/day occurring after complete remission obtained for >1 month.
SSNS	Complete remission after 4 weeks of prednisone or prednisolone at standard dose (children)
IRNS	One relapse per 6 months or less than four relapses per 12 months
FRNS	Two or more relapses per 6 months, or four or more relapses per 12 months
SDNS	Relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
SRNS	Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose (children) Persistence of proteinuria despite prednisone therapy, 1 mg/kg/day for 16 weeks

(adults)

Initial responder

Attainment of complete remission within initial 4 weeks of corticosteroid therapy

Late responder

Complete remission at 6 weeks (children)

CNI-responsive SRNS

Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels

CNI-resistant SRNS

Absence of partial remission after 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels

Multidrugresistant SRNS

Absence of complete remission after 12 months of treatment with two mechanistically distinct steroid-sparing agents at standard doses

Secondary SRNS

A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

CNI, Calcineurin inhibitor; FRNS, frequent-relapsing nephrotic syndrome; IRNS, infrequent-relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; uPCR, urinary protein to creatinine ratio.

an induction phase consisting of prednisone 60 mg/day/m2 (equivalent to 2 mg/kg, with a maximum of 60 mg/day for children and 80 mg/day for adolescents) for 4 weeks.2 Most nephrologists administer 2 mg/kg of prednisone as a single morning daily dose based on evidence that it provides equal efficacy than three times a day, and it is associated with less adrenal insufficiency and better adherence.

Although the German Arbeitsgemeinschaft für Pädiatrische Nephrologie reported a greater rate of sustained remission in patients treated with extended versus short (6 vs. 4 weeks) therapy with steroids,33 this was not confirmed by the Southwest Pediatric Nephrology Study Group.34 Given these results, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of the initial episode of nephrotic syndrome in children with daily oral prednisone or prednisolone at 60 mg/m2/day or 2 mg/kg/day (maximum 60 mg/day) as induction therapy for 4 to 6 weeks.35

Most children enter remission during the induction phase, but treatment is continued to the 4-week or 6-week time point, and then prednisone is slowly tapered to reduce the risk of side effects. During the tapering phase, prednisone is administered on alternate days, but there is no agreement on the duration or dose.

The 2021 KDIGO guidelines recommended oral prednisone at 40 mg/m2 or 1.5 mg/kg on alternate days and continued for another 4 to 6 weeks.35 A Cochrane systematic review in 2015 concluded that a 6-month prednisone course does not reduce the risk of relapse compared with a 2- or 3-month course in children aged 1 to 17 years at presentation. More recently, the PREDNOS study found no difference in time or number of relapses or relapse pattern among

children who received standard (4-week course with prednisone 40 mg/m2 on alternate days) or long taper regimen (12-week therapy starting at 60 mg/m2 on alternate days and tapering by 10 mg/m2 every 2 weeks).36 Thus, the 2020 Cochrane update concluded that there is no benefit of prolonging prednisone therapy beyond 2 to 3 months in the first episode of steroid sensitive nephrotic syndrome (SSNS).37

Treatment of Relapses

There is no consensus on the prednisone regimen for induction and tapering phases. The ISKDC recommends prednisone at 60 mg/m2/day until response (maximum of 4 weeks) followed by prednisone 40 mg/m2/day for 3 consecutive days in a week for a total of 4 weeks.2 Recently, the PROPINE trial found no differences in outcomes among patients who, after remission, received a short (18 doses of prednisone 40 mg/m2 on alternate days) versus extended taper (prednisone at 40 mg/m2 dose on alternate days tapered over 72 days by steps of six doses).38 Other groups have studied the efficacy of different doses of steroids. In a prospective study, Borovitz and colleagues showed that children receiving prednisone at 1 mg/kg/day and followed by stepwise taper had similar rate of remission and relapse rate than those treated with a standard regimen (prednisone 2 mg/kg/day until remission followed by slow taper over 10–12 weeks).39

The ISKDC and KDIGO provided arbitrary definitions regarding the relapse pattern, grouping patients as steroid dependent (SDNS) and frequent relapsers (FRNS) (see Table 18.2).2 35 These are widely used, but the distinction between them should be made carefully to select appropriate therapy based on the available studies because definitions of steroid dependence can vary among different centers.

Steroid-Sparing Therapies

Whereas initial treatment of relapsing patients usually involves repeated courses of steroids, long-term exposure to steroids can cause significant toxicity, including behavioral changes, growth impairment, cataracts, hypertension, and diabetes among others. Therefore, alternative therapies are often required in children with MCD who are steroid dependent and/or relapse frequently. Patients should be ideally in remission prior to the initiation of any steroid-sparing agent. This is particularly important when using cyclophosphamide to minimize the risk of hemorrhagic cystitis. There is no consensus on the best secondline therapy for children with MCD.

Dorresteijn and colleagues found that children receiving MMF had a higher risk for relapse than those on cyclosporine, though the difference did not reach statistical significance.43 In a larger crossover trial using MMF or cyclosporine, patients on MMF suffered more relapses than those on cyclosporine, though patients with higher plasma levels of MMF (area under the curve >50 µg/h/mL) had a similar course to those treated with cyclosporine.44 MMF is a relatively safe drug that can be associated with mild and dose-dependent side effects (gastrointestinal, bone marrow suppression) but not nephrotoxicity. Therefore, MMF seems a reasonable alternative as a steroid-sparing drug, especially if plasma levels are closely monitored. However, MMF is teratogenic, so caution is required when used in young females.

Other Medications

This alkylating agent has been used in MCD for decades and used to be the most common first-line steroid-sparing agent. Cyclophosphamide can induce sustained remission, particularly in patients with FRNS, whereas its efficacy is lower in those with SDNS.35 The optimal length of cyclophosphamide therapy is debatable and varies from 8 to 12 weeks. The most common side effect is bone marrow suppression, so weekly cell blood count is recommended, with adjustment of dosage or cessation of therapy if necessary. Second courses of cyclophosphamide should not be given (maximum cumulative dose of 168 mg/kg) to minimize gonadal toxicity. Some centers may favor other newer therapies due to a theoretical safer profile.

Levamisole. One RCT showed sustained remission in 26% of patients treated with levamisole compared with 6% in the placebo group.45 Levamisole was more effective in patients from India than Europe. It is unclear whether this is because SDNS was more common in Europe or because helminthic infections could trigger MCD. Still, the use of levamisole is limited as it is not available in some countries and because it is associated with agranulocytosis and antineutrophil cytoplasmic antibody vasculitis.

Adrenocorticotrophic hormone. The ATLANTIS trial found a similar rate of relapse in children with FRNS and SDNS who received adrenocorticotrophic hormone (ACTH) therapy versus no relapsepreventing treatment,46 so there is no evidence to support the use of ACTH in children with MCD.

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Treatment in Adults

Cyclophosphamide

Treatment with cyclosporine results in a similar rate of remission compared with cyclophosphamide and chlorambucil. However, its longterm efficacy is hampered by frequent relapse shortly after calcineurin inhibitor (CNI) withdrawal. Tacrolimus appears to have efficacy similar to that of cyclosporine.40 The recommended dose for cyclosporin and tacrolimus are 4 to 5 mg/kg/day (in two divided doses) and 0.1 mg/kg/day (in two divided doses) with target 12-hour trough levels of 60 to 150 ng/mL and 5 to 10 ng/mL, respectively, aiming for the lowest levels to maintain remission and avoid toxicity. These recommendations are largely based on the experience in kidney transplantation, but have not been formally validated in MCD. The length of therapy varies from 12 to 24 months.35 Mild to moderate cyclosporine-associated nephrotoxicity has been reported in up to one-third of MCD patients treated with cyclosporine for more than 3 years.

Rituximab

Rituximab has been used in MCD for over a decade. The 2021 KDIGO Guidelines and the 2020 Cochrane update recommend rituximab as a steroid-sparing agent.35,37 Iijima and colleagues found a significantly longer relapse-free period and fewer relapses in patients who received rituximab compared with those receiving a placebo.41 A recent randomized controlled trial (RCT) showed that rituximab was associated with a higher 12-month relapse-free survival rate than tacrolimus (90% vs. 63.3%, respectively) in children with SDNS, suggesting that rituximab could potentially be used as a first-line steroid-sparing agent in these children.42 Overall, rituximab is well tolerated. Infusion reactions are the most common adverse event. Serious complications include rituximab-associated lung injury, colitis, multifocal leukoencephalopathy, persistent hypogammaglobulinemia, and infections.

Mycophenolate Mofetil

Uncontrolled studies suggested beneficial effects of mycophenolate mofetil (MMF) therapy, but this has not been confirmed in RCT.

Initial Treatment

A summary of treatment recommendations given here is shown in Fig. 18.4. Although a small proportion of patients with MCD will spontaneously remit, withholding immunosuppression has been shown to be associated with increased risk of acute kidney injury and steroid resistance.47

Steroids

Steroids are widely used as the initial therapy for MCD. Studies comparing different steroid regimens in adults with MCD are limited and regimens are extrapolated from successful approaches in children with steroid-sensitive nephrotic syndrome, although often with slightly lower doses of oral prednisolone (1 mg/kg/day, up to maximum 80 mg/day).48 There is no good evidence that alternate-day steroids (prednisolone 2 mg/kg, up to maximum 120 mg) offer any clinical advantages over daily dosing; however, induction with methylprednisolone pulses may lead to more rapid responses and fewer relapses.49

Response is often delayed in comparison with that in children, with a median time to remission of 10 weeks, and 25% fail to remit after 3 to 4 months.50 Although unclear, the reason may be that adults are often given a relatively lower dose of steroids or that a greater proportion of adults have FSGS, missed on the original biopsy, which is more likely to be steroid resistant (SR). More recent work has shown a correlation between reduced nephron mass and increased time to remission with steroids.51

The KDIGO guideline recommends that the duration of steroid treatment should be up to 6 months, but this is based on very low-grade evidence.35

The initial high dose of steroids, if tolerated, should be maintained for a minimum of 2 weeks after complete remission is achieved and for a maximum of 16 weeks if complete remission is not achieved. After this, steroids should be tapered over 24 weeks, although the rate of dose tapering and total length of treatment of the initial episode may need to be reduced if steroid toxicity is significant. If the patient has not responded after 12 to 16 weeks, genetic screening for FSGS or a repeat biopsy should be considered.

Suggested Treatment Algorithm in Adults With MCD

Yes

Relative contraindications to steroids/patient’s preference of steroid avoidance

Steroids

Tacrolimus

Sustained
remission/infrequent
relapses

Nonresponder

Tacrolimus
Treat relapses as per
initial presentation

Nonresponder

Patient choice after discussion
of side effects

Steroids
Tacrolimus

Cyclophosphamide

Rituximab

MMF

2nd line therapy

Relapsing/dependent disease

1st line therapy

No

2nd line therapy

1st line therapy

Adults with MCD

Sustained remission/
infrequent relapses

Treat relapses as per
initial presentation

Resistance to both treatments

3rd line treatment

Genetic testing and/or repeat
renal biopsy for FSGS

Treatment-resistant MCD:

Tacrolimus

Rituximab

Cyclophosphamide

MMF

Fig. 18.4 Algorithm for Treatment of Adult Minimal Change Disease (MCD). FSGS, Focal segmental glomerulosclerosis; MMF, mycophenolate mofetil.

Infrequent relapses should be treated in the same way as the initial presentation, but there is even less evidence that a prolonged course of steroids is beneficial in reducing the frequency of subsequent relapse. Although steroids are a highly effective treatment for MCD, prolonged courses of steroids often cause significant side effects. Up to 90% of adults taking steroids for more than 60 days report a side effect of steroid therapy; weight gain is the most commonly reported alongside skin changes, muscle weakness, sleep disturbance, cataracts, hyperglycemia, psychiatric disturbance, and bone demineralization leading to pathologic fractures. In other areas of nephrology such as kidney transplantation, steroid avoidance and early withdrawal protocols have led to improved outcomes, and similar strategies have been studied in MCD.

Calcineurin Inhibitors

A large RCT compared intravenous methylprednisolone followed by oral tacrolimus with oral prednisolone as initial therapy for MCD. This study found a similar rate of remission and relapse between both groups, but the oral prednisolone arm had a worse side effect profile.52

A more recent RCT compared low-dose prednisolone and tacrolimus with higher-dose prednisolone monotherapy. They found comparable rates of complete and partial remission but a significantly lower rate of relapse in the combination therapy group compared with steroids alone. This study showed a comparable rate of adverse events across both groups.53

Use of tacrolimus monotherapy with complete avoidance of steroids has also been shown to be effective. The MINTAC trial involved 55 adults who were given either tacrolimus or prednisolone as initial therapy. There was no significant difference in complete or partial remission rates after 8, 16, and 26 weeks of treatment. There was no significant difference in relapse rates and no significant difference in the rate of adverse events.54 This may be due to the relatively conservative steroid doses used in this trial. A second RCT also comparing tacrolimus with prednisolone as first-line MCD treatment also found similar remission and relapse rates, but adverse events were significantly more common in the steroid-treated group.55 Tacrolimus may be particularly useful for patients with contraindications to steroids, such as diabetes or psychosis.

Mycophenolate Mofetil

MMF has also been tried as a steroid sparing agent for initial therapy. Rémy and colleagues compared MMF plus low-dose prednisolone (0.5 mg/kg/day) with standard-dose prednisolone (1 mg/kg/day) alone in 116 adult patients and found no significant difference in rates of remission or relapse and no benefit in adverse events between the two treatment arms.56

Cyclophosphamide

Cyclophosphamide can also be used as initial therapy in MCD instead of steroids,48 although there are no RCTs to show efficacy. This may be suitable in older adults, where there is less concern regarding impacts on fertility or increased lifetime malignancy risk.

Rituximab

Other alternatives for first-line therapy include rituximab, although there is still a paucity of evidence relating to this. Fenoglio and colleagues gave rituximab as a first-line therapy to treatment-naive adult patients with MCD who had contraindications to steroid therapy; five out of six patients achieved complete remission and did not relapse until the end of the follow-up period. The remaining patient achieved partial remission.57 Patients may require enhanced dosing if rituximab is given when nephrotic due to protein binding of the drug.

Treatment of Relapses and Steroid-Sparing Therapies

As in children, some adults have transient nonnephrotic relapses, so it is important to establish that a full relapse has developed with persistent nephrotic range proteinuria before recommencing immunosuppression. Several different immunosuppressant therapies are effective for relapsing MCD; hence the choice of treatment should be tailored to individual patient’s needs.

The CNIs cyclosporine and tacrolimus have similar efficacy, inducing remission in up to 75% of patients, but as in children, relapse often follows dose reduction or withdrawal. Due to its side effect profile, tacrolimus may be preferred to cyclosporine.[58] Initial dosing is 0.05 to 0.1 mg/kg, with target tacrolimus levels of 4 to 8 ng/mL, but higher levels may be required to maintain remission. Tacrolimus is suitable for young adults wishing to preserve fertility and is safe in both pregnancy and breastfeeding.[59] Recommended dosing for cyclosporine is 4 to 6 mg/kg/day, aiming for trough whole-blood levels of 150 to 200 ng/mL. KDIGO guidelines recommend CNI therapy should continue for 1 to 2 years,[48] but some patients require longer or repeated courses of therapy.

Rituximab can reduce the frequency of relapses and need for concomitant immunosuppression,[60] although definitive RCTs in adults are awaited. Median time to relapse with rituximab has been reported as 18 months.[61] Longer-term maintenance dosing of rituximab can be guided by B cell monitoring, but relapse can recur quickly after repletion. For these patients, regular six-monthly dosing may be preferable and has been shown to be effective.[62] Rituximab is generally well tolerated in adults with MCD, but patients need to be monitored for hypogammaglobulinemia. For patients who struggle with adherence to a daily oral medication, rituximab may offer some advantage due to its administration by intermittent infusion. Optimal doses and schedule remain to be determined.[24]

A 12-week course of oral cyclophosphamide 2 to 2.5 mg/kg/day induces a longer-term remission more often in adults than children (75% and 66% at 2 and 5 years, respectively).[63] Although there are no satisfactory studies comparing 8-week and 12-week courses in adults, the 12-week course is logical based on the pediatric experience. If this treatment is selected, the opportunity for banking sperm or retrieval of ova should be considered before treatment in appropriate patients. Intravenous cyclophosphamide has been recommended to limit the cumulative dose: intravenous cyclophosphamide 0.5 g/m^2 per month adjusted upward to 1 g/m^2 based on the leukocyte count after 2 weeks with a target nadir of 3000 cells/mm^3

Several uncontrolled reports suggest that MMF is effective in inducing remission in steroid- and cyclosporine-dependent patients[29] and is generally well tolerated. However, it may not be suitable in young women due to teratogenicity.

Steroid Resistant Disease

For the 10% to 30% adults who do not remit with primary therapy, treatment of MCD may be challenging. For patients not remitting on steroids, tacrolimus can be used as second-line therapy, and vice versa for patients failing to remit on tacrolimus. Patients should be offered genetic testing or repeat biopsy to look for FSGS. For patients with truly SR MCD, case series have shown that CNIs, cyclophosphamide,[64] MMF,[65] and rituximab[66] can all induce remission.

MINIMAL CHANGE DISEASE WITH NONNEPHROTIC PROTEINURIA

It is possible to have MCD with subnephrotic proteinuria. These patients may be treated with antiproteinuric medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers. If there is any uncertainty regarding diagnosis, a repeat biopsy should be offered.

Treatment of Secondary Minimal Change Disease

MCD secondary to NSAIDs requires discontinuation of the offending medication. Many patients are treated with a course of steroids

for MCD (higher dose) or for acute interstitial nephritis (see Chapter 64), but evidence of benefit is uncertain. Secondary MCD from Hodgkin disease usually responds to treatment of the lymphoma.
Some patients will also receive a drug regimen for MCD as adjunctive therapy in addition to the chemotherapy directed at the tumor in particular if MCD remission does not occur quickly with adequate chemotherapy.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding the presentation of MCD is correct?
A. Less than 1% of adults present with AKI.
B. Microscopic hematuria excludes a diagnosis of MCD.
C. Edema is rarely the first presenting feature.
D. Children may present with abdominal pain, ascites, and diarrhea.
E. Urinary frothiness indicates a patient has achieved remission.
2. Which of the following statements regarding the natural history of MCD is correct?
A. Seventy-five percent of children presenting with MCD never relapse.
B. Most patients with MCD will undergo one or more relapses.
C. End-stage kidney disease is seen in up to 30% patients who present as adults.
D. MCD resolves with puberty.
E. Patients requiring kidney replacement therapy in MCD rarely recover kidney function.

3. Which treatment is most appropriate for a 24-year-old woman with relapsing minimal change disease hoping to conceive in the next year?
A. Tacrolimus
B. Rituximab
C. Mycophenolate mofetil
D. Cyclophosphamide
E. Adalimumab
4. Which of the following statements regarding complications of MCD is true?
A. Hyperlipidemia is a rare complication of MCD.
B. Thrombotic events in MCD are usually arterial.
C. The enhanced risk of infection in MCD is only due to the immunosuppressive therapy seen.
D. AKI occurs in most adults.
E. Rituximab can contribute to hypogammaglobulinemia.

REFERENCES

1. Vivarelli M, et al. Minimal change disease. Clin J Am Soc Nephrol. 2017;12(2):332–345.

2. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr. 1981;98(4):561–564.

3. Feehally J, et al. High incidence of minimal change nephrotic syndrome in Asians. Arch Dis Child. 1985;60(11):1018–1020.

4. Lemley KV, et al. The effect of a gluten-free diet in children with difficult-to-manage nephrotic syndrome. Pediatrics. 2016;138(1).

5. Chehade H, et al. Two new families with hereditary minimal change disease. BMC Nephrol. 2013;14:65.

6. Dufek S, et al. Genetic identification of two novel loci associated with steroid-sensitive nephrotic syndrome. J Am Soc Nephrol. 2019;30(8):1375–1384.

7. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet. 1974;2(7880):556–560.

8. Koyama A, et al. A glomerular permeability factor produced by human T cell hybridomas. Kidney Int. 1991;40(3):453–460.

9. Ali AA, et al. Minimal-change glomerular nephritis. Normal kidneys in an abnormal environment? Transplantation. 1994;58(7):849–852.

10. Kim AH, et al. B cell-derived IL-4 acts on podocytes to induce proteinuria and foot process effacement. JCI Insight. 2017;2(21).

11. Liu L-l, et al. Th17/Treg imbalance in adult patients with minimal change nephrotic syndrome. Clin Immunol. 2011;139(3):314–320.

12. Garin EH, West L, Zheng W. Effect of interleukin-8 on glomerular sulfated compounds and albuminuria. Pediatr Nephrol. 1997;11(3): 274–279.

13. Koukouritaki SB, et al. TNF-alpha induces actin cytoskeleton reorganization in glomerular epithelial cells involving tyrosine phosphorylation of paxillin and focal adhesion kinase. Mol Med. 1999;5(6):382–392.

14. Ishimoto T, et al. Toll-like receptor 3 ligand, polyIC, induces proteinuria and glomerular CD80, and increases urinary CD80 in mice. Nephrol Dial Transplant. 2013;28(6):1439–1446.

15. Chen S, et al. Loss of heparan sulfate glycosaminoglycan assembly in podocytes does not lead to proteinuria. Kidney Int. 2008;74(3):289–299.

16. Moeller MJ, Tenten V. Renal albumin filtration: alternative models to the standard physical barriers. Nat Rev Nephrol. 2013;9(5):266–277.

17. Ma H, et al. Inhibition of podocyte FAK protects against proteinuria and foot process effacement. J Am Soc Nephrol. 2010;21(7):1145–1156.

18. Uchida K, et al. Decreased tyrosine phosphorylation of nephrin in rat and human nephrosis. Kidney Int. 2008;73(8):926–932.

19. Cara-Fuentes G, et al. Glomerular endothelial cells and podocytes can express CD80 in patients with minimal change disease during relapse. Pediatr Nephrol. 2020;35(10):1887–1896.

20. Gonzalez Guerrico AM, et al. Urinary CD80 discriminates among glomerular disease types and reflects disease activity. Kidney Int Rep. 2020;5(11):2021–2031.

21. Clement LC, et al. Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. Nat Med. 2011;17(1):117–122.

22. Cara-Fuentes G, et al. Angiopoietin-like-4 and minimal change disease. PLoS One. 2017;12.

23. Zhang SY, et al. c-mip impairs podocyte proximal signaling and induces heavy proteinuria. Sci Signal. 2010;3(122):ra39.

23b. Watts AJB, Keller KH, Lerner G, et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. J Am Soc Nephrol. 2022;33(1):238–252.

24. Gauckler P, et al. Rituximab in adult minimal change disease and focal segmental glomerulosclerosis - what is known and what is still unknown? Autoimmun Rev. 2020;19(11):102671.

25. Panzer SE, et al. IgM exacerbates glomerular disease progression in

complement-induced glomerulopathy. Kidney Int. 2015;88(3):528–537.
26. Meyrier A Niaudet p. Acute kidney injury complicating nephrotic syndrome of minimal change disease. Kidney Int. 2018;94(5):861–869.

27. Carpenter SL, et al. Association of infections and venous thromboembolism in hospitalized children with nephrotic syndrome. Pediatr Nephrol. 2019;34(2):261–267.
28. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. Pediatr Nephrol. 2014;29(6):989–997.
29. Waldman M, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007;2(3):445–453.
30. Ho JJ, et al. Human albumin infusion for treating oedema in people with nephrotic syndrome. Cochrane Database Syst Rev. 2019;7(7):Cd009692.
31. Medjeral-Thomas N, et al. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. Clin J Am Soc Nephrol. 2014;9(3):478.
32. Lin R, et al. A systematic review of prophylactic anticoagulation in nephrotic syndrome. Kidney Int Rep. 2020;5(4):435–447.
33. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft für Pädiatrische Nephrologie Eur J Pediatr. 1993;152(4):357–361.
34. Lande MB, et al. Long versus standard initial steroid therapy for children with the nephrotic syndromeA report from the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol. 2003;18(4):342–346.
35. KDIGO Clinical Practice Guideline on Glomerular Diseases. Kidney Disease: Improving Global Outcomes; 2021.
36. Webb NJA, et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. Bmj. 2019;365:l1800.
37. Larkins NG, et al. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev. 2020;4(4):Cd002290.
38. Gargiulo A, et al. Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children. Kidney Int. 2021;99(2):475–483.
39. Borovitz Y, et al. Lower prednisone dosing for steroid-sensitive nephrotic syndrome relapse: a prospective randomized pilot study. Eur J Pediatr. 2020;179(2):279–283.
40. Gulati S, et al. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant. 2007;23(3):910–913.
41. Iijima K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2014;384(9950):1273–1281.
42. Basu B, et al. Efficacy of rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial. JAMA Pediatr. 2018;172(8):757–764.
43. Dorresteijn EM, et al. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol. 2008;23(11):2013–2020.
44. Gellermann J, et al. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. J Am Soc Nephrol. 2013;24(10):1689–1697.
45. Gruppen MP, et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int. 2018;93(2):510–518.
46. Wang CS, et al. Adrenocorticotropic hormone for childhood nephrotic syndrome: the ATLANTIS randomized trial. Clin J Am Soc Nephrol. 2018;13(12):1859–1865.
47. Maas RJ, et al. The clinical course of minimal change nephrotic syndrome with onset in adulthood or late adolescence: a case series. Am J Kidney Dis. 2017;69(5):637–646.
48. Chapter 5: minimal-change disease in adults. Kidney Int Suppl.

2012;2(2):177–180.
49. Shinzawa M, et al. Comparison of methylprednisolone plus prednisolone with prednisolone alone as initial treatment in adult-onset minimal change disease: a retrospective cohort study. Clin J Am Soc Nephrol. 2014;9(6):1040–1048.
50. Szeto CC, et al. Long-term outcome of biopsy-proven minimal change nephropathy in Chinese adults. Am J Kidney Dis. 2015;65(5):710–718.
51. Sasaki T, et al. Nephron number and time to remission in steroid-sensitive minimal change disease. Kidney Med. 2020;2(5):559–568.e1.

References

52. Li X, et al. Tacrolimus monotherapy after intravenous methylprednisolone in adults with minimal change nephrotic syndrome. J Am Soc Nephrol. 2017;28(4):1286–1295.
53. Chin HJ, et al. Comparison of the efficacy and safety of tacrolimus and low-dose corticosteroid with high-dose corticosteroid for minimal change nephrotic syndrome in adults. J Am Soc Nephrol. 2020. SN.2019050546.
54. Medjeral-Thomas NR, et al. Randomized, controlled trial of tacrolimus and prednisolone monotherapy for adults with de novo minimal change disease: a multicenter, randomized, controlled trial. Clin J Am Soc Nephrol. 2020;15(2):209–218.
55. Patil M, et al. Tacrolimus as the first-line agent in adult-onset minimal change disease: a randomized controlled study. Saudi Journal of Kidney Diseases and Transplantation. 2019;30(1):129–137.
56. Rémy P, et al. An open-label randomized controlled trial of low-dose corticosteroid plus enteric-coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults (MSN Study). Kidney Int. 2018;94(6):1217–1226.
57. Fenoglio R, et al. Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome. Oncotarget. 2018;9(48):28799–28804.
58. Li X, et al. Tacrolimus as a steroid-sparing agent for adults with steroiddependent minimal change nephrotic syndrome. Nephrol Dial Transplant. 2007;23(6):1919–1925.

59. Bramham K, et al. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. Clin J Am Soc Nephrol. 2013;8(4):563–567.
60. Kronbichler A, Gauckler, Bruchfeld A. Rituximab in Minimal Change Disease and Focal Segmental Glomerulosclerosis. Nephrology Dialysis Transplantation; 2019.
61. Guitard J, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. Nephrol Dial Transplant. 2014;29(11):2084–2091.
62. Taguchi S, et al. Efficacy of repeat-dose rituximab maintenance therapy for minimal change disease in adults. Clin Exp Nephrol. 2020.
63. Nolasco F, et al. Adult-onset minimal change nephrotic syndrome: a longterm follow-up. Kidney Int. 1986;29(6):1215–1223.
64. Li H, et al. Tacrolimus versus intravenous pulse cyclophosphamide therapy in Chinese adults with steroid-resistant idiopathic minimal change nephropathy: a multicenter, open-label, nonrandomized cohort trial. Clin Ther. 2012;34(5):1112–1120.
65. Mogyorósi A, Lippman HR, Feldman GM. Successful treatment of steroid-resistant minimal change disease with mycophenolate mofetil. Am J Nephrol. 2002;22(5–6):569–572.
66. Nishikawa M, et al. Long-term successful treatment of rituximab for steroid-resistant minimal change nephrotic syndrome and idiopathic thrombocytopenic purpura. Intern Med. 2020;59(7):983–986.

19

Primary and Secondary (Nongenetic) Causes of Focal and Segmental Glomerulosclerosis

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of glomerular injury that represents the final common pathway of podocyte injury and depletion. FSGS may be primary (idiopathic) or secondary to diverse causes1-3 (see also Chapter 20). Early in the disease process, the pattern of glomerulosclerosis is focal, involving a minority of glomeruli, and segmental, involving a portion of the glomerular tuft.4 As FSGS progresses, more diffuse and global glomerulosclerosis evolves.4 Although it accounts for only a small proportion of nephrotic syndrome in young children, FSGS represents as many as 35% of cases of primary nephrotic syndrome in adults and is a major cause of endstage kidney disease (ESKD) in the United States.5

FSGS can be caused by a diverse set of pathogenetic mechanisms, some of which manifest as particular histologic subtypes of disease. Although primary (idiopathic) FSGS is potentially treatable and curable in many patients, the optimal type and duration of immunosuppressive, as well as adjunctive therapy, remain controversial. For secondary FSGS, effective therapies exist to slow or modify the disease course (see Chapter 82).

ETIOLOGY AND PATHOGENESIS

FSGS is a pattern of glomerular injury that represents a common final pathway of podocyte depletion. Primary FSGS underlies a subset of idiopathic nephrotic syndrome and is thought to be mediated by circulating permeability factors.6-8 Distinct causes of secondary FSGS (Box 19.1) include genetic variants in podocyte and glomerular basement membrane components (see Chapter 20), viral infections, drug toxicity, maladaptive responses to a reduced number of functioning nephrons, and hemodynamic stress placed on an initially normal nephron population. In all forms of FSGS, injury directed at or inherent to the podocyte mediates altered cell signaling and reorganization of the actin cytoskeleton resulting in foot process effacement, and eventually podocyte depletion though detachment and apoptosis.1 9 Podocytes are terminally differentiated, postmitotic cells with limited hypertrophic capacity. Furthermore, regeneration mediated by resident podocyte progenitor cells along Bowman’s capsule is inefficient. Therefore, stress placed on the remaining podocytes may lead to local propagation of damage (see Chapter 81).

Injury to podocytes may spread to adjacent podocytes by reduction in supportive factors such as nephrin signaling, increased toxic factors such as angiotensin II (Ang II), or mechanical strain on remnant podocytes.9 10 Cell-to-cell spread of podocyte injury until the entire glomerular lobule is captured could explain the segmental nature of the sclerosing lesions.10 Repeated and diverse stresses to the podocyte could explain the FSGS pattern of injury in age-related nephrosclerosis and glomerular senescence.1 9

CLASSIFICATION OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS

The terms primary and idiopathic FSGS have been used interchangeably, leading to confusion. Thus, we avoid the term idiopathic in this section. The following definitions are suggested by the KDIGO Guideline.11

Primary Focal Segmental Glomerulosclerosis

Primary FSGS is diagnosed when the nephrotic syndrome is present (in particular, the presence of hypoalbuminemia) and diffuse podocyte foot process effacement is observed on kidney biopsy without evidence for other causes of FSGS.11 Primary FSGS, together with minimal change disease (MCD; see Chapter 18), are the main causes of idiopathic nephrotic syndrome and are collectively referred to as primary podocytopathies. Compared with MCD, primary FSGS is associated with a higher likelihood of steroid resistance and progression to CKD, leading most experts to conclude that they are separate diseases. Despite these clinical differences, MCD and primary FSGS may represent a disease spectrum in which the severity and duration of podocyte injury, inherent susceptibility of the podocyte to injury, and comorbid conditions all influence the disease phenotype.12 Indeed, follow-up kidney biopsies from patients with refractory nephrotic syndrome suggest that FSGS may evolve from an initial MCD pattern.13 In some instances this may be attributed to sampling variability. However, sequential biopsy samples of kidney allografts show that recurrent FSGS may pass through an early stage of podocytopathy with MCDlike pathology.14 Animal models of persistent nephrotic syndrome also show progression from an initial MCD-like phase to FSGS.15

Both MCD and primary FSGS are thought to be mediated by as-yet unidentified circulating permeability factors.6,16 Alterations in glomerular capillary wall permeability may occur in response to circulating “humoral” substances that act on the podocyte to promote foot process effacement. Circulating permeability factors that enhance in vitro permeability of glomeruli to albumin have been found in some FSGS patients. An in vitro assay of cultured podocytes has been used to detect the presence of circulating permeability factors.17 Some patients with recurrent FSGS after transplantation achieve remission of nephrotic syndrome after plasma exchange or use of a protein A adsorption column, supporting the role of a circulating factor8,18 (see Chapter 113). However, none of several candidate proteins, including suPAR, B7-1 (also known as CD-80), or cardiotrophin-like cytokine 1 (CLC1), a member of the interleukin (IL)-6 family, has been consistently shown to be the permeability factor in human FSGS.19

Glomerular hypertrophy (or glomerulomegaly) may identify children with MCD at risk for development of FSGS. In early idiopathic FSGS and in many secondary forms of FSGS, such as obesity-related FSGS, there is initially glomerular hypertrophy and high glomerular filtration rate (GFR) associated with glomerular hypertension.20 Similarly, in secondary forms of FSGS with reduced nephron numbers, maladaptive

Etiologic Classification of Focal Segmental Glomerulosclerosis

BOX 19.1

Primary
- Presumably mediated by circulating/permeability factor(s)

Genetic Causes
- (See Chapter 20)

Secondary

Virus Associated
- HIV-1 (HIV-associated nephropathy)
- SARS-CoV-2 (COVID-19 associated nephropathy)
- Parvovirus B19
- CMV
- EBV

Drug Induced
- Interferon
- Pamidronate
- Sirolimus
- Anabolic steroids

Adaptive Changes to Glomerular Hyperfiltration

Reduced Kidney Mass
- Oligomeganephronia
- Very low birth weight (correlating with low nephron endowment)
- Unilateral kidney agenesis
- Kidney dysplasia
- Reflux nephropathy
- Sequela to cortical necrosis
- Surgical kidney ablation
- Any advanced kidney disease with reduction in functioning nephrons

Initially Normal Kidney Mass
- Hypertension
- Atheroemboli or other acute vasoocclusive processes
- Obesity
- Bodybuilders
- Cyanotic congenital heart disease
- Sickle cell anemia

Uncertain Cause

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

hemodynamic alterations may be associated with glomerular hyperfiltration. Intraglomerular coagulation and abnormalities of lipid metabolism may also contribute to glomerulosclerosis in these patients (see Chapter 81). Although immunoglobulin (Ig) M and C3 are regarded as nonspecifically trapped in areas of sclerosis, they may contribute to glomerular injury through activating complement and binding antigens.21 22 Recent studies document both reparative and sclerosing roles for parietal epithelial cells in FSGS. In vivo microscopy has illustrated that parietal cells can rapidly cover sites of podocyte denudation and depletion in FSGS but make a limited contribution to podocyte regeneration.23 24 Parietal cells may also directly contribute to glomerulosclerosis by migrating onto the glomerular tufts and synthesizing extracellular matrix proteins.25

variants or polymorphisms in podocyte genes. Genetic predisposition may underlie the susceptibility to second hits, whereby viral factors, immune stimuli, and other insults lead to the initiation or acceleration of disease. For example, APOL1 gene variants predispose to FSGS, as well as HIV nephropathy, chronic hypertensive nephrosclerosis, and lupus nephritis among African Americans.26 G1 and G2 variants in APOL1 protect against infection by Trypanosoma brucei, the parasite that causes African sleeping sickness. Similar to the gene for sickle cell disease, which confers protection against malaria, the G1 and G2 variants became prevalent because they protect against infection. Although APOL1 is expressed by glomerular endothelial cells and podocytes, it is not entirely clear how sequence variations in APOL1 cause glomerulosclerosis. Various mechanisms have been proposed including increased podocyte membrane pores promoting intracellular potassium depletion and induction of stress-activated protein kinases27 and impairment of podocyte endocytic functions and autophagy.28

Secondary Focal Segmental Glomerulosclerosis

When an FSGS lesion is found together with a process associated with FSGS, we refer to this as secondary FSGS.11 The known/presumptive etiologies of secondary FSGS include viral infections, drug toxicities, and maladaptive responses to glomerular hyperfiltration and are listed in Box 19.1

Virus-Associated Focal Segmental Glomerulosclerosis

Viral infections (particularly HIV) can cause podocytopathies, particularly collapsing FSGS (see Chapter 58). Other potential viral triggers include parvovirus B-19, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) infections. During the COVID-19 pandemic, collapsing FSGS was linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients of African ancestry.29 30 The heightened cytokine release associated with viral infections may place patients with the high-risk APOL1 genotype at risk of interferonmediated podocyte injury, as can occur in other virally mediated, interferon therapy–induced, and HIV-associated forms of collapsing FSGS.31 32

Drug-Induced Focal Segmental Glomerulosclerosis

Several drugs and medications are associated with the FSGS phenotype, including heroin, lithium, pamidronate, sirolimus, calcineurin inhibitors (CNIs), tyrosine kinase inhibitors, and interferons α, β, and γ (Box 19.1). Heroin is associated with the nephrotic syndrome and FSGS (heroin nephropathy), although its incidence has diminished markedly in recent years. Pamidronate is a bisphosphonate used to prevent bone resorption in myeloma and metastatic tumors and is associated with collapsing FSGS and MCD.33 Stabilization of kidney function and resolution of nephrotic syndrome may follow withdrawal of these medications. Long-term anabolic steroid use by bodybuilders is associated with FSGS,34 although this observation could be confounded by use of high-protein diets and other potential nephrotoxins such as growth hormone. Putative mechanisms of glomerular injury include direct toxic effects of anabolic steroids on glomerular cells, as well as adaptive responses to elevated lean body mass. In a small series, all patients who developed FSGS secondary to interferon therapy have been shown to carry double APOL1 risk alleles and to activate a viral innate immunity program in podocytes upon interferon exposure, supporting a two-hit model of podocyte injury.35

Genetic Focal Segmental Glomerulosclerosis

Focal Segmental Glomerulosclerosis From Adaptive Changes to Glomerular Hyperfiltration

Genetic and familial forms of FSGS are covered in detail in Chapter 20. Many cases of apparently primary FSGS may harbor unrecognized

Many secondary forms of FSGS are mediated by adaptive structuralfunctional responses leading to podocyte detachment and subsequent sclerosis.36 These adaptive forms include patients with both congenital and acquired reduction in the number of functioning nephrons, whereas other secondary forms are associated with hemodynamic stress placed on an initially normal nephron population (Box 19.1). Obesity-related glomerulopathy is increasingly common worldwide and may be associated with metabolic syndrome, including hypertension, diabetes, and hyperlipidemia.37 Low birth weight associated with prematurity and reduced nephron endowment also may lead to glomerular hypertrophy, with secondary FSGS developing in adolescence or adulthood.38 Biopsy specimens with secondary adaptive FSGS typically show glomerulomegaly and perihilar lesions of segmental sclerosis and hyalinosis. These conditions resemble experimental models of kidney ablation in which the surgical reduction in kidney mass causes functional hypertrophy of remnant nephrons with increased glomerular plasma flows and pressures. Although these changes are initially “adaptive,” the resultant hyperfiltration and increased glomerular pressure become “maladaptive” and serve as mechanisms for progressive glomerular damage.36

Focal Segmental Glomerulosclerosis From Uncertain Cause

FSGS can also occur without a genetic or identifiable secondary cause, in the absence of nephrotic syndrome (NS), and without diffuse foot process effacement on electron microscopy of the kidney biopsy. This form of FSGS is distinct from primary FSGS based on its clinical and histologic manifestations. The KDIGO Guideline proposes calling this entity FSGS of unknown cause.11 Patients with FSGS of unknown cause may have secondary or genetic forms of FSGS that have not yet been elucidated.

normal serum albumin concentration.37,46 Patients with genetic FSGS may have variable degrees of proteinuria and serum albumin levels.46 Hypertension is found in 30% to 65% of children and adults with FSGS at diagnosis. Microhematuria is found in 30% to 75% of these patients, and decreased GFR is noted at presentation in 20% to 50%.1 Daily urinary protein excretion ranges from less than 1 to more than 30 g/day. Proteinuria is typically nonselective. Complement levels and other serologic test results are normal. Occasional patients will have glycosuria, aminoaciduria, phosphaturia, or a concentrating defect indicating functional tubular damage and glomerular injury.

Different histologic patterns of FSGS may display unique clinical features.47 The clinical presentation of patients with the tip variant of FSGS resembles MCD.48 They often present with an abrupt clinical onset of the full nephrotic syndrome (almost 90%), shorter time course from onset to kidney biopsy, more severe proteinuria, and less chronic tubulointerstitial disease than in FSGS not otherwise specified (NOS).48 The cellular variant also typically manifests with greater proteinuria and higher incidence of nephrotic syndrome than FSGS NOS.49 The collapsing variant usually manifests with greater proteinuria, severe nephrotic syndrome, and lower GFR.47,50

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

There is substantial variation in the reported frequency of primary glomerular diseases between different geographic and among racial populations.39 40 The reasons for these differences may be multifactorial (e.g., bias in referral patterns and who undergoes biopsy, environmental or racial predispositions such as the presence of APOL1 genetic variants in people of African descent). The prevalence of FSGS varies across countries. In a study from China, FSGS was diagnosed in 2.45%

of biopsies.41 In a Danish kidney biopsy registry study, an incidence of 1.5 to 5.7 patients per million/year was reported.42 In a single-center study from Germany, FSGS accounted for 6.1% of biopsies, and its frequency rose 3.9-fold over a 24-year period beginning 1990.43 An analysis of the prevalence of ESKD in the United States caused by FSGS during a 21-year period showed an increase from 0.2% in 1980 to 2.3% in 2000, and FSGS was the most common primary glomerular disease leading to ESKD.5 Although some changes in prevalence may relate to changes in biopsy practice or disease classification, the true frequency of FSGS has likely increased over time.

Primary FSGS is slightly more common in males than females, and the incidence of ESKD secondary to FSGS in males of all races is 1.5 to 2 times higher than in females. The incidence in both children and adults is higher in African Americans than in Whites and those of Asian descent.1 44 This most likely relates to the presence of G1 and G2 variants of the apolipoprotein L1 genes in African Americans.26

Except for genetic forms of FSGS, a firm diagnosis of FSGS requires a kidney biopsy. Tests for permeability factors are neither reliable nor available in routine clinical practice. In children with FSGS, most of whom present with nephrotic syndrome, the major differential is between MCD and other variants of corticosteroid-resistant nephrotic syndrome. In adults with subnephrotic proteinuria, the differential includes almost all glomerular diseases without positive serologic results. In adults with nephrotic syndrome, MN and MCD may present in an identical manner, and only a kidney biopsy will clarify the diagnosis (except for MN patients, in whom the presence of M-type phospholipase A2 receptor [PLA2R] antibody and possibly other autoantibodies may provide the diagnosis without a biopsy; see Chapter 21). Focal sclerosing lesions caused by other glomerulopathies (e.g., segmental scarring from chronic glomerulonephritis) must be excluded pathologically. Moreover, because the defining glomerular lesion of FSGS is focal and may be confined to deeper juxtamedullary glomeruli early in the disease, it may not be sampled on kidney biopsy. A large sample of more than 20 glomeruli for light microscopy or serial sections of the biopsy core may increase the likelihood of identifying the diagnostic segmental lesions.

Even after the diagnosis of FSGS is established, the primary form must be distinguished from secondary forms by careful clinicopathologic correlation (Box 19.2). In general, many forms of adaptive FSGS have lower levels of proteinuria than primary FSGS, a lower incidence of hypoalbuminemia, and, on biopsy, lesser degrees of foot process effacement.11,46 In patients younger than 25 years and especially in those with a family history of FSGS, genetic screening for variants in podocin, TRPC6, α-actinin-4, inverted formin 2, or other podocyte genes may be useful (see Chapter 20). Similarly, in young adults with sporadic corticosteroid-resistant FSGS, genetic testing may yield pathogenic variants, albeit in a lower proportion compared with children.51,52

CLINICAL MANIFESTATIONS

PATHOLOGY

Patients with primary FSGS typically present with the full nephrotic syndrome (especially hypoalbuminemia).11 45 Secondary forms of FSGS associated with hyperfiltration typically have lower levels of proteinuria, and many such patients have subnephrotic proteinuria and

The pathologic manifestations of FSGS are heterogeneous.1,3 A hierarchical classification of FSGS by histologic variants (Table 19.1) can be applied to both primary and secondary forms of FSGS (see Box 19.1).47 This working classification has been applied successfully to

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retrospective and prospective biopsy series. Other, more controversial histologic variants of FSGS include FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see Chapter 29). Some think these are distinct disease entities, whereas others think they are merely subgroups of FSGS.[53,54]

BOX 19.2

Definition of Remission, Relapse, Resistance, and Therapy Dependence for Focal Segmental Glomerulosclerosis

Complete Remission	Reduction of proteinuria to <0.3 g/day or urine PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine, and serum albumin >3.5 g/dL (or 35 g/L)
Partial Remission	Reduction of proteinuria to 0.3–3.5 g/day or urine PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse	Proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission
Steroid-Resistant	Persistence of proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/day or 2 mg/kg every other day for at least 16 weeks
Steroid-Dependent	Relapse occurring during or within 2 weeks of completing glucocorticoid therapy
CNI-resistant FSGS	Persistence of proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/mL or tacrolimus treatment at trough levels of 5–10 ng/mL for >6 months
CNI-Dependent	Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months

CNI, Calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; PCR, polymerase chain reaction.

Modified from KDIGO GN Guideline. Kidney Int. 2021;100(4S):S1–S276.

TABLE 19.1

Classification

Classic Focal Segmental Glomerulosclerosis Not Otherwise Specified

FSGS NOS requires exclusion of the more specific subtypes described later. This is the most frequent variant and may occur in primary or secondary forms of FSGS, including genetic forms. It is defined by segmental obliteration of the glomerular tuft by matrix accumulation, which may be accompanied by hyalinosis and/or endocapillary foam cells (Fig. 19.1).[47] Adhesions or synechiae to Bowman’s capsule are common, and overlying visceral epithelial cells often appear swollen and form a cellular “cap” over the sclerotic segment. Glomerular lobules unaffected by segmental sclerosis appear normal on light microscopy, except for mild podocyte swelling. Tubular atrophy and interstitial fibrosis are commensurate with the degree of glomerulosclerosis. Immunofluorescence (IF) typically reveals focal and segmental granular deposition of IgM, C3, and more variably C1q in the distribution of the segmental glomerular sclerosis (Fig. 19.2). On electron microscopy (EM), segmental sclerotic lesions exhibit increased extracellular matrix (ECM), wrinkling and retraction of the glomerular basement membrane (GBM), accumulation of inframembranous hyaline, and resulting narrowing or occlusion of the glomerular capillary lumina. Electron-dense immune-type deposits should be absent and, if present, should raise suspicion for chronic glomerulonephritis. Overlying the segmental sclerosis, there is often podocyte detachment with parietal cell coverage (Fig. 19.3). The adjacent nonsclerotic glomerular capillaries show foot process effacement with variable microvillous transformation (slender projections resembling villi along the surface of podocytes).

Perihilar Variant of Focal Segmental Glomerulosclerosis

The perihilar variant is defined as hyalinosis and sclerosis at the vascular pole involving more than 50% of glomeruli with segmental lesions (Fig. 19.4).47 This category requires exclusion of the cellular, tip, and collapsing variants. Although the perihilar variant may occur in primary FSGS, it is particularly frequent in secondary forms of FSGS mediated by adaptive structural-functional responses, accompanied by glomerular hypertrophy (glomerulomegaly) and relatively mild foot process effacement. In this setting, reflex dilation of the afferent arteriole and the greater filtration pressures at the proximal end of the

Morphologic Variants of Focal Segmental Glomerulosclerosis : Columbia

Variant	Defining Features	Clinical Features	Associations
Collapsing	Implosive retraction of capillaries with overlying GEC hyperplasia, severe tubular injury, tubular microcysts, severe FPE	Primary or secondary, severe nephrotic syndrome and AKI, Black racial predominance, worst prognosis	Viral infections (HIV, SARS-CoV-2, CMV), autoimmune SLE, drugs (pamidronate, INF), vasoocclusion, APOL1
Tip	Adhesion of tuft at tubular pole with foam cells, severe FPE	Usually primary, abrupt-onset nephrotic syndrome	Usually steroid responsive, favorable prognosis
Cellular	Expansile lesion with endocapillary hypercellularity (foam cells, leukocytes)		

Usually primary

Perihilar

Hyalinosis and sclerosis centered at vascular pole,
glomerulomegaly, focal FPE

Usually secondary, adaptation to glomerular
hyperfiltration

NOS

Does not meet criteria for any above variant

Most common variant, primary or secondary

Obesity, HTN, low nephron number, sickle
cell nephropathy

AKI, Acute kidney injury; CMV, cytomegalovirus; FPE, foot process effacement; FSGS, focal segmental glomerulosclerosis; GEC, glomerular epithelial cell; HIV, human immunodeficiency virus; HTN, hypertension; INF, interferon; NOS, not otherwise specified; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus.

Fig. 19.1 Focal Segmental Glomerulosclerosis Not Otherwise Specified. A glomerulus with discrete lesion of segmental sclerosis involving a portion of the tuft characterized by accumulation of acellular matrix material, hyalinosis, and adhesion of the tuft to Bowman's capsule. (PAS; ×400.)

Fig. 19.2 Focal Segmental Glomerulosclerosis Not Otherwise Specified. The lesions of segmental sclerosis contain deposits of immunoglobulin M (IgM) corresponding to areas of increased matrix and hyalinosis. Weaker staining for IgM is also seen in the adjacent mesangium. (Immunofluorescence micrograph; ×400.)

Fig. 19.4 Focal Segmental Glomerulosclerosis (FSGS), Perihilar Variant. A discrete lesion of segmental sclerosis and hyalinosis is located at the glomerular vascular pole (i.e., perihilar). The glomerulus is hypertrophied. The patient had secondary FSGS in the setting of severe obesity. (PAS; ×400.)

Fig. 19.5 Focal Segmental Glomerulosclerosis, Cellular Variant. The glomerular capillary lumina are segmentally occluded by endocapillary cells, including foam cells, infiltrating mononuclear leukocytes, and pyknotic debris. The findings mimic a proliferative glomerulonephritis because of the hypercellularity and absence of extracellular matrix material. There are hypertrophy and hyperplasia of the overlying visceral epithelial cells, some of which contain protein resorption droplets. (PAS; ×400.)

glomerular capillary bed may favor the development of lesions at the vascular pole.20 36

Cellular Variant of Focal Segmental Glomerulosclerosis

Fig. 19.3 Focal Segmental Glomerulosclerosis Not Otherwise Specified. Electron micrograph illustrates the lesion of segmental sclerosis with obliteration of the glomerular capillaries by increased extracellular matrix with wrinkled and retracted glomerular basement membranes. The overlying podocytes are detached (arrow). (×3000.)

The cellular variant is characterized by focal and segmental endocapillary hypercellularity that may mimic a form of focal proliferative glomerulonephritis.47 49 Glomerular capillaries are segmentally occluded by endocapillary hypercellularity, including foam cells, infiltrating leukocytes, karyorrhectic debris, and hyaline (Fig. 19.5). There is often hyperplasia of the visceral epithelial cells, which may appear swollen, sometimes forming pseudocrescents. Foot process effacement is typically severe. This variant requires that tip lesions and collapsing lesions be excluded. Cellular FSGS is thought to represent an early stage in the development of segmental lesions and is usually primary.

Fig. 19.6 Focal Segmental Glomerulosclerosis, Collapsing Variant. There is global implosive collapse of the glomerular tuft with obliteration of capillary lumina. The overlying visceral epithelial cells appear hypertrophied and hyperplastic, show prominent cytoplasmic vacuolization, and contain enlarged nuclei and nucleoli. There are no adhesions to Bowman’s capsule. (Jones methenamine silver; ×400.)

Fig. 19.8 Focal Segmental Glomerulosclerosis, Collapsing Variant. An attenuated lesion of collapsing focal segmental glomerulosclerosis shows global retraction and early solidification of the glomerular tuft, which is capped by reactive-appearing glomerular epithelial cells (Jones methenamine silver; ×400.)

Fig. 19.7 Focal Segmental Glomerulosclerosis, Collapsing Variant. In this example, exuberant proliferation of glomerular epithelial cells forms a pseudocrescent that obliterates the urinary space. The hypertrophied and hyperplastic glomerular epithelial cells contain abundant intracytoplasmic protein droplets. The pseudocrescent lacks the spindle cell morphology, ruptures of Bowman’s capsule, or pericellular matrix typically seen in true inflammatory crescents of parietal epithelial origin. (Jones methenamine silver; ×400.)

Fig. 19.9 Focal Segmental Glomerulosclerosis, Collapsing Variant. The kidney parenchyma contains abundant tubular microcysts with proteinaceous casts. (H&E; ×200.)

Collapsing Variant of Focal Segmental Glomerulosclerosis

The collapsing variant is defined by at least one glomerulus with segmental or global collapse and overlying hypertrophy and hyperplasia of visceral epithelial cells (Fig. 19.6). In these areas, there is occlusion of glomerular capillary lumina by implosive GBM wrinkling and collapse.47 50 The collapsing lesion is more often global than segmental.

Overlying visceral epithelial cells display hypertrophy and hyperplasia and express proliferation markers. These glomerular epithelial cells often contain prominent intracytoplasmic protein resorption droplets and may fill Bowman’s space, forming pseudocrescents (Fig. 19.7). Attenuated collapsing lesions are characterized by retraction and solidification of the tuft, which is often capped by a layer of reactive glomerular epithelial cells (Fig. 19.8). Studies suggest that dysregulated podocytes, activated parietal cells (expressing claudin and CD44), and progenitor cells (expressing stem cell markers CD133 and CD24) that line Bowman’s capsule contribute to the glomerular epithelial cell hyperplasia and glomerulosclerosis.55

In collapsing FSGS, there is prominent tubulointerstitial disease, including acute tubular injury, tubular atrophy, interstitial fibrosis, interstitial edema, and inflammation. A distinctive feature is the presence of dilated tubules forming microcysts that contain proteinaceous casts (Fig. 19.9). On EM, there is typically severe foot process effacement affecting both collapsed and noncollapsed glomeruli. Collapsing glomerulopathy may occur as a primary form of FSGS.56 It is also frequently observed in secondary FSGS caused by viral infections (including HIV and SARS-CoV-2), lupus podocytopathy, hemophagocytic syndrome, and interferon therapy in conjunction with high-risk APOL1 variants.29 32 57 The presence of endothelial tubuloreticular inclusions helps to identify collapsing glomerulopathy secondary to HIV-associated nephropathy, COVID-19–associated nephropathy

Fig. 19.10 Focal Segmental Glomerulosclerosis, Collapsing Variant, COVID-19–associated nephropathy. A glomerular endothelial cell contains a large intracytoplasmic tubuloreticular inclusion (“interferon footprint”; arrow) composed of interanastomosing tubular structures within a dilated cisterna of endoplasmic reticulum. (EM; ×40,000.)

Fig. 19.12 Focal Segmental Glomerulosclerosis, Tip Lesion Variant. A sclerosing tip lesion forms an adhesion to the tubular pole (arrow). (PAS; ×200.)

Fig. 19.11 Focal Segmental Glomerulosclerosis, Tip Lesion Variant. A cellular tip lesion displays engorgement of glomerular capillaries by foam cells and adhesion of the involved segment to the origin of the proximal tubule/tubular pole (arrow). (PAS; ×200.)

Fig. 19.13 Focal Segmental Glomerulosclerosis, Tip Lesion Variant. Electron microscopy reveals complete podocyte foot process effacement with matting of the actin cytoskeleton, selling of podocyte cell bodies, and focal microvillous transformation of podocyte cytoplasm. (EM; ×3000).

lupus podocytopathy, or interferon therapy. These “interferon footprints” consist of 24-nm interanastomosing tubular structures located within dilated cisternae of endoplasmic reticulum (Fig. 19.10).

and favorable prognosis relative to other FSGS variants. Higher shear stress and tuft prolapse at the tubular pole are likely to play a role in the morphogenesis of this lesion.4

Tip Variant of Focal Segmental Glomerulosclerosis

Other Variants of Focal Segmental Glomerulosclerosis

The tip variant is defined by the presence of at least one segmental lesion involving the tip domain, the outer 25% of the tuft next to the origin of the proximal tubule.47 48 58 There is either adhesion between the tuft and Bowman’s capsule or confluence of swollen podocytes with parietal or tubular epithelial cells at the tubular lumen or neck. The segmental lesions may be cellular or sclerosing (Figs. 19.11 and 19.12). The presence of perihilar sclerosis or collapsing sclerosis rules out the tip variant. In one study of FSGS tip lesions, biopsy specimens had glomerular tip lesions alone in 26% and glomerular tip lesions plus other peripheral FSGS lesions in the other 74%.48 The degree of foot process effacement is usually severe (Fig. 19.13). Most cases are primary and resemble MCD with respect to abrupt onset of full nephrotic syndrome, high likelihood of responsiveness to corticosteroid therapy,

Two histologic variants often included within the FSGS spectrum are FSGS with diffuse mesangial hypercellularity and C1q nephropathy (see Chapter 29).1 FSGS with diffuse mesangial hypercellularity has lesions of FSGS on a background of generalized mesangial hypercellularity. By IF, there is often diffuse mesangial positivity for IgM, with more variable mesangial staining for C3. EM reveals extensive foot process effacement. Amorphous hyaline-like electron-dense deposits are variably present in the paramesangial region. This variant occurs almost exclusively in young children.59 60

C1q nephropathy is defined by dominant or codominant IF staining for C1q, mesangial electron-dense deposits, and light microscopic findings resembling FSGS or MCD with variable mesangial hypercellularity. In one study, 17 patients had a light microscopic appearance of

Risk Factors for Progressive Kidney Disease in Focal Segmental Glomerulosclerosis

BOX 19.3

Clinical Features at Biopsy
- Severity of nephrotic-range proteinuria
- Elevated serum creatinine
- Black race

Histopathologic Features at Biopsy
- Collapsing variant
- Tubulointerstitial fibrosis

Clinical Features During Disease Course
- Failure to achieve partial or complete remission

FSGS (including six collapsing and two cellular) and three of MCD.53 In addition to C1q staining, biopsy specimens may show deposition of other immunoglobulins (particularly IgG) and complement components (C3), making it important to exclude other clinical disease such as lupus nephritis. In C1q nephropathy, electron-dense deposits are typically located in the paramesangial region subjacent to the GBM reflection. There is variable foot process effacement. In one series of C1q nephropathy, many cases represented a subgroup of primary FSGS or MCD, whereas in others, an idiopathic immune complex–mediated glomerulonephritis was noted.54

Distinguishing Pathologic Features of Secondary Focal Segmental Glomerulosclerosis

Although the pathology of some secondary forms of FSGS closely resembles primary FSGS, there are several noteworthy differences. Collapsing FSGS, particularly when tubuloreticular inclusions are present, should prompt exclusion of viral, autoimmune, or druginduced causes of disease. In secondary adaptive forms of FSGS, kidney biopsy typically shows glomerulomegaly and predominantly perihilar lesions of segmental sclerosis and hyalinosis. In secondary FSGS resulting from loss of kidney mass, such as from reflux nephropathy or hypertensive arterionephrosclerosis, FSGS is usually seen on a background of extensive global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. In secondary FSGS related to sickle cell disease, glomerular hypertrophy and sclerosis are associated with capillary congestion by sickled erythrocytes and double contours of the GBM resembling those seen in chronic thrombotic microangiopathy.61 62 In adaptive forms of FSGS, the degree of foot process effacement tends to be relatively mild, affecting less than 50% of the total glomerular capillary surface area. In one study, a cutoff of greater than 1500 nm for mean foot process width was able to distinguish primary from adaptive FSGS.16

NATURAL HISTORY AND PROGNOSIS

The natural history of FSGS is varied. Without response to therapy, patients with primary FSGS experience a progressive increase in proteinuria and progression to kidney failure. Spontaneous remission is uncommon.63 In treatment-refractory patients, ESKD occurs 5 to 20 years from presentation, with approximately 50% of such patients developing kidney failure within 10 years.64

Certain epidemiologic, clinical, and histologic findings at diagnosis help predict the long-term course of patients with FSGS (Box 19.3). African Americans with FSGS experience a more rapid progression to ESKD than people of other races.65 At biopsy, reduced GFR, greater degrees of proteinuria, and greater degrees of interstitial fibrosis predict a more progressive course.66 67 In general, outcomes are best for tip variant and worst for collapsing variant of primary FSGS, with intermediate outcome in FSGS NOS.47 68 In a comparative series, the percentage of complete and partial remission was greatest for tip lesion (76%), lowest for collapsing variant (13%), and intermediate for cellular (44%) and FSGS NOS (39%). There was a strong inverse correlation between remission rates and progression to ESKD among these subgroups. Accordingly, the likelihood of ESKD was greatest for collapsing variant (65%), lowest for tip lesion (6%), and intermediate for cellular variant (28%) and FSGS NOS (35%).47 Although collapsing variant has the worst outcome among the FSGS variants, when patients with collapsing variant are matched with patients with FSGS NOS for baseline levels of kidney function, proteinuria, and immunosuppression, responses to treatment are similar, highlighting the importance of early detection and aggressive therapy.50 A key predictor of prognosis is remission of proteinuria. Complete remission of the nephrotic syndrome is associated with excellent kidney survival compared with those who do not remit.64 Even patients with a partial remission of nephrotic syndrome have a lower rate of long-term kidney failure.64

TREATMENT

Before considering the treatment of FSGS, it is useful to define remission of proteinuria. There has been considerable variability in the definition of remission, and the KDIGO Guideline has attempted to unify these definitions (Box 19.2).11 Recently a novel definition of partial remission (40% proteinuria reduction and proteinuria <1.5 g/g) was useful in predicting prognosis.69

Although FSGS is common in adults, there are few randomized controlled trials (RCTs) on which to base treatment decisions.11 However, almost all patients with FSGS will benefit from good supportive care (e.g., blockade of the renin-angiotensin-aldosterone system), as described in Chapter 82. The optimal treatment of FSGS is not well defined. In part, this relates to properly defining primary and secondary forms of the disease, including unrecognized genetic variants (Fig. 19.14). For example, even after biopsy, it is not always clear whether an obese person with glomerulomegaly, FSGS lesions, and nephrotic-range proteinuria has secondary or primary disease. This problem of heterogeneity in the patient population also potentially translates to varying treatment responses in clinical trials.70 In general, we recommend treating patients with presumed primary FSGS with immunosuppressive medications. In contrast, immunosuppression is not needed in patients with subnephrotic proteinuria, genetic or secondary FSGS, or FSGS of uncertain etiology (Fig. 19.14).11

First-Line Therapy for Focal Segmental Glomerulosclerosis

Corticosteroids as Initial Therapy (Table 19.2)

Corticosteroids appear to increase the likelihood of remission64 71-73 and are considered first-line therapies for primary FSGS.11 Although earlier reports suggested that primary FSGS is a steroid-resistant disease with poor outcomes,74 subsequent studies showed that longer treatment duration with higher doses of corticosteroids was associated with improved response rates of 50% to 60%,63 66 75 and in one study up to 80%.76 The suggested regimens (as per KDIGO Guideline) are shown in Box 19.2 11 A suggested maximum duration of high-dose corticosteroid treatment for remission to be achieved is 16 weeks. However, based on available evidence, it is uncertain whether the side effects of 16 weeks of high-dose glucocorticoid treatment outweigh benefits in primary FSGS, as studies have been inconsistent in the reporting of adverse events. The optimal duration of glucocorticoid therapy is

Evaluation of a Patient with FSGS and No Evidence
of Glomerular Pathology
Patient with FSGS lesion
on kidney biopsy

Presence of nephrotic syndrome

Absence of nephrotic syndrome

Proteinuria >3.5 g/day
AND
serum albumin <30 g/L
with or without edema
especially in the presence of
diffuse foot process effacement

1. Nephrotic-range proteinuria >3.5 g/day
but serum albumin >30 g/L
OR
2. Proteinuria <3.5 g/day with or
without hypoalbuminemia

Likely primary FSGS
- Treat with immunosuppression
- If no response, consider
genetic testing

- Evaluate for an underlying cause, exclude
secondary forms of FSGS
- Consider genetic screening (where appropriate)
to exclude genetic forms
- Do not start immunosuppression
- Supportive therapy
- Monitor proteinuria and serum albumin

Worsening proteinuria and
reduction in serum albumin

Fig. 19.14 Evaluation of a patient with focal segmental glomerulosclerosis (FSGS) lesion on the kidney biopsy and no evidence of other glomerular pathology. (From KDIGO GN Guideline. Kidney Int. 2021;100(4S):S1–S276.)

unknown. A slow taper is suggested after initial response, and for such patients, the suggested total period of glucocorticoid treatment is 6 months as tolerated.11 If there is no remission in proteinuria, corticosteroids should be tapered off after 16 weeks.

azathioprine, and 86% for prednisone plus cyclosporine.72 In a large retrospective study, 173 patients were treated with corticosteroids alone and 90 treated with CNIs with or without corticosteroids; the risk of ESKD was similar in the two groups.80

Corticosteroid-Sparing or Noncorticosteroid Regimens as Initial Therapy

Corticosteroid-Resistant Focal Segmental Glomerulosclerosis

Patients may not tolerate high doses of glucocorticoids, and with the need for prolonged treatment regimens for FSGS, adverse effects of corticosteroids may be unacceptable (Table 19.2). Moreover, in patients with obesity, uncontrolled diabetes, psychiatric disease, or severe osteoporosis, corticosteroids may be relatively contraindicated.77 CNIs (cyclosporine or tacrolimus) and antimetabolites (azathioprine or mycophenolic acid analogs) have been used to avoid or reduce exposure to corticosteroids. In a small observational study, tacrolimus monotherapy achieved partial remission in all six patients after about 6 months.78 In a randomized study of 33 FSGS patients, mycophenolate mofetil (MMF) 2 g/day for 6 months with prednisolone 0.5 mg/kg/day for 2 to 3 months was compared with conventional therapy with prednisolone 1 mg/kg/day for 3 to 6 months. Remission was similar in the MMF group 70% versus 69% in the conventional corticosteroid group.79 A retrospective observational study compared high-dose oral prednisone (1 mg/kg/day) for at least 4 months followed by a taper, with lower dose prednisone (0.5 mg/kg/day) in combination with cyclosporine (3 mg/kg/day initially, tapering to 50 mg/day) or azathioprine (2 mg/kg/day initial dose, tapering to 0.5 mg/kg/day). Average duration of treatment was 20 months. Low-dose prednisone was given to 16 patients with obesity, bone disease, or mild diabetes. Remission rates were comparable: 63% for prednisone, 80% for prednisone plus

For patients with corticosteroid-resistant FSGS, the CNIs (cyclosporine or tacrolimus) are recommended.11 Other options include MMF, rituximab, and corticotrophin.

Calcineurin Inhibitors (Table 19.3)

In one study, steroid-resistant adult patients with FSGS randomized to either cyclosporine with low-dose corticosteroids or the same low dose of corticosteroids alone for a 6-month period exhibited a much higher remission rate (12% complete and >70% complete or partial) in the group treated with cyclosporine.81 Despite some relapses after cyclosporine discontinuation, the treated group had significantly more patients in remission and better GFR at long-term follow-up. In another randomized controlled study, cyclosporine monotherapy was used, with similar results.82 Although data on tacrolimus are more limited, results are similar.83 Because the major side effects (nephrotoxicity, hypertension, and hyperkalemia) are similar with cyclosporine and tacrolimus, the choice depends on other adverse effects (e.g., gum swelling, tremor, hirsutism with cyclosporine, and diabetes with tacrolimus). Because there is a high relapse rate when cyclosporine is discontinued early,81 we use a 1-year treatment course with a slow taper in patients with a favorable reduction of proteinuria on CNIs.11

TABLE 19.2

Initial Treatment of Primary Focal Segmental Glomerulosclerosis

Treatment

Dose and Duration

Glucocorticoids

Starting Dose
- High-dose glucocorticoid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)

High-Dose Glucocorticoid Treatment Duration
- Continue high-dose glucocorticoid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier
- Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high-dose treatment
- It may not be necessary to persist with high-dose glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects

Glucocorticoid Tapering
- If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months.
- If partial remission is achieved within 8–12 weeks of high dose glucocorticoid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months.
- If the patient proves to be steroid resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI inhibitor should be considered

CNIs

Starting Dose
- Cyclosporine 3–5 mg/kg/day in two divided doses or tacrolimus 0.05–0.1 mg/kg/day in two divided doses
- Target trough levels could be measured to minimize nephrotoxicity
- Cyclosporine target trough level: 100–175 ng/mL
- Tacrolimus target trough level: 5–10 ng/mL

Treatment Duration for Determining CNI Efficacy
- Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment

Total CNI Treatment Duration
- In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses
- The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated
- Consider discontinuing CNI if the eGFR continues to decline to <30 mL/min/1.73 m2

CNI, Calcineurin inhibitor; eGFR, Estimated glomerular filtration rate.
Modified from KDIGO GN Guideline. Kidney Int. 2021;100(4S):S1–S276.

TABLE 19.3

Treatment of Steroid-Resistant Primary Focal Segmental Glomerulosclerosis

Treatment

Dose and Duration

CNIs

Starting Dose

- Cyclosporine 3–5 mg/kg/day in two divided doses or tacrolimus 0.05–0.1 mg/kg/day in two divided doses
- Target trough levels could be measured to minimize nephrotoxicity
- Cyclosporine target trough level: 100–175 ng/mL
- Tacrolimus target trough level: 5–10 ng/mL

Treatment Duration for Determining CNI Efficacy

- Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months before considering the patient to be resistant to CNI treatment

Total CNI Treatment Duration

- In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses
- The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated
- Consider discontinuing CNI if the eGFR continues to decline to <30 mL/min/1.73 m2

Inability to tolerate or contraindications to CNIs

- Lack of quality evidence for any specific alternative agents
- MMF and high-dose dexamethasone, rituximab, and ACTH have been considered
- Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression
- Patients should be referred to specialized centers with the appropriate expertise and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

ACTH, Adrenocorticotrophic hormone; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil.
Modified from KDIGO GN Guideline. Kidney Int. 2021;100(4S):S1–S276.

Mycophenolic Acid Analogs

Mycophenolic acid analogs (mycophenolate-MMF and mycophenolic acid) have been used successfully in several uncontrolled series of patients with FSGS.84 85 One multicenter prospective RCT of cyclosporine versus oral MMF plus dexamethasone in 138 children and adults up to age 40 years who had corticosteroid-resistant FSGS showed no difference in remission rates.86 However, this trial did not meet recruitment targets and was likely underpowered. Further, as with other clinical trials of FSGS, patients with secondary FSGS were likely included.

Other Therapies

Use of sirolimus has been limited since the drug was reported to induce proteinuria and FSGS lesions in kidney transplant recipients. In one series, sirolimus was associated with worsening of kidney function, episodes of acute kidney injury, and no remissions of the nephrotic syndrome.87 The addition of plasmapheresis to immunosuppressive medications, which has been successful in treating some patients with recurrent FSGS in the kidney allograft (see Chapter 113), has not been evaluated in patients with native kidney FSGS. Likewise, use of lowdensity lipoprotein apheresis and galactose (a monosaccharide sugar with a high affinity for CLC1, a putative permeability factor in patients with FSGS) has been anecdotal.88 89 Rituximab has been used anecdotally in several studies of small numbers of patients with FSGS who have either not responded to other treatments or have become dependent on these therapies. It has proved more successful for steroid-dependent90 than steroid-resistant patients.91 Corticotropin (adrenocorticotropic hormone) has shown benefit in small numbers of patients with FSGS resistant to multiple other immunosuppressive agents, but it also has not been studied in large RCTs.92

Therapy of Secondary Focal Segmental Glomerulosclerosis

For patients with secondary forms of FSGS, treating the underlying cause should be the initial step. Patients with FSGS secondary to obesity and heroin nephropathy have had remissions of proteinuria after weight reduction or cessation of heroin use, respectively. In HIVassociated nephropathy, therapy with highly active antiretroviral drugs and blockers of the renin-angiotensin system has proven useful (see Chapter 58). The role of immunosuppression has not yet been proven in RCTs in any form of secondary FSGS. In all forms of secondary FSGS, supportive therapy as outlined in Chapter 82 is essential to prevent progressive kidney disease. In patients with primary idiopathic or a secondary form of FSGS who remain nephrotic, fluid retention and edema can be managed with salt restriction and diuretics (see Chapter 16). In general, genetic forms of FSGS are not responsive to immunosuppressive medications. Although blockers of the renin-angiotensin system are commonly used, there are no studies that have reported outcomes. A small proportion of children with genetic FSGS have demonstrated proteinuria reduction with CNIs.93 94

KIDNEY TRANSPLANTATION

Approximately 30% of patients with primary FSGS who develop ESKD and undergo kidney transplantation develop recurrent FSGS in the allograft. Risk factors for recurrence include early-onset FSGS, and severe proteinuria with a rapid course to ESKD. Patients who have lost a prior allograft due to recurrent FSGS are at highest risk for recurrence. Treatment protocols include plasmapheresis, rituximab, highdose CNIs, and renin-angiotensin system blockers.95 Recurrent FSGS is further discussed in Chapter 113

SELF-ASSESSMENT QUESTIONS

1. Use of which of the following medications has not been associated with proteinuria and the histologic pattern of FSGS?

A. Interferon β
B. Pamidronate
C. Sirolimus
D. Amlodipine
E. Lithium

2. Which histologic feature on kidney biopsy suggests a secondary FSGS pattern related to structural-functional adaption?

A. Adhesions or synechiae to Bowman’s capsule
B. Glomerulomegaly and perihilar segmental sclerosis and hyalinosis
C. Hypertrophy and hyperplasia of the visceral epithelial cells
D. Diffuse mesangial hypercellularity
E. Collapse of part of or all the glomerular tuft

3. Which of the following statements about the prognosis of primary FSGS is true?

A. The outcome is worse for patients with the tip variant versus other patterns.
B. The outcome is better for patients with the collapsing variant versus other patterns.
C. Remission of proteinuria is a strong predictor of a favorable outcome.
D. African Americans have a prognosis similar to that of Whites if controlling for hypertension and degree of proteinuria.
E. The degree of glomerular sclerosis is the strongest histologic predictor of a poor kidney outcome.

REFERENCES

1. D’Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365(25):2398–2411.
2. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2017;12(3):502–517.
3. Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol. 2004;15(8):2169–2177.
4. D’Agati VD. The spectrum of focal segmental glomerulosclerosis: new insights. Curr Opin Nephrol Hypertens. 2008;17(3):271–281.
5. Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis. 2004;44(5):815–825.
6. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2010;5(11):2115–2121.
7. Maas RJ, Deegens JK, Wetzels JF. Permeability factors in idiopathic nephrotic syndrome: historical perspectives and lessons for the future. Nephrol Dial Transplant. 2014;29(12):2207–2216.
8. Savin VJ, Sharma R, Sharma M, et al. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. N Engl J Med. 1996;334(14):878–883.
9. D’Agati VD. Podocyte injury in focal segmental glomerulosclerosis: lessons from animal models (a play in five acts). Kidney Int. 2008;73(4):399–406.
10. Matsusaka T, Sandgren E, Shintani A, et al. Podocyte injury damages other podocytes. J Am Soc Nephrol. 2011;22(7):1275–1285.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–S276.
12. Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016;12(12):768–776.
13. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007;2(3):445–453.
14. DH IJ, Farris AB, Goemaere N, et al. Fidelity and evolution of recurrent FSGS in renal allografts. J Am Soc Nephrol. 2008;19(11):2219–2224.
15. Matsusaka T, Xin J, Niwa S, et al. Genetic engineering of glomerular sclerosis in the mouse via control of onset and severity of podocytespecific injury. J Am Soc Nephrol. 2005;16(4):1013–1023.
16. Deegens JK, Dijkman HB, Borm GF, et al. Podocyte foot process effacement as a diagnostic tool in focal segmental glomerulosclerosis. Kidney Int. 2008;74(12):1568–1576.
17. den Braanker DJW, Maas RJ, Deegens JK, et al. Novel in vitro assays to detect circulating permeability factor(s) in idiopathic focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2021;36(2):247–256.
18. Dantal J, Godfrin Y, Koll R, et al. Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol. 1998;9(9):1709–1715.
19. De Vriese AS, Wetzels JF, Glassock RJ, Sethi S, Fervenza FC. Therapeutic trials in adult FSGS: lessons learned and the road forward. Nat Rev Nephrol. 2021.
20. D’Agati VD, Chagnac A, de Vries AP, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol. 2016;12(8):453–471.
21. Strassheim D, Renner B, Panzer S, et al. IgM contributes to glomerular injury in FSGS. J Am Soc Nephrol. 2013;24(3):393–406.
22. Zhang YM, Gu QH, Huang J, et al. Clinical significance of IgM and C3 glomerular deposition in primary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2016;11(9):1582–1589.
23. Audard V, Zhang SY, Copie-Bergman C, et al. Occurrence of minimal change nephrotic syndrome in classical Hodgkin lymphoma is closely related to the induction of c-mip in Hodgkin-Reed Sternberg cells and

podocytes. Blood. 2010;115(18):3756–3762.

24. Smeets B, Kuppe C, Sicking EM, et al. Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. J Am Soc Nephrol. 2011;22(7):1262–1274.

25. Kuppe C, Grone HJ, Ostendorf T, et al. Common histological patterns in glomerular epithelial cells in secondary focal segmental glomerulosclerosis. Kidney Int. 2015;88(5):990–998.

26. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841–845.

27. Olabisi OA, Zhang JY, VerPlank L, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. Proc Natl Acad Sci U S A. 2016;113(4):830–837.

28. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. Nat Med. 2017;23(4):429–438.

29. Kudose S, Batal I, Santoriello D, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):1959–1968.

30. Velez JCQ, Caza T, Larsen CP. COVAN is the new HIVAN: the reemergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol. 2020;16(10):565–567.

31. Goyal R, Singhal PC. APOL1 risk variants and the development of HIVassociated nephropathy. FEBS J. 2020.

32. Markowitz GS, Nasr SH, Stokes MB, D’Agati VD. Treatment with IFN{alpha}, -{beta}, or -{gamma} is associated with collapsing focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2010;5(4):607–615.

33. Markowitz GS, Appel GB, Fine PL, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol. 2001;12(6):1164–1172.

34. Herlitz LC, Markowitz GS, Farris AB, et al. Development of focal segmental glomerulosclerosis after anabolic steroid abuse. J Am Soc Nephrol. 2010;21(1):163–172.

35. Nichols B, Jog P, Lee JH, et al. Innate immunity pathways regulate the nephropathy gene Apolipoprotein L1. Kidney Int. 2015;87(2):332–342.

36. Kriz W, Lemley KV. Mechanical challenges to the glomerular filtration barrier: adaptations and pathway to sclerosis. Pediatr Nephrol. 2017;32(3):405–417.

37. Kambham N, Markowitz GS, Valeri AM, Lin J, D’Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int. 2001;59(4):1498–1509.

38. Hodgin JB, Rasoulpour M, Markowitz GS, D’Agati VD. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4(1):71–76.

39. Swaminathan S, Leung N, Lager DJ, et al. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. Clin J Am Soc Nephrol. 2006;1(3):483–487.

40. Hanko JB, Mullan RN, O’Rourke DM, McNamee PT, Maxwell AP, Courtney AE. The changing pattern of adult primary glomerular disease. Nephrol Dial Transplant. 2009;24(10):3050–3054.

41. Hu R, Quan S, Wang Y, et al. Spectrum of biopsy proven renal diseases in Central China: a 10-year retrospective study based on 34,630 cases. Sci Rep. 2020;10(1):10994.

42. Heaf JG, Sorensen SS, Hansen A. Increased incidence and improved prognosis of glomerulonephritis: a national 30-year study. Clin Kidney J. 2021;14(6):1594–1602.

43. Zink CM, Ernst S, Riehl J, et al. Erratum: trends of renal diseases in Germany: review of a regional renal biopsy database from 1990 to 2013. Clin Kidney J. 2021;14(1):462.

44. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis. 1996;27(5):647–651.

45. Praga M, Morales E, Herrero JC, et al. Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. Am J Kidney Dis. 1999;33(1):52–58.
46. De Vriese AS, Sethi S, Nath KA, Glassock RJ, Fervenza FC. Differentiating primary, genetic, and secondary FSGS in adults: a clinicopathologic approach. J Am Soc Nephrol. 2018;29(3):759–774.
47. D’Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43(2):368–382.

48. Stokes MB, Markowitz GS, Lin J, Valeri AM, D’Agati VD. Glomerular tip lesion: a distinct entity within the minimal change disease/focal segmental glomerulosclerosis spectrum. Kidney Int. 2004;65(5):1690–1702.
49. Stokes MB, Valeri AM, Markowitz GS, D’Agati VD. Cellular focal segmental glomerulosclerosis: clinical and pathologic features. Kidney Int. 2006;70(10):1783–1792.
50. Laurin LP, Gasim AM, Derebail VK, et al. Renal survival in patients with collapsing compared with not otherwise specified FSGS. Clin J Am Soc Nephrol. 2016;11(10):1752–1759.
51. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med. 2019;380(2):142–151.
52. Yao T, Udwan K, John R, et al. Integration of genetic testing and pathology for the diagnosis of adults with FSGS. Clin J Am Soc Nephrol. 2019;14(2):213–223.
53. Markowitz GS, Schwimmer JA, Stokes MB, et al. C1q nephropathy: a variant of focal segmental glomerulosclerosis. Kidney Int. 2003;64(4):1232–1240.
54. Vizjak A, Ferluga D, Rozic M, et al. Pathology, clinical presentations, and outcomes of C1q nephropathy. J Am Soc Nephrol. 2008;19(11):2237–2244.
55. Barisoni L, Kriz W, Mundel P, D’Agati V. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 1999;10:51–61.
56. Schwimmer JA, Markowitz GS, Valeri A, Appel GB. Collapsing glomerulopathy. Semin Nephrol. 2003;23(2):209–218.
57. Bomback AS, Markowitz GS. Lupus podocytopathy: a distinct entity. Clin J Am Soc Nephrol. 2016;11(4):547–548.
58. Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int. 2006;69(5):920–926.
59. Childhood nephrotic syndrome associated with diffuse mesangial hypercellularity. A report of the Southwest Pediatric Nephrology Study Group. Kidney Int. 1983;24(1):87–94.
60. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. Kidney Int. 1981;20(6):765–771.
61. Walker BR, Alexander F, Birdsall TR, Warren RL. Glomerular lesions in sickle cell nephropathy. J A M A. 1971;215:437–440.
62. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015;11(3):161–171.
63. Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis. 1998;32(1):72–79.
64. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Toronto Glomerulonephritis Registry G. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16(4):1061–1068.
65. Sorof JM, Hawkins EP, Brewer ED, Boydstun II , Kale AS, Powell DR. Age and ethnicity affect the risk and outcome of focal segmental glomerulosclerosis. Pediatr Nephrol. 1998;12(9):764–768.
66. Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis. 1995;25(4):534–542.
67. Wehrmann M, Bohle A, Held H, Schumm G, Kendziorra H, Pressler H. Long-term prognosis of focal sclerosing glomerulonephritis. An analysis of 250 cases with particular regard to tubulointerstitial changes. Clin Nephrol. 1990;33:115–122.
68. D’Agati VD, Alster JM, Jennette JC, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. Clin J Am Soc

Nephrol. 2013;8(3):399–406.
69. Troost JP, Trachtman H, Nachman PH, et al. An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2018;13(3):414–421.
70. Gipson D. Clinical trials in FSGS: past challenges and new trial designs. Semin Nephrol. 2016;36(6):453–459.
71. Banfi G, Moriggi M, Sabadini E, Fellin G, D'Amico G, Ponticelli C. The impact of prolonged immunosuppression on the outcome of idiopathic

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focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. Clin Nephrol. 1991;36(2):53–59.
Goumenos DS, Tsagalis G, El Nahas AM, et al. Immunosuppressive treatment of idiopathic focal segmental glomerulosclerosis: a five-year follow-up study. Nephron Clin Pract. 2006;104(2):c75–82.
Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P. Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. Am J Med. 1987;82(5):938–944.
Cameron JS, Turner DR, Ogg CS, Chantler C, Williams DG. The longterm prognosis of patients with focal segmental glomerulosclerosis. Clin Nephrol. 1978;10:213–218.
Ponticelli C, Villa M, Banfi G, et al. Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? Am J Kidney Dis. 1999;34(4):618–625.
Stirling CM, Mathieson P, Boulton-Jones JM, et al. Treatment and

outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units. QJM. 2005;98(6):443–449.

Oh GJ, Waldo A, Paez-Cruz F, et al. Steroid-Associated side effects in patients with primary proteinuric kidney disease. Kidney Int Rep. 2019;4(11):1608–1616.

Duncan N, Dhaygude A, Owen J, et al. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. Nephrol Dial Transplant. 2004;19(12):3062–3067.

Senthil Nayagam L, Ganguli A, Rathi M, et al. Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study. Nephrol Dial Transplant. 2008;23(6):1926–1930.

Laurin LP, Gasim AM, Poulton CJ, et al. Treatment with glucocorticoids or calcineurin inhibitors in primary FSGS. Clin J Am Soc Nephrol. 2016;11(3):386–394.

Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. Kidney Int. 1999;56:2220–2226.

Ponticelli C, Rizzoni G, Edefonti A, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int. 1993;43:1377–1384.

Ramachandran R, Kumar V, Rathi M, et al. Tacrolimus therapy in adultonset steroid-resistant nephrotic syndrome due to a focal segmental glomerulosclerosis single-center experience. Nephrol Dial Transplant. 2014;29(10):1918–1924.

Choi MJ, Eustace JA, Gimenez LF, et al. Mycophenolate mofetil treatment for primary glomerular diseases. Kidney Int. 2002;61(3):1098–1114.

Cattran DC, Wang MM, Appel G, Matalon A, Briggs W. Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. Clin Nephrol. 2004;62(6):405–411.

Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int. 2011;80(8):868–878.

Fervenza FC, Fitzpatrick PM, Mertz J, et al. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies. Nephrol Dial Transplant. 2004;19(5):1288–1292.

Hattori M, Chikamoto H, Akioka Y, et al. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. Am J Kidney Dis. 2003;42(6):1121–1130.

Trachtman H, Vento S, Herreshoff E, et al. Efficacy of galactose and adalimumab in patients with resistant focal segmental glomerulosclerosis: report of the font clinical trial group. BMC Nephrol. 2015;16:111.

Kronbichler A, Konig P, Busch M, Wolf G, Mayer G, Rudnicki M. Rituximab in adult patients with multi-relapsing/steroid-dependent minimal change disease and focal segmental glomerulosclerosis: a report of 5 cases. Wien Klin Wochenschr. 2013;125(11–12):328–333.

Fernandez-Fresnedo G, Segarra A, Gonzalez E, et al. Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4(8):1317–1323.

92. Hogan J, Bomback AS, Mehta K, et al. Treatment of idiopathic FSGS with adrenocorticotropic hormone gel. Clin J Am Soc Nephrol. 2013;8(12):2072–2081.
93. Klaassen I, Ozgoren B, Sadowski CE, et al. Response to cyclosporine in steroid-resistant nephrotic syndrome: discontinuation is possible. Pediatr Nephrol. 2015;30(9):1477–1483.

94. Kemper MJ, Lemke A. Treatment of genetic forms of nephrotic syndrome. Front Pediatr. 2018;6:72.
95. Weber LT, Tonshoff B, Grenda R, et al. Clinical practice recommendations for recurrence of focal and segmental glomerulosclerosis/steroid-resistant nephrotic syndrome. Pediatr Transplant. 2021;25(3):e13955.

20

Inherited Causes of Nephrotic Syndrome

Ronen Schneider, Friedhelm Hildebrandt

INTRODUCTION

Etiology

The discovery of the genes encoding the slit membrane proteins nephrin (NPHS1),1 podocin (NPHS2),2 and phospholipase C epsilon 1 (PLCE1)3 as causing steroid-resistant nephrotic syndrome (NS), if mutated, has stimulated extensive research into monogenic causes of NS. In the last 20 years, acceleration of next-generation sequencing has permitted identification of more than 63 monogenic causes of NS, and this number is rapidly increasing (Fig. 20.1 and references in Table 20.1). Most of these genes are highly expressed in the glomerular podocytes, implicating podocytes as the primary site of injury in NS. The encoded proteins of these genes cluster within functional pathways critical for podocyte biology and cause disruption of the filtration barrier if mutated.

The proteins encoded by the genes that cause monogenic SRNS map back onto distinct structural protein complexes and signaling pathways that reveal what is essential for glomerular function (see Fig. 20.1). In particular, it has been determined that almost all mutations involve genes/proteins important for the slit diaphragm function or essential pathways in podocytes. Interdigitations of podocyte foot processes form the glomerular slit membrane between them, which is critical for the filtering process and retention of protein in the bloodstream (see also Chapter 1). The integrity of the glomerular slit membrane is lost in NS. Thus, identification of monogenic causes of NS revealed dozens of proteins, each of which is an indispensable component of glomerular function, because loss of their function in a monogenic form of NS inescapably leads to proteinuria and FSGS. Knowledge of these mutations helps to understand the physiology of the glomerular filtration barrier and the pathogenic mechanisms which cause NS.
These functional complexes include proteins involved in glomerular slit membrane–associated components, actin-binding proteins, actinregulating small GTPases of the Rho/Rac/Cdc42 family, coenzyme Q10 (CoQ10) biosynthesis, sphingosine-1-phosphate (S1P) metabolism, nuclear transcription factors, nucleoporins, lysosomal proteins, endosomal trafficking regulating proteins, tRNA modification (KEOPS complex), and laminin/integrin receptors (focal adhesions) (see Fig. 20.1).
The power of identification of such single-gene causes of NS lies in the fact that recessive mutations (and to a lesser degree, dominant mutations) almost always convey full penetrance and thereby represent the cause of NS (i.e., the etiology) rather than representing only an increased risk for acquiring disease (see Box 20.1). Thus, mutations in the 63 monogenic genes can be considered causative of NS (see Table 20.1).

Epidemiology

Steroid-resistant nephrotic syndrome (SRNS) is the second leading cause of pediatric chronic kidney disease (CKD), responsible for 15% of all CKD cases before the age of 25 years. A monogenic cause of SRNS can be found in 10% to 30% of cases. Specific SRNS genes or distinct mutations (alleles) in the same SRNS gene may cause characteristic phenotypes, which may pertain to age of onset of disease.4 5 Adultonset NS is of heterogeneous origin and may include causes such as membranous glomerulonephritis, minimal change nephropathy, diabetic nephropathy, and amyloid nephropathy. The majority of these diseases do not seem to have a genetic basis, at least not a monogenic one, and genetic workup for polymorphisms in these diseases (e.g., PLA2R polymorphisms) does not have clinical relevance so far. However, genetic testing should be considered in selected cases of adult-onset focal segmental glomerulosclerosis (FSGS) (see “Diagnosis” section).

A study using next-generation sequencing tested a large international cohort of patients with SRNS manifesting before age 25 years (1783 families).4 The diagnostic panel included 21 genes with a recessive mode of inheritance and six genes with a dominant mode of inheritance. A genetic diagnosis was established in 526 of 1783 families (29.5%) in whom the condition manifested before age 25 years.4

Stringent criteria for calling mutations “disease causing” were applied (Box 20.1). The highest rate of mutation detection of 69% was in the youngest group of patients (0–3 months), a percentage that decreased with older age (Fig. 20.2).

A recent study used whole-exome sequencing (WES) analysis and established a genetic diagnosis in 25% of individuals younger than 25 years who had SRNS.6 This study showed that four genes were major SRNS genes: NPHS1 (4.3% of 300 individuals with SRNS), PLCE1 (3.7%), NPHS2 (2.7%), and SMARCAL1 (2.7%) (Fig. 20.3). The most prevalent SRNS dominant genes are INF2, TRPC6, and ACTN4 (see Fig. 20.3 and Table 20.1).6

CLINICAL PRESENTATION

Mutations in recessive genes tend to cause SRNS in early childhood, whereas there is a tendency for mutations in dominant SRNS genes (e.g., TRPC6, INF2) to cause adult-onset SRNS,7,8 with the exception of WT1.4 In a study, mutations in WT1 have been shown to exhibit a biphasic distribution for onset of NS with a first peak at 4 to 12 months and a second peak for age of onset beyond 18 years of age (see Fig. 20.2).4 This difference in age of presentation between recessive and dominant diseases is a well-reported genetic phenomenon that is not completely understood. Perhaps late onset could be explained by molecular mechanisms in dominant diseases that can result in an age-related penetrance. These mechanisms include haploinsufficiency, gain-of-function, and dominant-negative effects that often do not

Proteins That, if Mutated, Can Cause Monogenic Steroid-Resistant Nephrotic Syndrome
Podocyte
foot process

Endosomal
CoQ10

RECESSIVE
DOMINANT

ADCK4

Nucleus

ANKFY1

Mitochondria
COQ6
PDSS2

COQ2

NUP85

LMX1B

TBC1D8B

NUP133

TRIM8

MTTL1

NUP93

SMARCAL1

SGPL1

NUP205
XPO5

S1P metabolism
tRNA modification

NUP107

WT1

GAPVD1

Lysosome
SCARB2

OSGEP

Rho/Rac/Cdc42

TP53RK
TPRKB
LAGE3

CUBN

AC
ITGB4

EMP2

P VT
ITGA3

PTPRO

TN
4

WDR73

DAAM2
INF2

ARHGAP24

Slit membrane

MYO1E
MYH9

ANLN

AVIL

CRB2
CD2AP
NPHS2

PLCE1

FAT1
NPHS1
NPHS1
TRPC6
DGKE

ARHGDIA
KANK1,2,4
ITSN1
ITSN2

TNS2
DLC1
CDK20
NOS1AP

Rho/Rac/Cdc42

CFH
LAMB2

MAGI2

Glomerular basement membrane
Endothelial Cell

Fig. 20.1 Proteins Whose Genes, if Mutated, Cause Monogenic Steroid-Resistant

Nephrotic Syndrome (SRNS) Define Essential Podocyte Functions. Identification of 63 single-gene (monogenic) causes of SRNS has revealed the glomerular epithelial cell, the podocyte, as central to the pathogenesis of SRNS, because almost all of the related genes are relevantly expressed in podocytes. Identification of genes that, if mutated, cause SRNS revealed distinct proteins and functional pathways as essential for glomerular function, because a mutation in any single one of them is sufficient to cause SRNS. This figure depicts a simplified cross section through a podocyte (tan) and a neighboring podocyte foot process, which is attached to the glomerular basement membrane (green) by laminin-integrin receptors. Fifty-three proteins whose genes, if mutated, cause recessive monogenic forms of SRNS are shown in red, and 10 proteins whose genes, if mutated, cause dominant forms of SRNS are shown in blue (see Tables 20.1 and 20.2). The 63 SRNS-related proteins were found to be part of proteinprotein interaction complexes that participate in defined structural components or signaling pathways of podocyte function (shown within black dashed boxes). These proteins include proteins involved in coenzyme Q10 biosynthesis, S1P metabolism, nuclear transcription factors, nucleoporins, lysosomal proteins, actin-regulating small GTPases of the Rho/Rac/Cdc42 family, glomerular slit membrane–associated components, actin-binding proteins, tRNA modification (KEOPS complex), endosomal trafficking regulators, and laminin/integrin receptors (focal adhesions). Proteins that are encoded by recessive NS genes are marked in red. ADCK4, aarF domain containing kinase 4; ANKFY1, Rabankyrin-5; ARHGDIA, Rho GDP dissociation inhibitor (GDI) α; AVIL, advillin; CD2AP, CD2-associated protein; CDK20, cyclin-dependent kinase 20; COQ2, coenzyme Q2 4-hydroxybenzoate polyprenyltransferase; COQ6, coenzyme Q10 monooxygenase 6; CRB2, crumbs family member 2; CUBN, cubilin (intrinsic factor-cobalamin receptor); DAAM2, disheveled-associated activator of morphogenesis 2; DGKE, diacylglycerol kinase; DLC1, deleted in liver cancer 1; EMP2, epithelial membrane protein 2; FAT1, FAT tumor suppressor homolog 1; GAPVD1, GTPase-activating protein and VPS9 domain-containing protein 1; GON7, EKC/KEOPS complex subunit GON7; ITGA3, integrin, α3; ITGB4, integrin, β4; ITSN1, intersectin 1; ITSN2, intersectin 2; KANK, KN motif and ankyrin repeat domains 1/2/4; LAGE3, L antigen family member 3; LAMB2, laminin, β2; MAGI2, membrane-associated guanylate kinase, WW and PDZ domain containing 2; MTTL1, mitochondrial tRNA leucine 1; MYO1E, Homo sapiens myosin 1e; NOS1AP, Carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase protein; NPHS1, nephrin; NPHS2, podocin; NUP85, nucleoporin 85 kDa; NUP93, nucleoporin 93 kDa; NUP107, nucleoporin 107 kDa; NUP133, nucleoporin 133 kDa; NUP205, nucleoporin 205 kDa; OSGEP, O-sialoglycoprotein endopeptidase; PDSS2, prenyl (decaprenyl) diphosphate synthase, subunit 2; PLCE1, phospholipase C, ε 1; PTPRO, protein tyrosine phosphatase, receptor type O; SCARB2, scavenger receptor class B member 2; SGPL1, sphingosine-1-phosphate lyase 1; SMARCAL1, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1; TBC1D8B, TBC1 domain family member 8B TNS2, tensin 2; TP53RK, TP53-regulating kinase; TPRKB, TP53RK-binding protein; WDR73, WD repeat domain 73; and XPO5, Exportin; YRDC, YrdC domain-containing protein, mitochondrial 5. Proteins that are encoded by dominant NS genes are marked in blue: ACTN4, actinin, α4; ANLN, anillin; ARHGAP24, Rho GTPase-activating protein 24; INF2, inverted formin, FH2 and WH2 domain containing; LMX1B, LIM homeobox transcription factor 1-β; MYH9, myosin, heavy chain 9; TRIM8, E3 ubiquitin-protein ligase TRIM8; TRPC6, transient receptor potential cation channel, subfamily C, member 6; WT1, Wilms tumor 1. (Modified from Lovric S, Ashraf S, Tan W, Hildebrandt F. Genetic testing in steroid-resistant nephrotic syndrome: when and how? Nephrol Dial Transplant. 2016;31[11]:1802–1813.)

Genes That, if Mutated, Cause Monogenic Steroid-Resistant, Steroid-Sensitive, or Dependent Nephrotic Syndrome a

TABLE 20.1
Gene

Mode of Inheritance

Clinical Aspects

Reference

Genetic Causes of Nephrotic Syndrome That First Manifest in Adolescents and Adults
AD
Potential neurologic manifestations (Charcot-Marie-Tooth syndrome, see Table 20.2)
INF2 b

8

WT1b

39

AD

Biphasic age of onset
Risk for WT/gonadoblastoma (mutation dependent, see Table 20.2)

ACTN4b

AD

Screen for mutation in family members if kidney donation is considered

40

TRPC6

AD

Familial FSGS, screen for mutation in family members if kidney donation is considered
NS onset can present in up to fifth decade of life

7

MYH9

AD

Screen for mutation in family members if kidney donation is considered

41

PAX2

AD

Screen for mutation in family members if kidney donation is considered
Variable age of presentation (2–20 years)

42

ANLN

AD

Screen for mutation in family members if kidney donation is considered

43

Genetic Causes of Nephrotic Syndrome That First Manifest in Infancy to Early Childhood
AR
Congenital nephrotic syndrome
NPHS c
Common in Finland
Infants born prematurely with massive proteinuria and often have low-set ears and a small
nose
Mutation-dependent prognosis; ESKD in most cases by age 3 years

1

NPHS2 c

AR

Early childhood or adolescent-adult onset, mutation dependent

PLCE1c

AR

Incomplete penetrance was observed (very rare for AR disease)

3

LAMB2c

AR

Potential eye abnormalities (Pierson syndrome; see Table 20.2)

44

2

SMARCAL1c

AR

Potential skeletal abnormalities (Schimke immuno-osseus dysplasia; see Table 20.2)

45

LMX1B

AD

See Table 20.2

46
33

ARHGDIA

AR

May be responsive to eplerenone treatment

CDK20

AR

May respond to steroid treatment

15

COQ2, COQ6, COQ8/
ADCK4, PDSS2

AR

May respond to CoQ10 supplementation

10, 19, 47

CUBN

AR

Can manifest as proteinuria with no progression to ESKD; may respond to treatment with
vitamin B12

31

DGKE

AR

Can present as SRNS in first decade of life or as an acute episode of aHUS during first year 48
of life

DLC1

AR

May respond to steroid treatment

15

EMP2

AR

May respond to steroid treatment

20

FAT1

AR

Potential syndromic features (allele dependent): colobomatous microphthalmia, ptosis,
syndactyly

49, 50

ITSN1

AR

May respond to steroid treatment

15

ITSN2

AR

May respond to steroid treatment

15

MAGI2

AR

May respond to steroid treatment

51

TNS2

AR

May respond to steroid treatment

15

TRIM8

AD

All mutations described thus far are de novo
Extrarenal manifestation: epilepsy

52

[a]Genes

for which no clear clinical clues to diagnosis were described, or which are too rare as monogenic SRNS to have clinical considerations concluded, are not shown.
[b]Most common dominant SRNS causing genes.
[c]Most common recessive SRNS causing genes.
AD, Autosomal dominant; aHUS, atypical hemolytic uremic syndrome; AR, autosomal recessive; CoQ, coenzyme Q; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; WT, Wilms tumor.

result in a complete loss of function of the encoded proteins, as in recessive diseases.
SRNS manifests histologically as FSGS, a lesion characterized by segmental sclerosis often with diffuse podocyte foot process effacement.9
Diffuse mesangial sclerosis (DMS) is a pathogenic finding that

may occur in patients with early-onset NS. In DMS, light microscopy shows small, sclerosed glomeruli with a reduced number of capillary loops together with podocyte hypertrophy and mesangial matrix expansion. SRNS may rarely be associated with extrarenal manifestations such as neurologic defects (Table 20.2).10

Assignment of Mutations as Being Disease Causing

BOX 20.1

Basic Assumptions
- Defined clinical phenotype
- Known genes with similar phenotype have been excluded
- "Mutation" implies that an allele changes the phenotype
- Full (AR) or incomplete (AD) penetrance (age related)

Include Allele as Disease Causing if:
- Truncating mutation (stop, abrogation of start or stop, obligatory splice, frameshift) in an expressed gene (well-annotated mRNA, conservation, protein expression), or
- Missense mutation if:
- Continuously conserved at least up to Danio rerio (zebrafish), and
- Loss of function in human allele is supported by functional data, and
- Allele segregates with the affected status in the family
- Known genes with similar phenotype have been excluded

Exclude Allele as Disease Causing if:
- Heterozygous allele frequency >1% (for AR) or >0.1% (for AD) or reported homozygous in gnomAD (Genome Aggregation Database) in AR disease, or frequent heterozygously (>20) in AD disease
- AR: nonsegregation (e.g., "compound heterozygous" in cis; affected family member is without the variant; unaffected parent is with homozygous variant)
- AD: nonsegregation (e.g., affected family member is without the variant; but if an affected family member is with the allele, consider incomplete penetrance and variable expressivity)

AD, Autosomal dominant; AR, autosomal recessive.

Disease presentation of NS may vary in a gene-specific or even allelespecific manner (i.e., specific mutations within the same gene may determine a phenotypic range) that can affect age of onset, severity of disease, response to steroids, and associated syndromic features. For instance, mutations in NPHS1 encoding nephrin will most often result in congenital nephrotic syndrome (CNS) characterized by massive proteinuria not responding to steroids and will likely require kidney replacement therapy and bilateral nephrectomy at approximately 1 year of age. Until permissive body weight (>10 kg) is achieved to enable kidney transplantation, these infants are at a high risk of life-threatening complications. However, specific mutations, such as the introduction of a stop codon (non-sense mutation) at position p.1160 of nephrin, tend to cause a milder form of CNS that may respond to steroid treatment.11 In NPHS2 (encoding podocin) mutations, which are the most common causative mutations found in monogenic SRNS, the mutation R138Q causes onset in early childhood,12 whereas the mutation R229Q in compound heterozygosity with specific second mutations causes later-onset SRNS.13 With INF2, a heterozygous mutation will typically result in SRNS and FSGS with adolescent- or adult-onset disease, with or without neurologic manifestations (Charcot-Marie-Tooth syndrome; see Table 20.2).14 Mutations in recessive genes that cause SRNS/FSGS with syndromic features (see Table 20.2) tend to be of early onset, severe, and carry a poor prognosis. On the other hand, mutations in one of six recently discovered genes may result in partial SSNS15 (see Table 20.1).

DIAGNOSIS

Next-generation sequencing of a specified panel of genes, such as an SRNS-disease genes panel, or WES of mutations across the entire

Families with

dominant mutations (%)

Relative Distribution of Nephrotic Syndrome–Causative Genes by Age of Onset

12.5
10.0
7.5
5.0
2.5
0.0

Families with recessive
mutation(s)/age group (%)

25.0

39.9%

22.5
20.0

NPHS1

17.5
15.0
12.5
10.0

NPHS2

7.5

NPHS1
LAMB2
PLCE1
NPHS2
WT1
SMARCAL1
COQ6/COQ2/ADCK4/PDSS2
INF2
TRPC6
Other

5.0
2.5
0.0
0–3 months

4–12 months
1–6 years
7–12 years
13–18 years
19–25 years
Age of onset of proteinuria (month/years)

Fig. 20.2 Relative Distribution of Genes that Cause Nephrotic Syndrome, by Age of Onset. Percentages of families in an international cohort with steroid-resistant nephrotic syndrome resulting from mutations in recessive genes are interconnected by lines between age groups and shown in different colors for each causative gene (lower panel for recessive genes, upper panel for dominant genes). NPHS1 mutations (red), LAMB2 (orange), and PLCE1 (dark blue) have early age of onset and are rarely found in patients older than

6 years. The dominant genes INF2 (light blue) and TRPC6 (brown) manifest in early adulthood, and WT1 (black) shows a biphasic distribution with a first peak at 4 to 12 months and a second peak for age of onset beyond 18 years (upper panel). These findings are compatible with the notion that mutations in recessive disease genes are found more frequently in early-onset disease, whereas mutations in dominant genes more frequently cause adult-onset disease. (Modified from Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015;26[6]:1279–1289.)

Detection of a Causal Mutation in 300 Families by
Whole-Exome Sequencing
NPHS1 (4.3%), n=13
PLCE1 (3.7%), n=11
NPHS2 (2.7%), n=8

Unsolved (44%),
n=131

SMARCAL1 (2.7%),
n=8

Other SRNS genes
(11%), n=34

Phenocopy genes
(3.7%), n=11

Novel candidate gene(s)
identified (28%), n=84

Total families: n=300

Fig. 20.3 Detection of a Causal Mutation in 300 Families by Whole-Exome Sequencing. In 74 of 300 (25%) families with steroid-resistant nephrotic syndrome (SNRS), a causal mutation was detected in one of 20 genes known to cause steroid-resistant nephrotic syndrome (shades of blue). In 3.7% of families, a mutation was found in genes causing a kidney disease that may represent phenocopies of steroid-resistant nephrotic syndrome (orange). In 28% of families, one or more potential novel candidate genes were identified (red). In 44% of families, no causal mutations or candidate genes were detected. (From Warejko JK, Tan W, Daga A, et al. Whole exome sequencing of patients with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2018;13[1]:53–62.)

TABLE 20.2

Syndromic Proteinuric Kidney Disease

Syndrome

Gene(s),
Mode of
Inheritance

AMRF syndrome

CLINICAL FEATURES
Kidney Disease

Extrarenal Manifestations Management

Outcome

SCARB2, AR

Collapsing FSGS (tubular
proteinuria was also

described)
Deposition of C1q and IgM and
of C3 in capillary loops and
mesangium
Adolescent to adulthood age
of onset

Progressive myoclonus epilepsy

Supportive

Most affected individuals
die in third decade
of life

CMTDIE

INF2, AD

SRNS; FSGS; median onset of
proteinuria is 18 years

Sensorineural deafness; skeletal
abnormalities; peripheral
neuropathy with median age of
onset of 13 years

Supportive

ESKD develops at median
age of 21 years

Denys-Drash

WT1, AD

DMS; high incidence of severe
hypertension and rapid
progression to ESKD by 3
years of age

Male pseudohermaphroditism,
progressive glomerulopathy,
development of WT

Bilateral nephrectomy
at time of kidney
replacement
therapy initiation
is recommended
to prevent WT
development/relapse

Dependent on ESKD and
WT management
Most individuals live to
adulthood

Continued

TABLE 20.2

Syndromic Proteinuric Kidney Disease—cont’d

Syndrome	Gene(s), Mode of Inheritance	CLINICAL FEATURES		Management	Outcome
		Kidney Disease	Extrarenal Manifestations		
Frasier	WT1, AD	FSGS; NS may be slowly progressive, usually over 10 years, and is typically steroid resistant	Male pseudohermaphroditism typically present in phenotypic females with amenorrhea or NS, or both; development of genitourinary tumors	Screening for gonadoblastoma; WT not common Evaluate need for an early gonadectomy to prevent tumorigenesis	ESKD development at second to third decade of life Limited information on life expectancy
Galloway-Mowat	WDR73; WDR4; KEOPS complex (LAGE3, OSGEP, TP53RK, TPRKB, YRDC and GON7); PRDM15, All: AR	Kidney disease generally presents as NS within the			

first few months of life, with
rapid progression to ESKD

Microcephaly, abnormal cerebral
gyral patterns, seizures,
psychomotor delay, cranial
dysmorphia
Most affected children die before
age 6 years

Supportive

Most affected individuals
die in early childhood

Nail-Patella
(hereditary
onychoosteodysplasia;
Fong syndrome)

LMX1B, AD

NS, early childhood

Nail dysplasia, absence of or
poorly developed patellas,
dysplasia of the iliac horns and
elbows, cataracts, glaucoma

Treatment of joint
limitations, ocular and
kidney complications

Clinical expression
variable; cases range
from mild with no
functional impact
to severe leading to
disability
Kidney involvement
reported in 30%–60%
of cases; life span is
normal

Pierson

LAMB2, AR

Congenital NS; DMS on
biopsy; rapid progression
to ESKD

Hypoplasia of the ciliary body and
iris resulting in fixed narrowing
of the pupil (microcoria)

Supportive

Most patients progress
toward kidney failure
within the first year
of life
Visual prognosis is
generally poor

Schimke immunoosseus dysplasia

SMARCAL1, AR

SRNS, FSGS, ESKD

Growth retardation, T cell deficiency, bone dysplasia, cerebrovascular disease

Due to underlying immune disorder, immunosuppressive therapy after kidney transplantation is associated with increased risk of rejection and severe opportunistic infections

Most individuals do not survive beyond early adolescence due to stroke, infections, bone marrow failure, and kidney failure

SPLIS

SGPL1, AR

SRNS; FSGS; typically presents at early childhood (age 1–4 years)

Primary adrenal insufficiency, endocrine abnormalities, immunodeficiency, neurologic abnormalities (cranial nerve deficits, peripheral neuropathy, developmental delay), sensorineural hearing loss, ichthyosis

Multidisciplinary, supportive
Recent report[32] suggests potential response to treatment with vitamin B6

Overall prognosis is unclear (variable)
Risk of death due to infection complications

AD, autosomal dominant; AMRF, action myoclonus-renal failure; AR, autosomal recessive; CMTDIE, Charcot-Marie-Tooth Dominant intermediate E; DMS, diffuse mesangial sclerosis; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; IgM, immunoglobulin M; NS, nephrotic syndrome; SPLIS, Sphingosine phosphate lyase insufficiency syndrome; SRNS, steroid-resistant nephrotic syndrome; WT, Wilms tumor.

coding sequence, is increasingly available, albeit often limited to research initiatives (https://www.precisionnephrology.org, http://www.renalgenes.org). WES allows sequencing of all approximately 330,000 exons in the human genome (i.e., the exome).16 It is currently assumed that WES offers a theoretical likelihood of 86% of detecting the disease-causing mutation in a recessive disease.17 Besides its use to detect mutations in an established list of known disease-causing genes, WES was also very successfully applied to detecting novel diseasecausing genes (e.g., ADCK4, EMP2, CRB2, FAT1, NUP93, KEOPS complex, and TNS2).15 18-21

The indications for genetic testing in individuals with SRNS are based on several considerations:

1. Age of onset. Because of the high likelihood (~30%) of finding a causative monogenic mutation in SRNS with onset before age 25 years,4 5 and because of the many important implications for disease management, it is advisable to suggest genetic testing to all individuals with FSGS or with persistent proteinuria that manifests before age 25 years. In adult-onset FSGS, genetic testing should be considered if there is a positive family history22 23 or if there is clinical suspicion of a disease syndrome that may mimic SRNS by a phenocopy gene (as can be the case with mutations in type 4 collagen forming genes).24 25 Moreover, recent studies suggest a diagnostic yield for WES of up to 17.1% in adults with a clinical diagnosis of nephropathy of unknown origin,23 and therefore genetic testing should be considered in these cases as well. Finally, individuals of African ancestry with FSGS should be tested for the presence of the APOL1 risk alleles, at any age of presentation, because mutations in these alleles confer a 10-fold higher risk of end-stage kidney disease (ESKD) due to FSGS and sevenfold higher risk of ESKD due to hypertensive nephropathy.26
2. Consanguinity. The likelihood of finding a causative (recessive) mutation is higher in individuals with SRNS from consanguineous marriages than in outbred individuals.6 27
3. Family history. One of the most important genotype-phenotype correlations in SRNS is the distinction between recessive versus dominant SRNS genes (see Table 20.1). In recessive mutations, family history is most likely negative because parents of individuals with recessive mutations will usually be healthy heterozygous carriers, and no one in the ancestry will have had the disease. If there is any inherited mutation, it will have only been heterozygous in ancestors. However, in dominant disease, one of the parents of an affected individual will most likely be affected, and the disease may have been handed down through multiple generations (except for situations of incomplete penetrance or de novo mutations). Therefore, the detection of dominant mutations has important clinical implications, such as in situations of planned living-related donor kidney transplantation (see Table 20.1). Here, it will be important to exclude the presence of the disease-causing mutation in the related donor, in whom SRNS may not yet have manifested because of incomplete penetrance, which can be a feature of autosomal dominant inheritance. Kidney donation from a heterozygous carrier of a recessive gene is essentially harmless.
4. Syndromic features. The presence of extrarenal manifestations can suggest a mutation in a known gene that results in specific syndrome (see later) and hence increases the likelihood of detecting a monogenic cause of the disease (see Table 20.2).

Natural History and Management

The identification of causative monogenic mutations may have important therapeutic consequences in some cases:

1. Response to steroid treatment. In childhood SRNS, which manifests beyond the first year of life, often one attempt is made at treatment with corticosteroids.28 If a response is lacking, treatment attempts are made with calcineurin inhibitors, and, more recently, mycophenolate mofetil or rituximab. The majority of the patients with NS, in whom a single-gene cause is detected, do not respond to steroid treatment, and therefore the detection of a monogenic cause of SRNS can save unnecessary ineffective and potentially toxic treatment. Recently, however, six genes (EMP2, TNS2, DLC1, CDK20, ITSN1, ITSN2) were identified in which recessive mutations surprisingly cause NS that is partially or fully responsive to steroid therapy or cyclosporine A, for unknown reasons (see Table 20.1).3,15,20
2. Response to CoQ10 supplementation. In patients who carry mutations in a gene of CoQ10 biosynthesis (COQ2, COQ6, ADCK4, or PDSS2),19,29,30 treatment with CoQ10 may be indicated.29
3. Response to treatment with vitamin B. The CUBN gene encodes the cubilin protein, which functions as a receptor for intrinsic factor–vitamin B12 complexes. Mutations in CUBN may benefit the treatment with vitamin B12,31 those with sphingosine-1-phosphate lyase 1, encoding a mitochondrial lyase enzyme, may respond to vitamin B6.32
4. Response to other available drugs. Individuals with ARHGDIA mutations theoretically may be responsive to eplerenone treatment.33
   Finally, TRPC6 mutations may potentially be amenable to treatment with calcineurin inhibitors.7,34 However, no systematic studies exist for these theoretical treatment modalities.
5. Other considerations. Rare syndromic proteinuric kidney diseases require management of extrarenal manifestations (see Table 20.2). For instance, donor splice-site heterozygous mutations in intron 9 of the WT1 gene have been reported to alter the alternative splicing leading to two WT1 isoforms, with (+) or without (−) three amino acids, lysine-threonine-serine (KTS), between zinc fingers three and four. The detection of WT1 mutations often has clinical consequences as, for instance, KTS+ mutations, depending on karyotype, may confer a risk for gonadoblastoma.35

RECURRENCE

Childhood-onset SRNS carries a risk of about 33% for relapse in a kidney transplant, thereby causing recurrence of CKD36 (see Chapter 113). However, kidney transplantation in a child with a known monogenic cause of SRNS carries almost no risk of disease recurrence because the defective gene, which is usually exclusively expressed in the kidney, is now replaced with a normal one. A case of a truncating mutation (resulting in no formation of a functional protein) and the introduction of a novel protein through the donor kidney may rarely elicit an antibody response (such as in Alport posttransplant nephritis) and rejection of the transplanted organ.37 However, posttransplant immunosuppressive regimens probably protect against such a response in most cases (see Chapter 113).

FUTURE DIRECTIONS

Currently only “strong” mutations are considered as disease causing (see Box 20.1). However, it is very likely that a high percentage of adult-onset SRNS is caused by hypomorphic (“weak”) recessive alleles, which have not yet been revealed as deleterious (e.g., the allele R229Q of NPHS2). One of the most important tasks in the future for kidney geneticists is to use cell-based and animal model systems to explore whether “weak” recessive mutations (e.g., one hypomorphic heterozygous variant in a compound-heterozygous mutation) may cause adult-onset SRNS.

The recent identification of monogenic causes of NS that manifests before age 25 years in as many as 12% to 45% of individuals

TABLE 20.3 Implications of the Identification of Causative Mutations in Nephrotic Syndrome

Implication	Significance[a]
Unequivocal molecular genetic diagnosis	Avoidance of unnecessary diagnostic procedures; positive psychological impact on the individual and family members
Prediction of treatment response	Avoidance of steroids/immunosuppressive therapy
Establishment of genotype–phenotype correlations	Can assist in management (anticipated extrarenal manifestations or complications); etiologic stratification of participants for therapeutic studies by specific causative gene and mutation
Study of mutations' detrimental effects using genetic animal models	Study the pathogenesis of steroid-resistant nephrotic syndrome as the basis for targeted therapy development
Discovery of distinct mutations that may be amenable to treatment	May offer a curative therapy
Inform clinical decisions	Guide the identity of a living related donor in dominant diseases

[a] See

worldwide[4] has offered many advantages for future management of NS. With the available sequencing technology and the continuous reduction in sequencing cost, WES on a commercial or research basis should now be offered to every patient with persistent proteinuria occurring before age 25 years, or in patients with FSGS manifesting after age 25 years and positive family history, if the patient consents for clinical genetic testing for the following reasons (Table 20.3): (1) it will provide the patient and families with an unequivocal diagnosis; (2) it will establish genotype–phenotype correlations; (3) it may avoid the need for kidney biopsy; (4) it will further unravel the puzzle of pathogenic pathways of NS and enable etiologic stratification of participants for therapeutic studies by specific causative gene and mutation; (5) it will permit personalized treatment options for NS by discovery of distinct mutations that may be amenable to treatment (e.g., CoQ10-related genes), or on the other hand, support a decision to avoid immunosuppression or corticosteroids; and (6) it will help establish informed clinical decisions (e.g., in kidney transplantation) (see https://www.precisionnephrology.org).38

also https://www.precisionnephrology.org.

SELF-ASSESSMENT QUESTIONS

1. A 23-year-old man is admitted to the hemodialysis unit after inpatient hemodialysis initiation for ESKD secondary to FSGS. At initial evaluation, you obtain a detailed family history in which the patient discloses that his maternal grandfather, mother, and two brothers have received dialysis. You suspect familial FSGS as the cause of renal disease in this family. Based on the pattern of kidney disease occurrence in his family, what mode of inheritance would you suspect in this patient?
A. Autosomal recessive
B. X-linked recessive
C. Autosomal dominant
D. X-linked dominant
E. Both C and D are possible
2. You are called to consult on a patient with newly diagnosed FSGS. Her family history is significant for multiple family members with advanced CKD or ESKD requiring renal replacement therapy. Three family members are known to have had renal transplants without recurrence of disease. You construct a family pedigree that suggests an autosomal dominant inheritance pattern. Of the known genetic mutations to cause autosomal dominant FSGS, which gene may be affected in this patient?
A. NPHS1
B. MYO1E
C. INF2

D. NPHS2 (podocin)
3. Genetic mutations affecting which of the following cell populations have been identified as a cause of familial FSGS?
A. Glomerular epithelial
B. Glomerular endothelial
C. Glomerular mesangial
D. Tubular epithelial
4. What is the approximate likelihood of finding a monogenic cause of steroid-resistant nephrotic syndrome that manifests by age 25 years?
A. 5%
B. 30%
C. 50%
D. 80%
5. You are consulted on a 5-year-old girl with significant nephrotic range proteinuria. On genetic analysis, she is found to have a homozygous missense mutation in the COQ6 gene. Which of the following would be the most appropriate treatment that could help improve her condition?
A. Steroids
B. Coenzyme Q10
C. Eplerenone
D. Calcineurin inhibitors

REFERENCES

1. Kestila M, Lenkkeri U, Mannikko M, et al. Positionally cloned gene for a novel glomerular protein-nephrin-is mutated in congenital nephrotic syndrome. Mol Cell. 1998;1(4):575–582.
2. Boute N, Gribouval O, Roselli S, et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. Nat Genet. 2000;24(4):349–354.
3. Hinkes B, Wiggins RC, Gbadegesin R, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nat Genet. 2006;38(12):1397–1405.
4. Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015;26(6):1279–1289.
5. Hildebrandt F, Heeringa SF. Specific podocin mutations determine age of onset of nephrotic syndrome all the way into adult life. Kidney Int. 2009;75(7):669–671.
6. Warejko JK, Tan W, Daga A, et al. Whole exome sequencing of patients with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2018;13(1):53–62.
7. Winn MP, Conlon PJ, Lynn KL, et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science. 2005;308(5729):1801–1804.
8. Brown EJ, Schlondorff JS, Becker DJ, et al. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. Nat Genet. 2010;42(1):72–76.
9. Benoit G, Machuca E, Heidet L, Antignac C. Hereditary kidney diseases: highlighting the importance of classical Mendelian phenotypes. Ann N Y Acad Sci. 2010;1214:83–98.
10. Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, et al. COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. J Am Soc Nephrol. 2007;18(10):2773–2780.
11. Koziell A, Grech V, Hussain S, et al. Genotype/phenotype correlations of NPHS1 and NPHS2 mutations in nephrotic syndrome advocate a functional inter-relationship in glomerular filtration. Hum Mol Genet. 2002;11(4):379–388.
12. Hinkes B, Vlangos C, Heeringa S, et al. Specific podocin mutations correlate with age of onset in steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2008;19(2):365–371.
13. Tory K, Menyhard DK, Woerner S, et al. Mutation-dependent recessive inheritance of NPHS2-associated steroid-resistant nephrotic syndrome. Nat Genet. 2014;46(3):299–304.
14. Boyer O, Nevo F, Plaisier E, et al. INF2 mutations in Charcot-MarieTooth disease with glomerulopathy. N Engl J Med. 2011;365(25):2377–2388.
15. Ashraf S, Kudo H, Rao J, et al. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. Nat Commun. 2018;9(1):1960.
16. Teer JK, Mullikin JC. Exome sequencing: the sweet spot before whole genomes. Hum Mol Genet. 2010;19(R2):R145–R151.
17. Lifton RP. Individual genomes on the horizon. N Engl J Med. 2010;362(13):1235–1236.
18. Braun DA, Rao J, Mollet G, et al. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly. Nat Genet. 2017;49(10):1529–1538.
19. Ashraf S, Gee HY, Woerner S, et al. ADCK4 mutations promote steroidresistant nephrotic syndrome through CoQ10 biosynthesis disruption. J Clin Invest. 2013;123(12):5179–5189.
20. Gee HY, Ashraf S, Wan X, et al. Mutations in EMP2 cause childhoodonset nephrotic syndrome. Am J Hum Genet. 2014;94(6):884–890.
21. Braun DA, Sadowski CE, Kohl S, et al. Mutations in nuclear pore genes NUP93, NUP205 and XPO5 cause steroid-resistant nephrotic syndrome. Nat Genet. 2016;48(4):457–465.
22. Connaughton DM, Kennedy C, Shril S, et al. Monogenic causes of chronic kidney disease in adults. Kidney Int. 2019;95(4):914–928.

23. Groopman E, Goldstein D, Gharavi A. Diagnostic utility of exome sequencing for kidney disease. Reply. N Engl J Med. 2019;380(21):2080–2081.

24. Braunisch MC, Buttner-Herold M, Gunthner R, et al. Heterozygous COL4A3 variants in histologically diagnosed focal segmental glomerulosclerosis. Front Pediatr. 2018;6:171.
25. Schapiro D, Daga A, Lawson JA, et al. Panel sequencing distinguishes monogenic forms of nephritis from nephrosis in children. Nephrol Dial Transplant. 2019;34(3):474–485.
26. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841–845.
27. Hildebrandt F, Heeringa SF, Ruschendorf F, et al. A systematic approach to mapping recessive disease genes in individuals from outbred populations. PLoS Genet. 2009;5(1):e1000353.
28. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. a report of the International Study of Kidney Disease in Children. Kidney Int. 1978;13(2):159–165.
29. Heeringa SF, Chernin G, Chaki M, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest. 2011;121(5):2013–2024.
30. Atmaca M, Gulhan B, Atayar E, et al. Long-term follow-up results of patients with ADCK4 mutations who have been diagnosed in the asymptomatic period: effects of early initiation of CoQ10 supplementation. Turk J Pediatr. 2019;61(5):657–663.
31. Ovunc B, Otto EA, Vega-Warner V, et al. Exome sequencing reveals cubilin mutation as a single-gene cause of proteinuria. J Am Soc Nephrol. 2011;22(10):1815–1820.
32. Zhao P, Liu ID, Hodgin JB, et al. Responsiveness of sphingosine phosphate lyase insufficiency syndrome to vitamin B 6 cofactor supplementation. J Inherit Metab Dis. 2020;43(5):1131–1142.
33. Gee HY, Saisawat P, Ashraf S, et al. ARHGDIA mutations cause nephrotic syndrome via defective RHO GTPase signaling. J Clin Invest. 2013;123(8):3243–3253.
34. Reiser J, Polu KR, Moller CC, et al. TRPC6 is a glomerular slit diaphragmassociated channel required for normal renal function. Nat Genet. 2005;37(7):739–744.
35. Chernin G, Vega-Warner V, Schoeb DS, et al. Genotype/phenotype correlation in nephrotic syndrome caused by WT1 mutations. Clin J Am Soc Nephrol. 2010;5(9):1655–1662.
36. Hildebrandt F. Genetic kidney diseases. Lancet. 2010;375(9722):1287–1295.
37. Dehan P, Van den Heuvel LP, Smeets HJ, Tryggvason K, Foidart JM. Identification of post-transplant anti-alpha 5 (IV) collagen alloantibodies in X-linked Alport syndrome. Nephrol Dial Transplant. 1996;11(10):1983–1988.
38. Mann N, Braun DA, Amann K, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. J Am Soc Nephrol. 2019;30(2):201–215.
39. Jeanpierre C, Denamur E, Cabanis HMO, et al. Identification of constitutional WT1 mutations, in patients with isloated diffuse mesangial sclerosis, and analysis of genotype/phenotype correlations by use of a computerized mutation database. Am J Hum Genet. 1998;62:824–833.
40. Kaplan JM, Kim SH, North KN, et al. Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. Nat Genet. 2000;24:215–216.
41. Heath KE, Campos-Barros A, Toren A, et al. Nonmuscle myosin heavy chain IIA mutations define a spectrum of autosomal dominant macrothrombocytopenias: may-Hegglin anomaly and Fechtner, Sebastian, Epstein, and Alport-like syndromes. Am J Hum Genet. 2001;69:1033–1045.
42. Barua M, Stellacci E, Stella L, et al. Mutations in PAX2 associate with adult-onset FSGS. J Am Soc Nephrol. 2014;25:1942–1953.
43. Gbadegesin RA, Hall G, Adeyemo A, et al. Mutations in the gene that

encodes the F-actin binding protein anillin cause FSGS. J Am Soc Nephrol. 2014;25:1991–2002.
44. Zenker M, Aigner T, Wendler O, et al. Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. Hum Mol Genet. 2004;13:2625–2632.
45. Boerkoel CF, Takashima H, John J, et al. Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. Nat Genet. 2002;30:215–220.

References

46. Dreyer SD, Zhou G, Baldini A, et al. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. Nat Genet. 1998;19:47–50.
47. Heeringa SF, Chernin G, Moumita C, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest. 2011;121:2013–2024.
48. Ozaltin F, Li B, Rauhauser A, et al. DGKE variants ause a glomerular microangiopathy that mimics membranoproliferative GN. J Am Soc Nephrol. 2013;24:377–384.
49. Gee HY, Sadowski CE, Aggarwal PK, et al. FAT1 mutations cause a glomerulotubular nephropathy. Nat Commun. 2016;7:10822.

50. Lahrouchi N, George A, Ratbi I, et al. Homozygous frameshift mutations in FAT1 cause a syndrome characterized by colobomatousmicrophthalmia, ptosis, nephropathy and syndactyly. Nat Commun. 2019;10:1180.
51. Bierzynska A, Soderquest K, Dean P, et al. MAGI2 mutations cause congenital nephrotic syndrome. J Am Soc Nephrol. 2017;28:1614–1621.
52. Weng PL, Majmundar AJ, Khan K, et al. De novo TRIM8 variants impair its protein localization to nuclear bodies and cause developmental delay, epilepsy, and focal segment glomerulosclerosis. Am J Hum Genet. 2021;108:357–367.

21

Membranous Nephropathy

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DEFINITION

Membranous nephropathy (MN) is an immune complex disease in which deposits of immunoglobulin (Ig) G and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall. Podocyte injury resulting from the immune deposits increases glomerular permeability, which results in proteinuria and potentially in nephrotic syndrome.1,2 Primary (formerly called idiopathic) MN is an organ-specific autoimmune disease in which autoantibodies target an intrinsic podocyte antigen. It accounts for about 75% to 80% of patients with MN and typically occurs in the absence of any identifiable initiating event. It is the most common cause of primary nephrotic syndrome in older (>60 years) White adults, but the age range is broad and patients may present for the first time as teenagers.3 Various conditions have been identified in association with MN, some of which are likely to be causal, and are known as secondary MN (Table 21.1). The term “membranous” refers to thickening of the glomerular capillary wall on light microscopy of a kidney biopsy. Currently MN is more often defined by immunofluorescence and electron microscopy showing the pathognomonic diffuse, finely granular or electron-dense immune deposits in the subepithelial space. Consequently, MN is a pathologic diagnosis made in patients with proteinuria whose glomeruli exhibit these immune deposits without associated hypercellularity or inflammatory changes.

ETIOLOGY AND PATHOGENESIS

Experimental Membranous Nephropathy

Much of what we know about the pathogenesis of MN derives from observations in animal models.4 Studies of the Heymann nephritis model of MN in rats established that the subepithelial immune deposits form in situ when circulating antibodies bind to an intrinsic (“fixed”) antigen in the glomerular capillary wall. The antigen in rats was identified as megalin, a large transmembrane receptor of the lowdensity lipoprotein receptor family expressed on the basal surface of rat podocytes. Binding of circulating antimegalin antibodies induces capping and shedding of the antigen-antibody complexes, where they bind to the underlying glomerular basement membrane (GBM), resist degradation, and persist for weeks or months as immune deposits characteristic of MN (Fig. 21.1A). In this model, proteinuria is caused by antibodies in the deposits that overcome local complement regulatory mechanisms and activate complement in situ. Sublethal podocyte injury induced by the complement membrane attack complex C5b9 triggers a cascade of changes, including oxidative injury, calcium influx, activation of cytosolic phospholipase A2, production of arachidonic acid metabolites and cytokines, endoplasmic reticulum stress, DNA damage, and alterations in the ubiquitin-proteasome system4

(Fig. 21.2). Podocyte foot process effacement results from collapse of the actin cytoskeleton and loss of cell-GBM adhesion complexes, and the loss and displacement of slit diaphragms is associated with the onset of severe, nonselective proteinuria. Podocyte injury also leads to the production of new extracellular matrix proteins that are laid down around the immune deposits, giving rise to the characteristic “spikes” and GBM thickening.

Another mechanism of subepithelial immune deposit formation involves planted antigens2 (Fig. 21.1B). This is best exemplified by animal models immunized with cationized bovine serum albumin (cBSA). The cBSA binds to negatively charged residues in the GBM, where it serves as a target for circulating anti-BSA antibodies. As in the Heymann nephritis model, podocyte injury and proteinuria result from local complement activation.

Human Membranous Nephropathy

The first demonstration that circulating antibodies reactive with an intrinsic podocyte antigen might be involved in human MN (see Fig. 21.1) was provided by an unusual case of antenatal MN induced by the transplacental passage of alloantibodies to podocyte neutral endopeptidase (NEP).5 The mother of the affected child was deficient in NEP and had been immunized during a previous pregnancy and, like subsequent cases, produced complement-fixing anti-NEP alloantibodies. Although these anti-NEP alloantibodies are distinct from the autoantibodies responsible for adult primary MN, other alloantibodies probably explain the development of de novo MN after kidney transplantation and MN in the setting of chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (see Table 21.1).

Since this initial demonstration of a podocyte-expressed antigen in human MN, several additional target antigens have been identified. The predominant autoimmune system responsible for primary MN is that associated with autoantibodies directed at the M-type phospholipase A2 receptor (PLA2R) on podocytes.4,6 Circulating anti-PLA2R antibodies are detectable in the serum of 75% to 80% of patients with primary MN from all ethnic groups and are rarely found in secondary MN.2,7 The antibodies are predominantly IgG4, and the antigen (PLA2R) and antibodies (anti-PLA2R) colocalize in the immune deposits in primary (but not in secondary) MN.8,9 These IgG4 anti-PLA2R autoantibodies are able to initiate complement activation through the lectin pathway,10 although other subclasses of anti-PLA2R and other complement pathways are likely also involved. PLA2R is a transmembrane protein of the mannose receptor family11 (Fig. 21.3) that undergoes constitutive endocytosis between the plasma membrane and internal compartments; its role in podocytes is unknown.

In the 20% or more cases of primary MN not associated with antibodies to PLA2R, a number of distinct target antigens have been identified that now define subsets of MN, some of which have distinct

TABLE 21.1

Nephropathy

Classification of Conditions and Agents Associated With Membranous

Primary
PLA2R-associated (70%–80%)
Other antigens: NELL1 (5%–10%), THSD7A (1%–5%), Sema3B, PCDH7, HTRA1
Secondary

Common

Uncommon

Autoimmune diseases

Class V lupus nephritis
Can be associated with staining for EXT1/EXT2,
NCAM1, TGFBR3 in deposits

Rheumatoid arthritis
Autoimmune thyroid disease
IgG4-related systemic disease
Crescentic glomerulonephritis (anti-GBM or ANCA-associated)
can co-occur with MN

Infections

Hepatitis B

HCV
HIV
Syphilis
Schistosomiasis

Malignancy

Solid tumors (prostate, breast, lung, colon, stomach,
kidney)

Non-Hodgkin lymphoma
CLL
Melanoma

Drugs or toxins

NSAIDs and COX-2 inhibitors

Mercury-containing compounds
Gold salts
d-Penicillamine, bucillamine

Miscellaneous

Sarcoidosis
Anti-cationic bovine serum albumin

Alloimmune
Graft-versus-host disease following hematopoietic stem cell transplantation

De novo membranous nephropathy in kidney allograft
Fetomaternal alloimmunization to neutral endopeptidase
ANCA, Antineutrophil cytoplasmic antibody; CLL, chronic lymphocytic leukemia; COX-2, cyclooxygenase-2; EXT1/EXT2, exostosin 1/exostosin 2; GBM, glomerular basement membrane; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTRA1, serine protease HTRA1; Ig, immunoglobulin; MN, membranous nephropathy; NCAM1, neural cell adhesion molecule 1; NELL1, neural EGFL like 1; NSAID, nonsteroidal antiinflammatory drug; PCDH7, protocadherin 7; PLA2R, phospholipase A2 receptor; Sema3B, semaphorin 3B; TGFBR3, transforming growth factor beta receptor 3; THSD7A, thrombospondin type-1 domain-containing 7A.

phenotypes or associations. Antibodies to thrombospondin type 1 domain-containing 7A (THSD7A)12 account for about 5% of cases of primary MN in Western countries but appear to be more prevalent in Japanese patients with primary MN.13 THSD7A is localized on the basal surface of podocytes and, like PLA2R, it redistributes to form the subepithelial immune deposits. Neural EGFL-like 1 (NELL1) is the target of IgG1-predominant autoantibodies, and up to one-third of these MN cases may be associated with malignancy.14 15 Antibodies to semaphorin 3B can be found in some early childhood cases of MN but can rarely occur in adults as well.16 In all of these subsets of MN, the target antigen becomes localized within the immune deposits, allowing pathologists to query the tissue by immunostaining.

Reactivity to certain intracellular antigens, including aldose reductase, superoxide dismutase 2, and alpha-enolase, has been detected in primary MN and may contribute to the progression of podocyte injury.

The best evidence of a planted antigen mechanism is that described in children with MN who have been exposed to cBSA, presumably in bottled milk. In such cases, the cBSA localizes in the GBM, where it forms complexes with circulating anti-BSA.17 Planted antigens may also be responsible for immune deposition in class V (membranous) lupus nephritis and hepatitis B virus (HBV)-associated MN.

In all forms of MN, injury to the podocyte and glomerular filtration barrier continues as long as there is formation of subepithelial antibody-antigen complexes that can activate complement. In primary autoimmune forms, the persistence of circulating autoantibodies is the main factor causing continued disease activity. Only after

these autoantibodies decline and disappear (owing to a spontaneous or treatment-induced remission) can a clinical remission be attained. When immunologic remission occurs before extensive podocyte loss and GBM remodeling, complete recovery is possible, but proteinuria may persist for months. Once there is extensive podocyte loss, proteinuria persists despite immunologic remission, and glomerular sclerosis, tubular atrophy, and interstitial fibrosis may ensue.

EPIDEMIOLOGY AND GENETICS

MN may occur at any age and in all ethnic groups, but primary MN is twice as common in men than in women and is rare in children. Primary MN has its peak incidence during the fourth and fifth decades of life (Box 21.1). MN in childhood is more often secondary (e.g., caused by HBV). Primary MN is the most common cause of nephrotic syndrome in nondiabetic White adults. Estimated annual incidence is 8 to 10 cases per 1 million population in Western countries. Reported variation in incidence may reflect specific country/physician indication for kidney biopsy but could also represent real differences related to socioeconomic status, ethnicity, or environment in particular air pollution. Although association with certain human leukocyte antigen (HLA) class II immune response genes indicated a genetic predisposition, primary MN is typically not a familial disease. Studies from Korea and Taiwan suggested the presence of PLA2R1 risk variants that were nonsynonymous single-nucleotide polymorphisms (SNPs)18 19 in the first and seventh C-type lectin-like domains (CTLDs) of PLA2R (Fig. 21.3). A subsequent

Intrinsic Podocyte Antigens

urinary space

podocyte

GBM
Endo

Neutral endopeptidase (NEP) – alloimmune antenatal MN
Phospholipase A2 receptor (PLA2R) or thrombospondin
type 1 domain–containing 7A (THSD7A) – Primary MN
Megalin – Heymann nephritis in rats
Anti-NEP, anti-PLA2R, anti-THSD7A or anti-megalin

A

Extrinsic Planted Antigens

urinary space

podocyte

GBM

Endo

B

Cationized BSA – rabbit and mouse models, childhood MN
Anti-BSA

Fig. 21.1 Mechanisms of In Situ Immune Complex Formation in Experimental and Human Membranous Nephropathy (MN). (A) Circulating antibodies may cross the glomerular capillary wall and bind to podocyte antigens exposed on the foot process, as in Heymann nephritis in rats (megalin), alloimmune MN (neutral endopeptidase), and primary MN (PLA 2R or THSD7A). (B) Certain extrinsic antigens such as cationized bovine serum albumin (BSA) may bind to sites in the GBM and serve as planted antigens and form deposits with circulating antibody. Endo, Glomerular endothelial cell; GBM, glomerular basement membrane.

European genome-wide association study revealed strong associations with a noncoding SNP in PLA2R1 and another in HLA-DQA1, a member of HLA class II that includes isoforms that predispose carriers to autoimmunity.20 The odds ratio of MN was almost 80 in individuals who were homozygous for both HLA-DQA1 and PLA2R1 variants. No

unique coding variants have been found in PLA2R1, and the risk allele in PLA2R1 is proposed to lie in a regulatory region that may increase renal expression of the protein.21

Higher-resolution analysis of risk variants with MN in the Chinese population suggest that specific HLA molecules may be altered

Postulated Mechanisms of Injury in Experimental Membranous Nephropathy

Podocyte
foot process

Actin

Protein leak

Oxidants,
proteases

New matrix
production

GBM
Endo
Nephrin and slit diaphragm complex

Podocyte antigen in clathrin-coated pit

Integrin focal adhesion complex

Complement membrane attack complex
(C5b-9)

Antigen-antibody complexes shed into
subepithelial deposits

Fig. 21.2 Postulated Mechanisms of Injury in Experimental Membranous Nephropathy. Antibodies against a podocyte antigen in clathrin-coated pits on the foot processes (left podocyte) form complexes that are shed to form deposits in the subepithelial space (right podocytes) and induce complement activation leading to formation of C5b-9. Insertion of C5b-9 is insufficient to cause lysis but stimulates the podocyte to release a host of inflammatory mediators. Disruption of the actin cytoskeleton causes altered cell-matrix adhesion and loss or displacement of slit diaphragms, leading to foot process effacement and loss of the filtration barrier to protein. New matrix production by the damaged podocytes expands the glomerular basement membrane (GBM) between and around the deposits. Endo, Glomerular endothelial cells.

Clinical Features of Membranous Nephropathy

BOX 21.1

- Rare in children: <5% of total cases of nephrotic syndrome
- Common in adults: 15%–50% of total cases of nephrotic syndrome, depending on age; increasing frequency after age 40 years
- Males > females in primary forms; SLE-associated forms may be female predominant
- Can occur in all racial and ethnic groups
- Nephrotic syndrome in 60%–70% of cases
- Normal or mildly elevated blood pressure at presentation
- Urinary sediment reflective of lipiduriaa; trace hematuria possible, but no

RBC casts

- Nonselective proteinuria
- Tendency to thromboembolic disease[b]
- Associations to suggest possible secondary MN: infection, drugs, neoplasia, SLE

[a] Fatty

casts, oval fat bodies, cholesterol crystals.
venous thrombosis, renal vein thrombosis, and pulmonary embolism.
MN, Membranous nephropathy; RBC, red blood cell; SLE, systemic lupus erythematosus.

[b] Deep

specifically within the peptide binding groove,22 which may confer the ability to present regions of the PLA2R protein more effectively to the immune system. PLA2R1 gene variants may also contribute to the severity or likelihood of MN progression. Alternatively, the interaction of PLA2R1 with the autoimmune predisposition conferred by HLA

class II may set the stage for an external trigger to initiate MN.1 2 An example of such a trigger might be exposure to environmental pollutants.23 A second genome-wide association confirmed the risk variants within PLA2R1 and the HLA region and identified additional risk loci in IRF4 and NFKB1,21 although the implications of these findings are not yet known.

CLINICAL AND SEROLOGIC MANIFESTATIONS

A majority of patients (70%–80%) with MN present with the nephrotic syndrome. The remaining patients present with asymptomatic subnephrotic, nonselective proteinuria (<3.5 g/24 h) that may be present for months or even years before the diagnosis is made.24 Microscopic hematuria is common (30%–40%), but red blood cell (RBC) casts are rare and suggest a different or coexistent proliferative glomerular pathologic process. In primary MN, serologic tests for anti-PLA2R are positive in 75% to 80% of cases,1 2 whereas serum complement levels are normal despite evidence of intraglomerular complement activation, and serologic markers (e.g., antinuclear antibodies, antineutrophil cytoplasmic antibodies [ANCAs], rheumatoid factor) are normal or absent. At diagnosis, 10% to 20% of MN patients have hypertension and kidney function is usually normal, with only a small fraction (<10%) presenting with kidney impairment (Table 21.2). Hypertension and reduced GFR are more common at presentation in older patients; this may reflect tubulointerstitial and vascular changes on biopsy independent of the severity of the MN.25 Complications of the nephrotic syndrome including dyslipidemia, infections, thromboembolic events, and cardiovascular events may be present early in the course of the disease (see later).

Diagnosis and Management of
Patients With Membranous Nephropathy

TABLE 21.2

Phospholipase A2 Receptor

C
F

*1

Cysteine-rich domain

F
C

Fibronectin type II domain

2

*

Patient Groups

Test

All patients

Vital signs, especially blood pressure and weight
Kidney function (serum creatinine and eGFR)
Urine analysis
Urine protein excretion (24-hour urine or urine protein/creatinine ratio)
Serum albumin
Serum cholesterol, including LDL cholesterol
Anti-PLA2R
Kidney biopsya

Associated disease

Hepatitis B (HBs antigen)
Hepatitis C (HCV antibody)
ANA, anti–double-stranded DNA (hallmark of systemic lupus erythematosus)
Complement C3, C4 (usually normal in primary MN)

3

6
#

C-type lectin-like domains 1–8

4

5

*

7
8

249

*

Extracellular

Intracellular

Fig. 21.3 Structural Diagram of Phospholipase A2 Receptor (PLA2R), the Major Podocyte Antigen Targeted in Membranous Nephropathy. PLA2R is composed of 10 extracellular domains, starting with the N-terminal cysteine-rich domain (CysR; red hexagon) and followed by a single fibronectin type II domain (yellow diamond) and eight C-type lectin-like domains (CTLD; green circles). These domains form a compact structure with pH-dependent conformational relationships to each other that likely allow the receptor to release its cargo (such as secreted phospholipase A2 enzymes) in the more acidic intracellular organelles. A short C-terminal cytoplasmic domain (blue) contains a motif that allows for constitutive endocytosis of the receptor. Autoantibodies to PLA 2R target at least four different regions in the extracellular domain (CysR, CTLD1, CTLD7, and CTLD8; white asterisks). Within CysR, there is an immunodominant epitope of 31 amino acids that is recognized by all individuals with anti-PLA2R antibodies.33 (Data from Dong Y, Cao L, Tang H, Shi X, He Y. Structure of human M-type phospholipase A2 receptor revealed by cryo-electron microscopy. J Mol Biol. 2017;429[24]:3825–3835; and Yu B, Hu Z, Kong D, Cheng C, He Y. Crystal structure of the CTLD7 domain of human M-type phospholipase A2 receptor. J Struct Biol. 2019;207[3]:295–300.)

PATHOLOGY

The earliest pathologic feature of MN is the formation of subepithelial immune complexes of IgG and complement along the outer surface of the capillary wall in which glomeruli may appear histologically normal if only light microscopy is performed. Subsequent changes involve the podocyte, deposition of new extracellular matrix material between and around the immune deposits, thickening of the GBM (membranous change), and in some cases, focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

Light Microscopy

In the earliest stages of MN, the glomeruli and interstitium appear normal on light microscopy, and the diagnosis is made by immunohistology and electron microscopy (Fig. 21.4A). The next stage of MN involves a homogeneous thickening of the capillary wall, seen with light microscopy in sections stained with hematoxylin and eosin or with periodic acid–Schiff (PAS) reagent (Fig. 21.4B). On silver methenamine staining, early projections of the GBM between deposits may be detected in a characteristic spike-like configuration (see Fig. 21.4C). Later, lucencies may develop in the GBM as immune deposits are resorbed, resulting in craters within the thickened GBM.
Glomerular leukocyte infiltration and hypercellularity are absent, probably because chemotactic products of complement activation follow filtration forces into the urinary space, and the intervening GBM prevents immune adherence mechanisms from being operative.
The podocyte response to this form of injury includes effacement of foot processes visible only by electron microscopy. There typically are no visible endothelial cell abnormalities. The presence of significant

Select Patients
With suspected
thromboembolic events,

flank pain, hematuria,
acute kidney injury

Renal venous Doppler ultrasound
Contrast CT, MRI

With sudden decrease
in kidney function,
development of active
urine sediment

Anti-GBM antibody
ANCA
Assess for interstitial nephritis

Suggestive symptoms or
age >50 years

Diagnostic testing for cancer (see text)

aKidney

biopsy may not be necessary in certain situations if anti-PLA2R seropositivity is detected in an appropriate clinical setting.
ANA, Antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; Anti-PLA2R, anti–phospholipase A2 receptor antibody; CT, computed tomography; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; HCV, hepatitis C virus; LDL-HDL, low-density/high-density lipoprotein; MN, membranous nephropathy; MRI, magnetic resonance imaging.

mesangial hypercellularity suggests immune deposit formation in the mesangium and is more consistent with a secondary MN, such as class V lupus nephritis (see Chapter 27). In some patients with heavy proteinuria and progressive disease, glomeruli exhibit reduced podocyte numbers and areas of focal sclerosis that resemble secondary focal segmental glomerulosclerosis (FSGS; see Chapter 19). These patients often have a more rapidly progressive course and a poor response to therapy. These sclerotic lesions may be a consequence of glomerular hypertrophy accompanied by an inability of terminally differentiated podocytes to proliferate leading to areas of denuded GBM, attachment to Bowman’s capsule, and subsequent capillary collapse. As in all glomerular diseases, tubulointerstitial injury is common, and its severity correlates with both long-term kidney function and the level of proteinuria.

Immunohistology

Granular glomerular capillary wall staining for IgG in MN is characteristic (Fig. 21.5A). Positive staining for IgG marks the finely granular subepithelial deposits, which are present on the outer surface of all capillary walls. The predominant IgG subclass in many forms of primary MN is IgG4,6 12 although IgG1 may predominate in other types of MN.15 16

A

B

C

Fig. 21.4 Light Microscopy in Membranous Nephropathy (MN). (A) Early MN. Glomerulus from a patient with severe nephrotic syndrome exhibiting normal architecture and peripheral capillary basement membranes of normal thickness. (B) Morphologically advanced MN. Uniform increase in thickness of glomerular capillary walls throughout the glomerulus with no increase in glomerular cellularity. (C) More morphologically advanced MN, same patient as in (B). Discrete spikes of matrix emanating from outer surface of the basement membrane (arrow), indicative of advanced MN. (A and C, Silver methenamine stain, ×400. B, PAS, ×400.) (Courtesy C.E. Alpers.)

Positive staining for IgA, or IgM or significant staining in the glomerular mesangium suggests lupus or other causes of secondary MN.[26] Kappa and lambda light chain staining are typically equal, but rare cases of MN due to monoclonal IgG, including anti-PLA2R, have been reported.[26] Complement C3 is present in most cases of active disease and usually reflects staining for C3c, a breakdown product of C3b that itself is rapidly cleared. Consequently, positive C3 staining probably reflects active, ongoing immune deposit formation. When sought, staining for C5b-9 is generally present as well, consistent with the proposed pathogenetic role of C5b-9 in this disease.[4,27,28] Strong C1q staining is uncommon in primary MN (<20% of cases) but common in lupus-associated MN.[29] Positive staining for C4d in the absence of C1q is characteristic of primary MN.[30]

The identification of target antigens (or specific biomarkers associated with types of MN) now allows immunohistologic subtyping of MN biopsies. These antigens accumulate within immune deposits where they can demonstrate the same fine granular capillary wall pattern as IgG and C3 (because they all reside within the immune deposits). Many pathologists stain the biopsy for PLA2R and, if negative, may send the slides to be stained for other autoantigens at specialized centers. PLA2R staining in the immune deposits in a pattern that colocalizes with IgG is another feature that helps distinguish PLA2Rassociated MN from secondary MN (Fig. 21.5B) (Table 21.3).[6,8,9]

Electron Microscopy

The finding of subepithelial electron-dense deposits by electron microscopy (EM) parallels IgG staining. In primary MN, immune deposit formation occurs in a subepithelial distribution; subendothelial deposits are not seen and mesangial deposits are rare (Table 21.3). These deposits in early stages of the disease process are homogeneous and may even be confluent in some areas, with overlying podocyte foot process effacement and little change in the underlying GBM (stage I). As the disease persists, basement membrane material is laid down between the deposits and corresponds to the spikes seen on light microscopy and are easily visible by EM (stage II; Fig. 21.6A). Later, the spikes extend and the deposits may become surrounded by new basement membrane–like material (stage III; Fig. 21.6B). In stage IV disease, the basement membrane is overtly thickened, the deposits incorporated in it become more lucent, and the spikes are less apparent

A

B

Fig. 21.5 Immunofluorescence in Membranous Nephropathy. (A) Glomerulus with diffuse, finely granular deposits of Immunoglobulin (Ig) G along outer surface of all capillary walls. In primary membranous nephropathy, the antibodies eluted from the glomeruli are reactive with PLA 2R. (B) Glomerulus stained for PLA2R with diffuse, finely granular deposits of the antigen along outer surface of all capillary walls in a similar distribution as IgG. (Original magnification ×400.) (A, Courtesy C.E. Alpers.)

Histopathologic Features That
Help Distinguish Primary From Secondary
Membranous Nephropathy

protein reabsorption droplets within podocytes and proximal tubular cells. The presence of tubuloreticular inclusions in the endothelial cells is strongly suggestive of lupus-associated MN, although these may rarely be found in primary MN as well.31

Primary

Diagnosis and Differential Diagnosis

TABLE 21.3

Secondary

Immunofluorescence Microscopy
IgA and IgM absent

IgA and/or IgM may be present

IgG4 is predominant or codominant

IgG1, IgG2, or IgG3 predominant

Mesangial Ig staining absent

Mesangial Ig staining may be present

C1q negative or weak

C1q positive

PLA2R positive and colocalizes
with IgG

PLA2R negative
EXT1/EXT2, NCAM1, or TGFBR3
can colocalize with IgG in MN
associated with lupus

Electron Microscopy
Subepithelial deposits only ± rare
mesangial or paramesangial
deposits

Subepithelial deposits ± mesangial

and subendothelial deposits
Tubuloreticular inclusions in
endothelial cells

EXT1/EXT2, Exostosin 1/exostosin 2; Ig, immunoglobulin; MN, membranous nephropathy; NCAM1, neural cell adhesion molecule 1; PLA2R, phospholipase A2 receptor; TGFBR3, transforming growth factor beta receptor 3.

(stage IV; Fig. 21.6C). Although clearly reflecting the duration of disease, these GBM changes do not correlate well with clinical manifestations at time of biopsy or ultimate outcome. The overlying podocyte foot processes are effaced with condensation of the actin cytoskeleton; the filtration slits between the foot processes may be occluded; and in those still open, the slit diaphragms may be displaced or disrupted. Microvillous changes of the podocyte membrane are common, as are

When the initial presentation includes the nephrotic syndrome, the differential diagnosis includes minimal change disease (MCD), FSGS, the membranoproliferative glomerulonephritis (GN) spectrum of diseases (including C3 glomerulopathies and immune complex GN; see Chapters 22 and 23), amyloidosis, light-chain deposition disease, lupus nephritis, and diabetic nephropathy. In the 20% to 25% of patients whose initial presentation is asymptomatic nonnephrotic proteinuria, the differential is even more extensive. Although clinical clues in proteinuric patients may increase the likelihood of one specific histologic pattern over another, confirmation that MN is the underlying cause of nephrotic syndrome generally requires a kidney biopsy.

In the presence of proteinuria and a positive anti-PLA2R antibody test measured by both enzyme-linked immunosorbent assay and immunofluorescence assay, estimated GFR (eGFR) greater than 60 mL/min/$1.73 m^2$, and negative screening for autoimmune and infectious causes as well as malignancy, alternate diagnoses are rarely encountered and a biopsy is not necessary for diagnosis.[32] Also, when a biopsy cannot be performed, such as when uninterrupted anticoagulation is required, the diagnosis can be confidently made with a positive serologic test for anti-PLA2R or anti-THSD7A. On the other hand, negative tests for anti-PLA2R and anti-THSD7A do not exclude primary MN, as some patients may have positive glomerular staining for PLA2R or THSD7A despite negative serology early in the course of disease or during remission.[1] In addition, some patients have all the features of primary MN but may have MN associated with one of the other minor antigens noted above.[1,33]

Secondary MN represents 20% to 30% of all cases (see Table 21.1); the most common causes are systemic lupus, hepatitis B, malignant neoplasms, and drugs. In addition to a careful history and physical

GEC
GEC

CL

*

*

*

*
BM
BM

CL

A

CL

B

GEC

US

CL
BM
C

Fig. 21.6 Electron Microscopy in Membranous Nephropathy (MN). (A) Early (stage II) MN. Glomerular capillary wall with discrete, electron-dense deposits on the subepithelial surface of the basement membrane (BM) corresponding to granular deposits of IgG detected by immunofluorescence microscopy (corresponding to light micrograph in B). There are diffuse, granular immune complex deposits (white asterisks) along outer surface of the capillary wall, with effacement of overlying podocyte foot processes. Small extensions of BM between deposits (arrows) are also evident and represent the projections that are seen as spikes by light microscopy with silver methenamine staining. (B) More advanced (stage III) MN. Two glomerular capillary loops show involvement of the BM by the immune complex deposition (arrows). There is prominent membrane synthesis surrounding and incorporating these deposits into the BM (corresponding to spikes seen on silver-stained histologic preparations). Overlying cells continue to demonstrate widespread effacement of foot processes. (C) Morphologically advanced (stage IV) MN. Capillary BM is diffusely thickened; scattered electron-dense immune deposits (arrows) are present throughout its thickness, in addition to scattered subepithelial deposits. Overlying GECs continue to demonstrate effacement of foot processes. CL, Capillary lumen; GEC, glomerular epithelial cell; US, urinary space. (Original magnification ×18,000.) (Courtesy C.E. Alpers.)

examination, appropriate laboratory evaluation should include a complement profile, antinuclear antibodies, hepatitis and human immunodeficiency virus (HIV) serology, chest radiography, stool testing for occult blood, mammography in women, and prostate-specific antigen testing with digital rectal examination in men. In women aged 20 to 50 years, a high index of suspicion is warranted for underlying lupus. This diagnosis can be particularly difficult to make because most of these patients have no systemic symptoms, and serologic markers of systemic lupus erythematosus are often absent. Membranous lupus accounts for 8% to 27% of cases of lupus nephritis (see Chapter 27).

In adults, regardless of age, malignancy is an important secondary cause of MN (see Table 21.1) and in some patients, the tumor may not be evident at presentation. Although the diagnosis of anti-PLA2Rassociated MN renders an associated underlying malignancy unlikely,[34] given the therapeutic implications regarding immunosuppression affecting cancer growth and therapy, each case should still be carefully assessed and evaluations beyond routine age-appropriate testing considered if patients have risk factors for cancer. All anti-PLA2R-negative cases merit a more thorough search for a malignant tumor.[14,35]

HBV-associated MN is also a common secondary cause in countries where HBV is endemic and can occur with or without overt liver disease. It can affect both adults and children who are chronic carriers of HBV (positive HBsAg, HBcAg, and usually HBeAg). The presence of anti-PLA2R-antibodies is well documented in HBV-associated MN.[9,36]

Treatment of Membranous Nephropathy According to Risk of Disease Progression

All patients
Supportive therapy (as indicated)
- BP < 125/75 mm Hg
- ACEI/ARB, diuretic, statin
- Dietary sodium restriction

Low risk
Preserved GFR
Uprot < 3.5 g/d and
Salb > 3.0 g/dL
Asymptomatic

Moderate risk

High risk

Preserved GFR
Uprot 4–8 g/d despite 6 mo
optimal supportive care
± PLA 2R-ab > 50 RU/mL

Decreased GFR and/or
Uprot > 8 g/d, sustained despite
optimal supportive care × 3–6 mo
Salb < 2.5 g/d
± PLA 2R-ab > 150 RU/mL,
especially if levels are increasing

Monitor

Rituximab
Rituximab or
or CNI
cyclophosphamide/steroids

Fig. 21.7 Algorithm for Treatment of Membranous Nephropathy According to Risk of Disease Progression. All patients should receive supportive therapy. Low-risk patients can continue to be monitored on supportive therapy but should be periodically reassessed if they become symptomatic or their clinical parameters worsen. Close monitoring may also be appropriate for moderate-risk patients (dashed arrow), especially if they exhibit declining titers of anti-PLA2R. Rituximab or calcineurin inhibitors (CNIs) are appropriate for moderate-risk patients, whereas higher-risk patients may require cytoxic agents such as cyclophosphamide and corticosteroids, or extended durations of rituximab. Very high-risk patients (not shown), such as those with life-threatening complications of nephrotic syndrome or rapidly deteriorating kidney function, may warrant cytotoxic agents as first-line therapy. There are no threshold anti-PLA2R levels to dictate initiation of immunosuppressive treatment but, if present, they should be followed to see if they are increasing or decreasing before starting or modifying therapy. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; GFR, glomerular filtration rate; PLA2R-ab, anti-PLA2R antibodies; Salb, serum albumin (g/dL); Uprot, urine protein in grams/day.

In children, HBV-associated MN most often presents as the nephrotic syndrome and usually follows a benign course.37 In adults, progressive loss of GFR is a more common outcome, and a controlled trial to assess the utility of combined therapy with antiviral therapy and tacrolimus has been proposed (https://www.clinicaltrials.gov, NCT03062813).

MN secondary to drugs usually resolves after discontinuation of the offending agent. The time to resolution, however, varies significantly from as early as 1 week for the drugs more commonly implicated (e.g., for nonsteroidal antiinflammatory drugs and proton pump inhibitors), compared with several years for the more classic but rarely used drugs such as gold and d-penicillamine. Many other kidney disorders have been seen in association with or superimposed on MN, including IgA nephropathy, FSGS, anti-GBM disease, ANCA vasculitis, acute interstitial nephritis, and diabetic nephropathy.

NATURAL HISTORY AND PROGNOSIS

The clinical course of MN varies widely. Spontaneous remissions in proteinuria occur in up to 30% of patients. Female gender and lowergrade (nonnephrotic) proteinuria at presentation are the only two features associated with a higher likelihood of spontaneous remission.38

Inclusion of such patients with nonnephrotic-range proteinuria in natural history studies is likely to have produced a bias in kidney survival.

For example, one study of untreated patients reported 72% kidney survival at 8 years, although more than one-third did not have nephroticrange proteinuria at presentation and more than 50% had less than 5 g/day.39 Despite this, the rate of end-stage kidney disease (ESKD) was 25% at 8 years and almost 50% by 15 years. Patients presenting with

less than 3.5 g/day of proteinuria, no RBC casts, no hypertension, normal kidney function, and no systemic features suggestive of a secondary cause have a generally favorable prognosis. However, these patients must be monitored, because up to 50% will develop nephrotic-range proteinuria at some time in the disease course, often within 2 years after presentation.

Traditional clinical variables including sustained proteinuria and kidney function are associated with long-term kidney outcome and can be used to classify patients into low, moderate, or high risk for progression to kidney failure (Fig. 21.7). One validated model to calculate risk in MN takes into consideration the initial creatinine clearance, the slope of the creatinine clearance during a fixed period, and the lowest level of proteinuria during that observation period.40 The model predicts that patients with a normal creatinine clearance at presentation that remains stable during a 6-month period and persistent proteinuria of less than 4 g/24 h have a less than 5% chance of progression, and only conservative treatment is recommended. In contrast, patients with proteinuria of 4 to 8 g/24 h during the same time frame have a 55% probability for development of kidney impairment, and those with persistent proteinuria greater than 8 g/24 h have a 66% to 80% probability of progression to chronic kidney impairment within 10 years.

Anti-PLA2R-antibody titer at the time of diagnosis can assist in prognostication (Table 21.4), although serum anti-PLA2R titers have yet to be fully incorporated into prediction models. Testing for circulating anti-PLA2R antibody can detect increases in MN immunologic activity before changes in classic laboratory parameters become apparent1 41 (Fig. 21.8). The presence and titer of anti-PLA2R antibody

Risk Factors Associated With Loss of Kidney Function in Membranous Nephropathy

TABLE 21.4

Factors	Predictor
Clinical Features	
Age	Older > younger
Sex	Male > female
Hypertension	Present
Nephrotic syndrome	Present
Traditional Laboratory Parameters	
Albumin	<1.5 g/dL
Creatinine (eGFR)	Above normal (reduced)
Proteinuria	Sustained high-grade proteinuria
Kidney Biopsy Features	
Glomerulosclerosis (focal or global)	Present
Interstitial fibrosis	Present
Autoantibodies	
Anti-PLA2R titer	Highest tertile > lowest tertile
Epitope spreading	Spreading > No epitope spreading
Antibodies to intracellular antigens	Present
Treatment and Response	
Immunosuppression	Not used > used, if indicated
Response to treatment	No response > partial or complete

remission

eGFR, Estimated glomerular filtration rate; PLA2R, phospholipase A2 receptor.

can help diagnose primary MN, predict who might have spontaneous remission, monitor disease activity and response to therapy, identify those at risk for progression, and, most significantly, decide when to minimize or stop treatment.[42]

A low or decreasing serum anti-PLA2R antibody titer is associated with a greater likelihood of spontaneous and complete remission,[43, 44] but with a lag time that reflects the time required to stop forming deposits and allow the podocyte to recover from the complement-mediated injury. Conversely, an initially high or increasing trajectory of antiPLA2R suggests that the clinical manifestations will continue and may worsen in the short-term. The anti-PLA2R antibody titers cannot be regarded on their own as indication to postpone or initiate immunotherapy, as clinical parameters such as serum albumin and degree of proteinuria and kidney impairment also must factor into decisions.

Other factors relating to the repertoire of circulating autoantibodies have been proposed as negative prognostic factors. The presence of “epitope spreading,” that is, autoantibodies to portions of PLA2R in addition to the immunodominant N-terminal epitope (see Fig. 21.3), has been associated with worse clinical outcomes in some studies[45] but not others.[46] The presence of additional autoantibodies to intracellular antigens has been suggested to independently convey worse prognosis.[47]

Beyond anti-PLA2R, other biomarkers, including urinary α1 microglobulin, β2-microglobulin, IgM, and IgG, are also associated with MN progression.[48, 49] These markers measured together at a single time point have a higher positive predictive value than proteinuria alone, but independent prediction value beyond clinical variables and anti-PLA2R antibodies requires further exploration.

The severity of chronic changes seen on the biopsy specimen (i.e., degree of glomerulosclerosis, tubulointerstitial fibrosis, and vascular disease) is associated with a poor prognosis but more closely reflects initial GFR than the subsequent rate of decline in GFR.[25, 50, 51] Other pathologic features, including the percentage of glomeruli with glomerulosclerosis and the configuration of the immune deposits (synchronic/single stage or heterogeneous/multistage) on EM, have also been suggested as predictors of outcome and response to treatment, although these features did not add independent prognostic value in a larger cohort study.[25]

Importance of Complete or Partial Remission

Relapse from a complete remission (CR) occurs in approximately 25% to 40% of MN cases, but the timing is unpredictable. Relapses have been reported up to 20 years after the primary remission. However, most patients relapsing after CR only develop subnephrotic-range proteinuria and will maintain stable long-term kidney function with conservative management alone.[52] In contrast, the relapse rate is as high as 50% in those achieving only a partial remission (PR).

Ten-year kidney survival in patients with CR is 100%; with PR, 90%; and with no remission, only 45%.[53] CR was defined by proteinuria of 0.3 g/day or less, and PR was defined by a proteinuria value less than 3.5 g/day plus a 50% reduction from its peak value. A recent update in this cohort suggested that the durability of CR or PR, whether drug induced or spontaneous, is closely related to the long-term outcome.[54] This suggests that CR and PR may become acceptable shorter-term surrogate endpoints for kidney failure for clinical trials rather than reduction in GFR, which commonly takes years to evolve in MN.[55]

TREATMENT

Nonimmunosuppressive Therapy

Conservative management of MN is directed at control of edema, hypertension, hyperlipidemia, and proteinuria and is similar to that used for nephrotic syndrome of any etiology (see Chapter 16). For patients with proteinuria of greater than 1 g/day, the target for blood pressure is 125/75 mm Hg unless contraindicated for clinical reasons. Angiotensinconverting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can reduce proteinuria and slow progression of kidney disease (see Chapter 82). A meta-analysis of the largest kidney protection trials using ACE inhibitors showed that the degree of protection is closely correlated to the degree of proteinuria reduction. None of these studies has focused on the specific effect of renin-angiotensin system (RAS) blockade in MN. In secondary analyses, the number of patients with MN has been small, and although the use of ACE inhibitors has been associated with significant improvement in some series, their antiproteinuric effect was modest (<30% reduction in proteinuria) in others. When effective, the benefit of RAS blockade occurs early, usually within the first 3 months of initiation of treatment. Even patients at low risk for progression (proteinuria <4 g/24 h) should be treated with ACE inhibitors or ARBs because this may reduce proteinuria and offer additional kidney protection, with minimal risk of significant adverse effect. Patients must also follow a low-salt diet (1.5–2 g sodium/day) to achieve the maximum benefit from RAS blockade.

When the proteinuria is in the nephrotic range, there is a clear increase in cardiovascular risk, with a threefold to fivefold increase in both coronary events and death rates in this population.[56] Patients with significant proteinuria almost always have pronounced hyperlipidemia. Although not proven, we recommend the use of statins to reduce lowdensity lipoprotein cholesterol to less than 100 mg/dL (<2 mmol/L), especially if proteinuria remains in the nephrotic range (see Chapters 82 and 85). Both RAS blockade and lipid control should be initiated early in these nephrotic MN patients at higher risk of progression.

Natural History of Relapsing Membranous Nephropathy
Initial episode of MN

Relapse of MN

Start of immunosuppression or
spontaneous remission

Autoantibody titer

Partial clinical remission

*
Immunological disease

Proteinuria

CR

Proteinuria

Immunosuppression
is restarted

PR

*

CR

Immunological remission

CR or PR

Immunological disease

Proteinuria

Fig. 21.8 Relationship of Immunologic and Clinical Courses of Disease in Membranous Nephropathy During Initial Disease and Relapse. Autoantibody (e.g., anti-PLA2R) titer is depicted in red and reflects the time course of immunologic (or serologic) disease. The start of the immunologic disease typically predates the clinical detection of MN by many months. Autoantibodies start to decline after successful immunosuppressive therapy or the onset of a spontaneous remission. Once the antibodies have disappeared, the patient is in an immunologic remission. The proteinuria (blue) lags behind the autoantibody curve and requires more time for the patient to achieve a partial remission (PR) and then a complete remission (CR). In some patients (dashed blue line), due to prolonged disease and more permanent damage to the kidney, levels of proteinuria may remain elevated in the subnephrotic range despite immunologic remission. Note that there are periods (asterisks) when proteinuria may still be present in the absence of detectable autoantibody. In 25% to 30% of patients, an immunologic and clinical relapse may occur, requiring another round of immunosuppression.

Persistent nephrotic syndrome, especially when caused by MN, is associated with an important risk of thromboembolic events.57 Hypoalbuminemia appears to be a more robust predictor of venous thromboembolic events (VTEs) than the level of proteinuria. The risk of VTE increases dramatically if serum albumin is less than 2.5 g/dL.58 These events tend to occur within the first 6 months of diagnosis but may occur up to 2 years from initial presentation. Patients with MN are also at significant risk of arterial thrombotic and cardiovascular events. Early in the disease course, these events occur at a rate that is commensurate to or exceeding that of ESKD.

Prophylactic anticoagulation seems beneficial in reducing fatal thromboembolic episodes in nephrotic patients with MN, without a concomitant increase in the risk of bleeding.59 No randomized controlled trial (RCT) has ever been done, however, and thus there is no current consensus about prophylactic anticoagulation and no laboratory test that can predict with any accuracy such an event. Using VTE risk data informed by retrospective cohorts, and bleeding risk estimates based upon data from a large trial of warfarin in atrial fibrillation (ATRIA), a decision analysis balanced the risk of thrombosis versus bleed, considering risk thresholds for adverse events (https://www.med.unc.edu/gntools/).60 The benefits of prophylactic anticoagulant therapy with warfarin appear to outweigh the risks in patients with serum albumin less than 2 or 2.5 g/dL in patients with a low to intermediate risk of bleeding, according to criteria outlined in the ATRIA study.61 An independent retrospective cohort supported use of an alternate regimen of anticoagulation with low-molecular-weight heparin in patients with nephrotic syndrome due to a spectrum of

glomerular pathologies.62 A shortcoming of the available data is the challenge of quantifying bleeding risk in patients with nephrotic syndrome, which can impact stability of anticoagulation with warfarin and some formulations of low-molecular-weight heparin. There are little data regarding safety of direct oral anticoagulants in this patient population.

Immunosuppressive Therapy

Several regimens using a variety of immunosuppressive agents can successfully reduce proteinuria in MN patients. Many unresolved questions are discussed in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis, including duration of conservative therapy while awaiting a spontaneous remission, when to initiate immunosuppressive therapy, the most effective and safest of the available agents, and duration of treatment before treatment is considered futile.62a

Specific immunosuppressive drug therapy should not be considered unless the patient has had persistent nephrotic-range proteinuria (>4 g/day) and the proteinuria has not declined by more than 50% from baseline, over a minimum observation period of 6 months, despite maximum antihypertensive and antiproteinuric therapy.

Other suggested criteria for early intervention are the presence of severe disabling or life-threatening symptoms related to the nephrotic syndrome or a rise in serum creatinine of more than 30% within 12 months, which would define a very high risk patient per the KDIGO guidelines. Worsening GFR should be documented as related to disease progression and not a complication, such as renal vein thrombosis, transformation to crescentic MN variant, hemodynamic or volumerelated changes from medications, or drug-induced interstitial nephritis. Low and/or declining titers of the PLA2R antibody are associated with a higher likelihood of spontaneous remission, and very high levels of the anti-PLA2R might be an indication for early intervention.8,41

Corticosteroids

Three RCTs of corticosteroids in primary MN treatment showed no significant long-term beneficial effect on proteinuria, rate of disease progression, or kidney survival.63,64 The use of oral corticosteroids as a single agent for the treatment of MN is therefore not recommended. The one exception may be the Japanese population, in whom longterm observational studies have indicated improvement in both proteinuria and kidney function preservation with use of corticosteroids as monotherapy.65

Cytotoxic Agents Combined With Corticosteroids

In patients at moderate risk of progression, a significant benefit has been described with a regimen beginning with methylprednisolone pulses 1 g intravenously for 3 days at the start of months 1, 3, and 5 followed by oral prednisone 0.5 mg/kg/day for 27 days, and each cycle followed by 1 month of treatment with an oral cytotoxic agent (cyclophosphamide or chlorambucil).66 CR or PR was seen in almost 80% of treated patients, and both progression rate and kidney survival were significantly improved versus the supportive care group. Few adverse events were reported in this study, although relapses were seen within 2 years in 30% of the treatment group. Similar results were obtained in an RCT using the same cyclophosphamide-corticosteroid regimen to treat MN patients of Asian (East Indian) ethnicity.67 Because the results of a cyclophosphamide-based regimen were similar to one based on chlorambucil, cyclophosphamide is most often used because of a better safety profile.

The safe use of cytotoxic agents in patients with deteriorating kidney function remains a challenge, even with appropriate adjustments in dose. One trial enrolled participants with a greater than 20% decline in GFR from baseline and demonstrated that the combination of corticosteroids and a cytotoxic drug (chlorambucil) offered marginally better protection against progressive kidney disease than placebo or cyclosporine but was associated with a high proportion of severe adverse events and a high study dropout rate.68 Another study followed 65 high-risk patients with serum creatinine greater than 1.5 mg/dL treated with oral cyclophosphamide for 12 months plus corticosteroids.69 Most patients achieved PR and had good kidney survival at 5 years, but two-thirds of participants had treatment-related complications such as bone marrow suppression and infections. Most adverse events could be managed by dose reduction, although some required permanent discontinuation of treatment.

In summary, cyclophosphamide used in combination with corticosteroids appears to be effective in the treatment of patients with nephrotic-range proteinuria due to primary MN, especially if GFR is well preserved at initiation of therapy. This combination may work even in those with impaired kidney function, but the supporting evidence is much less compelling, adverse effects are higher, and the likelihood of benefit is reduced, especially in patients with advanced kidney failure (GFR <30 mL/min/1.73m2).69 The adverse effects of long-term cyclophosphamide therapy are the major drawbacks to the universal application of this treatment. These include increased susceptibility to infections, anemia, thrombocytopenia, nausea, vomiting, sterility, and, over time, malignant disease. Evidence from the MN literature suggests that the incidence of cancer is increased at a much lower level of exposure than previously considered; the number of malignant neoplasms increased with total cyclophosphamide exposure as low as 10 to 20 g

(~100 mg/day for 6 months).70 Therefore, the use of cytotoxic agents should be limited to those patients with the highest risk of progression or with life-threatening complications of the nephrotic syndrome.

Calcineurin Inhibitors

Early uncontrolled studies using the calcineurin inhibitor (CNI) cyclosporine suggested an initial benefit but a high relapse rate. Cyclosporine may reduce proteinuria through its immunosuppressive effects but also by direct effects on the podocyte. In a single-blinded RCT, patients with corticosteroid-resistant MN were treated for 6 months with cyclosporine plus low-dose prednisone and compared with placebo plus prednisone.71 Cyclosporine was started at 3.5 mg/kg/day and titrated to reach a 12-hour trough level of 125 to 225 µg/L, with a mean trough level of approximately 150 µg/L ultimately achieved in the cyclosporine group. CR or PR was seen in 75% of cyclosporine-treated patients versus 22% of the controls. Cyclosporine was well tolerated. However, 38% relapsed within 6 months of discontinuation of treatment.

Only one RCT has used cyclosporine in patients with high-grade proteinuria and progressive decline in GFR, and both proteinuria and rate of kidney function loss were reduced with cyclosporine compared with placebo.72 This improvement in proteinuria was sustained for up to 2 years after cyclosporine was discontinued. In contrast to the UK study,68 cyclosporine was introduced at a lower dose and slowly increased to minimize toxicity (treatment started at 3.5 mg/kg/day compared to 5 mg/kg/day in the UK study; target trough levels were similar). Treatment with longer-term cyclosporine (i.e., 12 months) has resulted in a higher rate of PR/CR (84%). Persistence of remission was maintained with doses of cyclosporine as low as 1 to 2 mg/kg, although relapses were still common if the cyclosporine level fell below 100 ng/mL.

Significant adverse effects seen with cyclosporine include hypertension, gingival hyperplasia, gastrointestinal complaints, muscle cramps, and, most important, nephrotoxicity. The latter depends on both dose and duration of treatment.

In a 12-month RCT (n = 48), monotherapy with tacrolimus was compared with a control group (conservative therapy only).73 Proteinuria remission was 76% with tacrolimus versus 35% in the control group, and progression rate was also substantially slowed by the CNI. The relapse rate after stopping of the drug, however, approached 50% by the end of 2 years of follow-up.

In summary, both cyclosporine and tacrolimus reduce proteinuria in MN. Although relapses are common after short exposure (6–12 months), a longer duration and lower maintenance doses of CNI can maintain partial remission. No studies using CNIs have been of sufficient duration to confirm that maintenance of remission in proteinuria prolongs kidney survival. Side effects are substantial, with the major concern being nephrotoxicity, particularly if the CNI is not introduced at a low dose and slowly increased until an effective drug level is reached. The potential for nephrotoxicity with the CNIs increases if GFR is less than 40% of normal or rapidly deteriorating, or if there is a high degree of interstitial or vascular pathology accompanying the membranous lesion.

Mycophenolate Mofetil

Studies using mycophenolate mofetil (MMF) in MN patients report conflicting results. However, even in the most optimistic study, although initial response was high (used in combination with prednisone), the relapse rate within months approached 50%.74 A comparison of MMF to a historical control group receiving cyclophosphamide showed no benefit of MMF in terms of effect or tolerability.75 The addition of MMF to CNI therapy also does not appear to improve efficacy or relapse rate.76

Rituximab

A favorable remission rate of 60% to 70% in patients treated with rituximab as a primary or salvage therapy prompted the design of larger RCTs to evaluate efficacy of this drug in MN.77,78 Furthermore, rituximab was shown to cause early reduction in anti-PLA2R antibodies, a finding consistent with a favorable kidney prognosis.79 Although the first RCT comparing rituximab plus conservative therapy to conservative therapy alone did not achieve a significant primary endpoint of remission at 6 months, anti-PLA2R levels were significantly reduced by rituximab.80 During the extended follow-up, remission rates after a mean of 17 months of observation increased to 65% in those treated with rituximab compared with 34% in those treated conservatively.

The largest RCT in primary MN (n = 130) was MENTOR (Membranous Nephropathy Trial of Rituximab), designed to test the hypothesis that rituximab was not inferior to cyclosporine for inducing and maintaining a complete or partial remission of proteinuria.81,82 Patients assigned to rituximab received 1 g on days 1 and 15. At 6 months, if proteinuria was reduced by more than 25% but there was no CR, a second course of rituximab was administered. In the cyclosporine group, trough levels of 125 to 175 ng/mL were targeted. If CR was observed at 6 months, cyclosporine was tapered and discontinued over 2 months. If proteinuria was reduced by more than 25%, cyclosporine was continued for an additional 6 months and then tapered and discontinued after 2 months. Sixty percent of patients in the rituximab group achieved the primary outcome PR/CR at 24 months versus only 20% in the cyclosporine group, supporting both noninferiority and statistical superiority for rituximab. At 12 months, 60% in the rituximab group and 52% in the cyclosporine group achieved PR/CR, demonstrating noninferiority for rituximab at this time point.

The duration of action of rituximab in terms of B cell depletion may have extended the period of immunosuppression well beyond the 12month treatment period. An important additional finding was a higher creatinine clearance at all time points in patients in remission within the rituximab group. In patients achieving remission, the anti-PLA2R titer declined more rapidly in those who received rituximab. The rate of serious adverse events was 17% in the rituximab group and 31% in the cyclosporine group. Thus, the MENTOR study suggests that rituximab is at least as efficacious as cyclosporine at inducing remission, and is associated with a lower risk of relapse, with better preservation of creatinine clearance at 24 months, and a trend toward less serious adverse events.

The Sequential Treatment with Tacrolimus and Rituximab Versus Alternating Corticosteroids and Cyclophosphamide in Primary MN (STARMEN) trial evaluated the cyclical cyclophosphamidecorticosteroid regimen versus a combination of tacrolimus with rituximab added prior to tapering in order to potentially affect the rate of relapse after CNI withdrawal.83 One group received the regimen with alternating months of corticosteroids and oral cyclophosphamide. The second group received tacrolimus targeted to achieve a trough level of 5 to 7 ng/mL for 6 months, followed by a single dose of 1 g of intravenous rituximab and a tacrolimus taper through the end of month 9.

The primary outcome of PR/CR at 24 months was achieved in 84% in the corticosteroid-cyclophosphamide arm and 58% in the tacrolimusrituximab arm. Patients treated with cyclophosphamide had a shorter time to PR/CR and immunologic remission and a trend toward better preservation of eGFR at 24 months. Patients in the cyclophosphamide group experienced more adverse events, including leukopenia and associated infections. Of note, two patients in the cyclophosphamide arm experienced reactivation of tuberculosis.

Although the STARMEN study provides important information, the short duration of tacrolimus therapy and the single dose of rituximab used in this trial do not allow clear comparison of either of these agents to the known efficacy of standard alkylating agent-based therapy. The Rituximab or Cyclophosphamide in the Treatment of Membranous Nephropathy (RI-CYCLO) study directly compared the standard alternating corticosteroid-cyclophosphamide regimen to a single rituximab cycle (two 1 g doses given on days 1 and 15).84 There was no significant difference in terms of PR/CR at 24 months between the groups, and adverse event rates were also similar. However, because longer-term adverse effects such as infertility or late malignancies, which could occur following treatment with cytotoxic agents, were not captured here, we still recommend consideration of rituximab as firstline treatment.

Complement Inhibition

Although products of complement activation are present in the glomeruli in a high fraction of cases of primary and secondary MN, presently there is no data from clinical trials to indicate if complement is a therapeutic target. An early 16-week RCT of the humanized anti-C5 monoclonal antibody, eculizumab, was terminated prematurely for lack of efficacy; however, there were concerns about adequate dosing because of proteinuria, and the results might be considered inconclusive. Given that complement inhibition would appear to be an appealing strategy during an early window of opportunity until effective immunosuppression lowers circulating autoantibody levels, various clinical trials have been initiated in patients with MN using LNP023 (iptacopan), a small molecule inhibitor of factor B of the alternative pathway; of OMS721 (narsoplimab), a neutralizing human monoclonal antibody targeting mannan-binding lectin-associated serine protease-2 (MASP-2) of the lectin pathway; and of APL-2 (pegcetacoplan), a small molecule C3 activation inhibitor.85

Adrenocorticotropic Hormone

Two small studies have reported the use of a synthetic form of adrenocorticotropic hormone (ACTH) in MN. The exact mechanism of action of this agent in MN is unknown but likely unrelated to corticosteroid effects because corticosteroids alone are not beneficial in MN. An early dose escalation study of synthetic ACTH showed improved lipid profiles, with a small subgroup who received therapy for 1 year demonstrating sustained reduction in proteinuria.86 In a small RCT, ACTH was compared with a standard cytotoxic plus corticosteroids regimen. The remission rate was the same in the two groups (80% vs. 90%), but the relapse rate in the ACTH group was lower (14% vs. 30%), after a follow-up of 1 year. Side effects of ACTH were few and included fluid retention, sleep disturbances, and bronze skin discoloration.87

A dose escalation study found that natural ACTH gel significantly reduces proteinuria in proportion to drug exposure among most MN patients, and has an acceptable adverse event profile.88 In contrast, a subsequent nonrandomized study using the synthetic agent found a substantially lower response rate and an incidence of adverse events approaching 95%, prompting the authors to suggest this agent not be used in MN.89 Therefore, the most effective formulation of ACTH must be assessed in a larger RCT before it is recommended as standard therapy.

Treatment Approach

Achieving either CR or PR of the nephrotic syndrome is associated with prolonged kidney survival and a slower rate of kidney disease progression in patients with MN. Supportive or conservative care should be provided to all patients first, including diuretics, antihypertensive agents such as ACE inhibitors and ARBs, and lipid-lowering agents, with lifestyle modifications such as salt restriction and efforts toward smoking cessation (see Chapter 82).

Decisions regarding initiation of immunosuppression can be guided by stratifying patients into categories based on the risk of progression to kidney failure. Although persistent proteinuria is a key factor informing risk stratification, severe hypoalbuminemia places patients at significant risk of life-threatening complications of nephrotic syndrome and should be evaluated in parallel with proteinuria and factored into clinical decisions. Fig. 21.7 outlines a suggested management algorithm based on the level and persistence of proteinuria and incorporates information such as serum albumin and antiPLA2R antibody titer into risk stratification.

The traditional 6-month period of observation on optimized conservative therapy continues to be recommended. This might also include prophylactic anticoagulation in the setting of severe hypoalbuminemia and low bleeding risk, as described previously. In patients with high-grade proteinuria (>8 g/day), with hypoalbuminemia and persistently elevated or rising anti-PLA2R antibody titer, initiation of immunotherapy can be considered after a shorter observation period (e.g., 3 months). Life-threatening complications of nephrotic syndrome such as thrombosis or worsening kidney function may also prompt earlier consideration of immunosuppression.

For patients at moderate risk of disease progression, evidence supports the use of either rituximab or a calcineurin inhibitor, although the MENTOR study supports a lower risk of relapse and better preservation of kidney function with rituximab. Cytotoxic/corticosteroid combinations are effective in moderate-risk or high-risk MN patients. This regimen, however, may be associated with important toxicity, and therefore is often reserved for patients at high risk of disease progression. Side effect profile, cost, and availability of these agents are important factors that will influence treatment selection for the individual patient.

Although beyond the scope of this discussion, bone protection and prophylaxis against Pneumocystis jiroveci pneumonia should be coadministered with corticosteroids and/or cytotoxic and rituximab therapy.

A reduction in anti-PLA2R antibody titer will often occur prior to improvement in serum albumin or proteinuria, and the first evidence of clinical response may not be evident for 3 to 4 months. In the case of resistance to a treatment regimen or untenable adverse effects, an attempt at a second treatment regimen is often explored. Ideally, the approach should leave 2 to 3 months between treatment regimens to help immune system recovery.

Patients with severely reduced eGFR (<30 mL/min/1.73 m2) are less likely to benefit from immunosuppressive therapy (especially if the MN course has been slowly progressive and histopathology indicates significant interstitial fibrosis and glomerular obsolescence), and conservative therapy may be the best option for such patients.

FUTURE DIRECTIONS

The ongoing identification of novel MN antigens continues to highlight new mechanisms of disease development and will help elucidate additional biomarkers that can be used for prognostication and to assist in treatment decisions and monitoring of treatment response. Although great strides have been made in the design and execution of multicenter RCTs in this disease, the rate of adverse events in these trials has remained significant. Furthermore, the response rate remains modest, with 30% to 40% of study participants having no response to the allocated treatment regimen. This highlights the need to continue to search for personalized, novel, and safe treatment strategies for this important cause of kidney failure.

SELF-ASSESSMENT QUESTIONS

1. Which statement on autoantigens in patients with membranous glomerulonephritis is true?
A. Phospholipase A2 receptor is the dominant autoantigen in Whites but not Asians.
B. THSD7A is a more common autoantigen in those of Japanese ancestry compared with Whites.
C. NELL1 is the autoantigen in most cases associated with malignancy.
D. Semaphorin 3B is the autoantigen in lupus-associated membranous glomerulonephritis.
E. Alpha-enolase is a membrane bound autoantigen, which is commonly shed into the glomerular basement membrane.

2. Which statement on MN is false?
A. Primary MN has its peak incidence during the fourth and fifth decades of life.
B. Estimated annual incidence is 8 to 10 cases per 1 million population in Western countries.
C. The odds ratio of MN is almost 80 in individuals who are homozygous for particular HLA-DQA1 and PLA2R1 variants.
D. A majority of patients (70%–80%) with MN present with the nephrotic syndrome.
E. Microscopic hematuria is uncommon (5%–10%).

3. Which statement on MN is false?

A. The predominant IgG subclass in many forms of primary MN is IgG3.
B. In earliest stages of MN, the glomeruli and interstitium appear normal on light microscopy.
C. In some patients with progressive disease, glomeruli exhibit areas that resemble secondary focal segmental glomerulosclerosis.
D. Granular glomerular capillary wall staining for IgG in MN is characteristic.
E. Phospholipase A2 receptor staining in the immune deposits exhibits a pattern that colocalizes with IgG.

4. Which statement on the therapy of patients with membranous glomerulonephritis (MN) is true?
A. For patients with proteinuria of greater than 1 g/day, the target for blood pressure is 140/90 mm Hg.
B. Prophylactic anticoagulation should be given to all patients with MN.
C. Immunosuppressive drug therapy should not be considered unless the patient has had persistent nephrotic-range proteinuria.
D. Oral corticosteroids as a single agent for the treatment of MN are often effective.
E. Rituximab should not be first-line treatment because of longerterm adverse effects, such as late malignancies.

REFERENCES

1. Francis JM, Beck Jr LH, Salant DJ. Membranous nephropathy: a journey from bench to bedside. Am J Kidney Dis. 2016;68(1):138–147.
2. Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient’s care. Lancet. 2015;385(9981):1983–1992.
3. Ayalon R, Beck Jr LH. Membranous nephropathy: not just a disease for adults. Pediatr Nephrol. 2015;30(1):31–39.
4. Beck Jr LH, Salant DJ. Membranous nephropathy: from models to man. J Clin Invest. 2014;124(6):2307–2314.
5. Debiec H, Guigonis V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002;346(26):2053–2060.
6. Beck Jr LH, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21.
7. Qin W, Beck Jr LH, Zeng C, et al. Anti-phospholipase A2 receptor antibody in membranous nephropathy. J Am Soc Nephrol. 2011;22(6):1137–1143.
8. Hoxha E, Kneißler U, Stege G, et al. Enhanced expression of the Mtype phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy. Kidney Int. 2012;82(7):797–804.
9. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol. 2013;26(5):709–715.
10. Haddad G, Lorenzen JM, Ma H, et al. Altered glycosylation of IgG4 promotes lectin complement pathway activation in anti-PLA2R1associated membranous nephropathy. J Clin Invest. 2021;131(5).
11. East L, Isacke CM. The mannose receptor family. Biochim Biophys Acta. 2002;1572(2–3):364–386.
12. Tomas NM, Beck Jr LH, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277–2287.
13. Iwakura T, Ohashi N, Kato A, Baba S, Yasuda H. Prevalence of enhanced granular expression of thrombospondin type-1 domain-containing 7A in the glomeruli of Japanese patients with idiopathic membranous nephropathy. PLoS One. 2015;10(9):e0138841.
14. Caza TN, Hassen SI, Dvanajscak Z, et al. NELL1 is a target antigen in malignancy-associated membranous nephropathy. Kidney Int. 2021;99(4):967–976.
15. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. Kidney Int. 2020;97(1):163–174.
16. Sethi S, Debiec H, Madden B, et al. Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. Kidney Int. 2020;98(5):1253–1264.
17. Debiec H, Lefeu F, Kemper MJ, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med. 2011;364:2101–2110.
18. Liu YH, Chen CH, Chen SY, et al. Association of phospholipase A2 receptor 1 polymorphisms with idiopathic membranous nephropathy in Chinese patients in Taiwan. J Biomed Sci. 2010;17(1):81.
19. Kim S, Chin HJ, Na KY, et al. Single nucleotide polymorphisms in the phospholipase A(2) receptor gene are associated with genetic susceptibility to idiopathic membranous nephropathy. Nephron Clin Pract. 2010;117(3):c253–c258.
20. Stanescu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. N Engl J Med. 2011;364(7):616–626.
21. Xie J, Liu L, Mladkova N, et al. The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis. Nat Commun. 2020;11(1):1600.

22. Le WB, Shi JS, Zhang T, et al. HLA-DRB1*15:01 and HLA-DRB3*02:02 in PLA2R-related membranous nephropathy. J Am Soc Nephrol. 2017;28(5):1642–1650.

23. Xu X, Wang G, Chen N, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. J Am Soc Nephrol. 2016;27(12):3739–3746.
24. Burbelo PD, Joshi M, Chaturvedi A, et al. Detection of PLA2R autoantibodies before the diagnosis of membranous nephropathy. J Am Soc Nephrol. 2020;31(1):208–217.
25. Troyanov S, Roasio L, Pandes M, Herzenberg AM, Cattran DC. Renal pathology in idiopathic membranous nephropathy: a new perspective. Kidney Int. 2006;69(9):1641–1648.
26. Jennette JC, Iskandar SS, Dalldorf FG. Pathologic differentiation between lupus and nonlupus membranous glomerulopathy. Kidney Int. 1983;24(3):377–385.
27. Cybulsky AV, Rennke HG, Feintzeig ID, Salant DJ. Complement-induced glomerular epithelial cell injury. Role of the membrane attack complex in rat membranous nephropathy. J Clin Invest. 1986;77(4):1096–1107.
28. Cybulsky AV, Takano T, Papillon J, McTavish AJ. Complement-induced phospholipase A2 activation in experimental membranous nephropathy. Kidney Int. 2000;57(3):1052–1062.
29. Jennette JC, Hipp CG. Immunohistopathologic evaluation of C1q in 800 renal biopsy specimens. Am J Clin Pathol. 1985;83(4):415–420.
30. Val-Bernal JF, Garijo MF, Val D, Rodrigo E, Arias M. C4d immunohistochemical staining is a sensitive method to confirm immunoreactant deposition in formalin-fixed paraffin-embedded tissue in membranous glomerulonephritis. Histol Histopathol. 2011;26(11):1391–1397.
31. Yang AH, Lin BS, Kuo KL, Chang CC, Ng YY, Yang WC. The clinicopathological implications of endothelial tubuloreticular inclusions found in glomeruli having histopathology of idiopathic membranous nephropathy. Nephrol Dial Transplant. 2009;24(11):3419–3425.
32. Bobart SA, De Vriese AS, Pawar AS, et al. Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. Kidney Int. 2019;95(2):429–438.
33. Fresquet M, Jowitt TA, Gummadova J, et al. Identification of a major epitope recognized by PLA2R autoantibodies in primary membranous nephropathy. J Am Soc Nephrol. 2015;26(2):302–313.
34. Timmermans SA, Ayalon R, van Paassen P, et al. Anti-phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. Am J Kidney Dis. 2013;62(6):1223–1225.
35. Hoxha E, Beck Jr LH, Wiech T, et al. An indirect immunofluorescence method facilitates detection of thrombospondin type 1 domaincontaining 7A-specific antibodies in membranous nephropathy. J Am Soc Nephrol. 2017;28(2):520–531.
36. Nikolopoulou A, Teixeira C, Cook HT, et al. Membranous nephropathy associated with viral infection. Clin Kidney J. 2020;14(3):876–883.
37. Safar-Boueri L, Piya A, Beck Jr LH, Ayalon R. Membranous nephropathy: diagnosis, treatment, and monitoring in the post-PLA2R era. Pediatr Nephrol. 2021;36(1):19–30.
38. Hladunewich MA, Troyanov S, Calafati J, Cattran DC. The natural history of the non-nephrotic membranous nephropathy patient. Clin J Am Soc Nephrol. 2009;4(9):1417–1422.
39. Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med. 1993;329(2):85–89.
40. Cattran DC, Pei Y, Greenwood CM, Ponticelli C, Passerini P, Honkanen E. Validation of a predictive model of idiopathic membranous nephropathy: its clinical and research implications. Kidney Int. 1997;51(3):901–907.
41. Kanigicherla D, Gummadova J, McKenzie EA, et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. Kidney

Int. 2013;83(5):940–948.
42. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol. 2017;28(2):421–430.
43. Jullien P, Seitz Polski B, Maillard N, et al. Anti-phospholipase A2 receptor antibody levels at diagnosis predicts spontaneous remission of idiopathic membranous nephropathy. Clin Kidney J. 2017;10(2):209–214.

References

44. Rodas LM, Matas-García A, Barros X, et al. Antiphospholipase 2 receptor antibody levels to predict complete spontaneous remission in primary membranous nephropathy. Clin Kidney J. 2019;12(1):36–41.
45. Seitz-Polski B, Dolla G, Payre C, et al. Epitope spreading of autoantibody response to PLA2R associates with poor prognosis in membranous nephropathy. J Am Soc Nephrol. 2016;27(5):1517–1533.
46. Reinhard L, Zahner G, Menzel S, Koch-Nolte F, Stahl RAK, Hoxha E. Clinical relevance of domain-specific phospholipase A2 receptor 1 antibody levels in patients with membranous nephropathy. J Am Soc Nephrol. 2020;31(1):197–207.
47. Ghiggeri GM, Seitz-Polski B, Justino J, et al. Multi-autoantibody signature and clinical outcome in membranous nephropathy. Clin J Am Soc Nephrol. 2020;15(12):1762–1776.
48. Branten AJW, du Buf-Vereijken PW, Klasen IS, et al. Urinary excretion of β2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: a validation study. J Am Soc Nephrol. 2005;16(1):169–174.
49. van den Brand JA, Hofstra JM, Wetzels JF. Low-molecular-weight proteins as prognostic markers in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2011;6(12):2846–2853.
50. Zhang XD, Cui Z, Zhang MF, et al. Clinical implications of pathological features of primary membranous nephropathy. BMC Nephrol. 2018;19(1):215.
51. He HG, Wu CQ, Ye K, et al. Focal segmental glomerulosclerosis, excluding atypical lesion, is a predictor of renal outcome in patients with membranous nephropathy: a retrospective analysis of 716 cases. BMC Nephrol. 2019;20(1):328.
52. Ponticelli C, Passerini P, Altieri P, Locatelli F, Pappalettera M. Remissions and relapses in idiopathic membranous nephropathy. Nephrol Dial Transplant. 1992;7(suppl 1):85–90.
53. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney Int. 2004;66(3):1199–1205.
54. Cattran DC, Kim ED, Reich H, Hladunewich M, Kim SJ. Toronto glomerulonephritis registry g. Membranous nephropathy: quantifying remission duration on outcome. J Am Soc Nephrol. 2017;28(3):995–1003.
55. Thompson A, Cattran DC, Blank M, Nachman PH. Complete and partial remission as surrogate end points in membranous nephropathy. J Am Soc Nephrol. 2015;26(12):2930–2937.
56. Lee T, Derebail VK, Kshirsagar AV, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. Kidney Int. 2016;89(5):1111–1118.
57. Barbour SJ, Greenwald A, Djurdjev O, et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012;81(2):190–195.
58. Lionaki S, Derebail VK, Hogan SL, et al. Venous thromboembolism in patients with membranous nephropathy. Clin J Am Soc Nephrol. 2012;7(1):43–51.
59. Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. Kidney Int. 1994;45(2):578–585.
60. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int. 2014;85(6):1412–1420.
61. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarinassociated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395–401.
62. Medjeral-Thomas N, Ziaj S, Condon M, et al. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in

nephrotic syndrome. Clin J Am Soc Nephrol. 2014;9(3):478–483.
62a. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–S276.
63. Cattran DC, Delmore T, Roscoe J, et al. A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. N Engl J Med. 1989;320(4):210–215.

64. Cameron JS, Healy MJ, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolone in idiopathic membranous nephropathy with nephrotic syndrome in adults. The MRC Glomerulonephritis Working Party. Q J Med. 1990;74(274):133–156.
65. Shiiki H, Saito T, Nishitani Y, et al. Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. Kidney Int. 2004;65(4):1400–1407.
66. Ponticelli C, Zucchelli P, Passerini P, et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int. 1995;48(5):1600–1604.
67. Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol. 2007;18(6):1899–1904.
68. Howman A, Chapman TL, Langdon MM, et al. Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. Lancet. 2013;381(9868):744–751.
69. du Buf-Vereijken PW, Branten AJ, Wetzels JF. Cytotoxic therapy for membranous nephropathy and renal insufficiency: improved renal survival but high relapse rate. Nephrol Dial Transplant. 2004;19(5):1142–1148.
70. van den Brand JA, van Dijk PR, Hofstra JM, Wetzels JF. Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2014;9(6):1066–1073.
71. Cattran DC, Appel GB, Hebert LA, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int. 2001;59(4):1484–1490.
72. Cattran DC, Greenwood C, Ritchie S, et al. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. Kidney Int. 1995;47(4):1130–1135.
73. Praga M, Barrio V, Juarez GF, Luno J. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney Int. 2007;71(9):924–930.
74. Dussol B, Morange S, Burtey S, et al. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. Am J Kidney Dis. 2008;52(4):699–705.
75. Branten AJ, du Buf-Vereijken PW, Vervloet M, Wetzels JF. Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. Am J Kidney Dis. 2007;50(2):248–256.
76. Nikolopoulou A, Condon M, Turner-Stokes T, et al. Mycophenolate mofetil and tacrolimus versus tacrolimus alone for the treatment of idiopathic membranous glomerulonephritis: a randomised controlled trial. BMC Nephrol. 2019;20(1):352.
77. Fervenza FC, Cosio FG, Erickson SB, et al. Rituximab treatment of idiopathic membranous nephropathy. Kidney Int. 2008;73(1):117–125.
78. Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol. 2012;23(8):1416–1425.
79. Beck Jr LH, Fervenza FC, Beck DM, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol. 2011;22(8):1543–1550.
80. Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol. 2017;28(1):348–358.
81. Fervenza FC, Canetta PA, Barbour SJ, et al. A multicenter randomized

controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (MENTOR). Nephron. 2015;130(3):159–168.

82. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med. 2019;381(1):36–46.

83. Fernandez-Juarez G, Rojas-Rivera J, Logt AV, et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. Kidney Int. 2021;99(4):986–998.

References

84. Scolari F, Delbarba E, Santoro D, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. J Am Soc Nephrol. 2021.
85. Thurman JM, Yapa R. Complement therapeutics in autoimmune disease. Front Immunol. 2019;10:672.
86. Berg AL, Nilsson-Ehle P, Arnadottir M. Beneficial effects of ACTH on the serum lipoprotein profile and glomerular function in patients with membranous nephropathy. Kidney Int. 1999;56(4):1534–1543.
87. Ponticelli C, Passerini P, Salvadori M, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis. 2006;47(2):233–240.
88. Hladunewich MA, Cattran D, Beck LH, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar(R) Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014;29(8):1570–1577.
89. van de Logt AE, Beerenhout CH, Brink HS, van de Kerkhof JJ, Wetzels JF, Hofstra JM. Synthetic ACTH in high risk patients with idiopathic membranous nephropathy: a prospective, open label cohort study. PLoS One. 2015;10(11):e0142033.

22

Immunoglobulin-Mediated Glomerulonephritis With a Membranoproliferative Pattern of Injury and Cryoglobulinemic Glomerulonephritis

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IMMUNOGLOBULIN-MEDIATED GLOMERULONEPHRITIS WITH A MEMBRANOPROLIFERATIVE PATTERN OF INJURY

Definition and Classification

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury resulting from subendothelial and mesangial deposition of immune complexes and/or complement factors and their products, along with proliferative changes in the glomeruli. This pattern does not represent a disease entity per se. We therefore prefer to use terminology that refers to the underlying disease, such as immunecomplex glomerulonephritis, monoclonal Ig glomerulonephritis, and C3 glomerulopathy.[1] Other terms, such as lobular glomerulonephritis and mesangiocapillary glomerulonephritis, should be avoided.

Former Classification

Previously, MPGN was classified as MPGN type I, MPGN type II, and MPGN type III based on ultrastructural characteristics. MPGN type I was defined by the presence of mesangial and subendothelial deposits. MPGN type II, also referred to as dense deposit disease (DDD), was characterized by mesangial and intramembranous highly electron-dense deposits. MPGN type III was defined by the presence of subendothelial, intramembranous, and subepithelial electron-dense deposits. However, some cases had glomerular deposition of immunoglobulins and complement components, whereas in others, only complement deposition was present. This insight engendered a new classification. Older publications regarding epidemiology, therapy, and transplantation may be difficult or impossible to interpret because, with the exception of DDD, immune-complex and complement-mediated MPGN were included together (see later discussion).

Newer Classification Based on Etiology and Pathogenesis

The Mayo Clinic classification of MPGN[2,3] divides MPGN based on two broad pathogenetic pathways: (1) immune complex or monoclonal immunoglobulin deposition in the glomeruli with or without complement deposition and (2) complement deposition subsequent to dysregulation of the complement system.

The MPGN pattern of injury secondary to deposition of immune complexes in the glomeruli can occur when there are persistent circulating antigen-antibody immune complexes resulting from chronic infections or autoimmune diseases. MPGN with immunoglobulin and complement deposits may also be observed in the setting of a monoclonal gammopathy.

On light microscopy, a proliferative glomerulonephritis is seen in the acute phase with initial influx of neutrophils followed by mononuclear inflammatory cells. In the repair phase, the injured mesangial cells and endothelium produce new basement membrane, and there is expansion of the mesangial matrix. As a result of remodeling, the glomerular basement membrane (GBM) thickens and glomeruli acquire a lobular appearance typical of MPGN pattern. The immune-complex and monoclonal immunoglobulin–mediated MPGN are differentiated by the presence of immunoglobulins on immunofluorescence (IF); in the former the deposits are polyclonal, whereas in the latter they are monoclonal. C3 is also usually present, indicating activation of the complement pathway. Complement-mediated MPGN is less common than immune complex–mediated MPGN and results from dysregulation of the complement alternative pathway (see Chapter

23).

A third pathogenic pathway with an MPGN pattern despite the absence of immune complex or complement deposition can occur with chronic thrombotic microangiopathy or chronic endothelial injury (Table 22.1).

Epidemiology

MPGN is decreasing in frequency in high-income countries (possibly because of better control of infectious diseases) but remains common in patients presenting with nephrotic syndrome in low- and middleincome countries in South America, Asia, and Africa. The incidence of MPGN in most high-income countries is less than 1 to 2 cases per million population per year.4 Only about 4% to 5% of kidney biopsy samples showing an MPGN pattern have underlying C3 glomerulonephritis (see Chapter 23).

Clinical Presentation and Pathology

Infection-Associated MPGN

Chronic viral infections such as hepatitis C (HCV) and B (HBV) are important causes of immune complex–mediated MPGN (cryoglobulinemic glomerulonephritis; see later discussion and Chapter 57).5,6

The exact mechanism of HCV-related glomerular disease is unknown.

Toll-like receptors, particularly TLR3, might play a role in HCVrelated MPGN.7

HBV most frequently causes a membranous nephropathy pattern of injury but can more rarely be associated with MPGN.

The pathology of HBV-related MPGN is likely related to the trapping of circulating immune complexes in the mesangium and subendothelial regions.8 It is also possible that mesangial cells are directly infected by HBV virions. Uncommonly, MPGN may be seen with acute viral infections, such as with Puumala hantavirus.9

Chronic bacterial infections can cause MPGN as a result of continuous low-grade antigenemia.10,11 Potential causative agents include Staphylococcus, Mycobacterium tuberculosis, Streptococcus,

TABLE 22.1

Causes of a Membranoproliferative Pattern of Glomerular Injury

Immune complex mediated, monoclonal immunoglobulin mediated

Deposition of immune complexes as a result of an infection

Viral: hepatitis B and C
Bacterial: endocarditis, infected ventriculoatrial shunt, visceral abscesses, leprosy, meningococcal meningitis
Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis

Deposition of immune complexes as a result of an autoimmune disease

Systemic lupus erythematosus
Sjögren syndrome
Rheumatoid arthritis

Deposition of monoclonal immunoglobulin as a result of a monoclonal gammopathy

Plasma cell or B-cell disorder

Complement-mediated (C3 glomerulonephritis and dense deposit disease)

Mutations in complement-regulating proteins CFH, CFI, CFHR5
Antibodies to complement regulating proteins C3/C4 nephritic factor, antibodies against CFH, CFI, or CFB
Mutations in complement factors C3, CFB
Monoclonal gammopathy

Non–immunoglobulin mediated, non–complement mediated

Healing phase of HUS/TTP
Antiphospholipid (anticardiolipin) antibodies syndrome
POEMS syndrome
Radiation nephritis
Nephropathy associated with bone marrow transplantation
Drug-associated thrombotic microangiopathies
Sickle cell anemia and polycythemia
Dysfibrinogenemia and other prothrombotic states
Transplant glomerulopathy

Idiopathic

None of the conditions previously mentioned present

CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; CFHR5, complement factor H related 5; HUS, Hemolytic uremic syndrome; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal

gammopathy, skin; TTP, thrombotic thrombocytopenic purpura.
Modified from Fervenza FC, Sethi S, Glassock RJ. Idiopathic membranoproliferative glomerulonephritis: Does it exist? Nephrol Dial Transplant. 2012;27(12):4288–4294.

Propionibacterium acnes, Mycoplasma pneumoniae, Coxiella burnetii, Nocardia, Brucella, and Meningococcus.12 13 So-called “shunt nephritis,” as may be seen with ventriculoatrial or ventriculocaval shunts for hydrocephalus or as a result of catheter infections (e.g., parenteral nutrition), is caused most commonly by coagulase-negative staphylococci. Fungal and parasitic infections less frequently cause an MPGN pattern of injury.14 15

In the setting of viral infections, IF typically shows granular deposition of immunoglobulin M (IgM), C3, and both kappa and lambda light chains (Fig. 22.1). IgG may or may not be present, and C1q is typically negative. The presence of IgG staining stronger than IgM and C3 is more often seen in bacterial infections, although in some cases with chronic infections the immunoglobulin staining may be weak compared with the C3 staining. Electron microscopy (EM) shows mesangial and subendothelial deposits. The capillary walls are thickened with entrapment of cellular elements, subendothelial electron-dense deposits, matrix-like material, and new GBM formation manifested as double contours on light microscopy.

Additional information on the glomerular diseases associated with infection can be found in Chapter 57

Autoimmune-Associated MPGN

An MPGN pattern of injury is commonly seen in patients with autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjögren syndrome, undifferentiated connective tissue disease, primary sclerosing cholangitis, and Graves disease.16 17 The majority of patients with Sjögren syndrome and glomerulonephritis (80%) have type II monoclonal cryoglobulinemia and low complement C4 levels.18 Sjögren syndrome is one of the most common causes of non–HCV-related cryoglobulinemia.19

On IF, a full house pattern with positive staining for IgG, IgA, IgM, C1q, C3, and kappa and lambda light chains is frequently seen, particularly in the setting of SLE. IgM may be the dominant immunoglobulin in MPGN associated with RA and primary Sjögren syndrome.

EM shows mesangial and subendothelial capillary wall electron-dense deposits. Subepithelial deposits may also be present. In such cases, an exostosin 1/exostosin 2–associated membranous nephropathy should be considered.20 Tubuloreticular inclusions are often present in the endothelial cells.

Monoclonal Immunoglobulin–Associated MPGN

Monoclonal gammopathies encompass disorders characterized by clonal proliferation of immunoglobulin-producing B lymphocytes or plasma cells. In most patients with monoclonal immunoglobulinassociated MPGN, a monoclonal immunoglobulin cannot be detected in the blood or urine21 22 with routine serum electrophoresis and immunofixation examination, and evidence of overt malignancies such as lymphoma, multiple myeloma, or Waldenström macroglobulinemia is absent. In those cases, the term monoclonal gammopathy of renal significance (MGRS) is used.23 The glomerular diseases included in this group are proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), amyloidosis, fibrillary glomerulonephritis (DNAJB9 positive), immunotactoid glomerulopathy, and monoclonal immunoglobulin deposition disease (see Chapter 28).24–26

Although each of these entities may have a varied morphologic appearance, the common pattern of glomerular injury is MPGN.

On kidney biopsy (Fig. 22.2), glomerular deposition of the monoclonal immunoglobulin usually results in an MPGN pattern.

Less common patterns of proliferative glomerulonephritis include mesangial proliferative, diffuse proliferative, crescentic, necrotizing,

A

B

C

D

Fig. 22.1 Membranoproliferative Glomerulonephritis (MPGN) Associated With Hepatitis C. (A) Light microscopy showing two glomeruli with an MPGN pattern of injury (PAS ×20). (B–C) Immunofluorescence microscopy showing bright granular staining for immunoglobulin M (B), and C3 (C). There was equal staining for kappa and lambda light chains (not shown). (D) Electron microscopy showing subendothelial electrondense deposits and double contour formation. Black arrows point to subendothelial deposits. (D, ×13,000.)

A

B

C

D

E

F

Fig. 22.2 Proliferative Glomerulonephritis With Monoclonal Immunoglobulin Deposits. (A) Light microscopy showing a membranoproliferative glomerulonephritis (MPGN) pattern of injury (PAS, ×40). (B–E) Immunofluorescence microscopy showing bright granular staining for immunoglobulin G (IgG) (B), kappa light chains (C), negative staining for lambda light chains (D), and positive staining for IgG3 subtype (E). (F) Electron microscopy showing subendothelial electron-dense deposits and double contour formation. Black arrows point to subendothelial deposits (F, ×4000.)

A

C

D

E

F

Fig. 22.3 Cryofibrinogen Glomerulopathy With a Membranoproliferative Pattern of Injury. (A–C) Light microscopy showing a membranoproliferative glomerulonephritis pattern of injury. Scattered fuschinophilic material can be seen with some capillary loops in part C. Immunofluorescence microscopy was negative for immune deposits. (D–F) Electron microscopy showing randomly arranged and loosely arranged subendothelial fibrillary deposits with tubular substructures (D) and aggregates of intraluminal tubular deposits with large central bore with double and triple layering (E–F). (A, H&E, ×20. B, Silver methenamine silver, ×40. C, Masson trichrome stain, ×40. D, ×30,000. E, ×9300. F, ×3000.)

and sclerosing glomerulonephritis.21 22 IF studies are crucial for the diagnosis and show mesangial and capillary wall monoclonal immunoglobulin deposits. The monoclonal immunoglobulin most often contains heavy chain IgG, less commonly IgM or, rarely, IgA, with kappa or lambda light chain restriction. Sometimes, only heavy or light chains may be present.27 EM shows mesangial and subendothelial electron-dense deposits, and, rarely, subepithelial and intramembranous deposits. Glomerular capillary wall remodeling with double contour formation is often present.

In cases in which the heavy chain consists of IgG, the IgG3 subclass is the most common subclass. Interestingly, this class of deposits is most likely to have undetectable circulating monoclonal immunoglobulin by routine serum and urine electrophoresis studies.28

In monoclonal immunoglobulin-associated MPGN, 30% of patients have a monoclonal or biclonal band on serum immunofixation studies. Of these, bone marrow studies revealed 16 cases of MGRS, of which two converted to multiple myeloma; two cases of chronic lymphocytic leukemia (CLL); one case of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; three cases of low-grade B-cell lymphoma not further classifiable; and six cases of multiple myeloma.25 Thus, all patients with MPGN associated with monoclonal immunoglobulin should be evaluated for an underlying plasma cell or B-cell proliferative disorder.

MPGN With Masked Immune Deposits

MPGN with isolated C3 deposits rarely occurs in the setting of monoclonal gammopathy.29 Hypocomplementemia is common. IF on formalin-fixed, paraffin-embedded tissue after protease digestion unmasks monoclonal immunoglobulin glomerular deposits. The immunoglobulin on the glomerular deposits matches the monoclonal protein on serum immunofixation. It is important that these cases are not misdiagnosed as C3 glomerulopathy because most are associated with a low-grade lymphoma or plasma cell dyscrasia. A C4d stain can be helpful in detecting masked immune deposits.30 31

Complement-Mediated MPGN

Complement-mediated MPGN is also the most common MPGN pattern seen in C3 glomerulopathy, a lesion that is characterized by dominant C3 staining with minimal or no immunoglobulin deposits (see Chapter 23).

MPGN Without Immunoglobulins or Complement

Glomeruli may demonstrate membranoproliferative-like changes in the absence of immunoglobulin or complement deposits in chronic thrombotic microangiopathy (see Chapter 30).

Uncommon Causes of MPGN

Cryofibrinogen-related MPGN. Cryofibrinogenemia is a rare disease resulting in an MPGN pattern of injury (Fig. 22.3). Cryofibrinogen is a cryoprecipitate that develops after refrigeration of plasma but not serum (when both serum and plasma form a precipitate on refrigeration, the responsible proteins are called cryoglobulins). Cryofibrinogenemia may be asymptomatic but can be associated with thromboembolic disease, particularly affecting the skin.

C4 glomerulopathy. C4 glomerulopathy is characterized by glomerular deposits of predominantly C4 with little or no immunoglobulin or C3 deposition. This glomerulopathy encompasses C4 DDD and C4 glomerulonephritis[32] and may be caused by an overactive lectin pathway of complement. Kidney biopsy shows a membranoproliferative pattern of injury with extremely thick glomerular capillary walls.

Collagen type III glomerulopathy. Collagen type III (collagenofibrotic) glomerulopathy is a rare disorder characterized by massive accumulation of atypical type III collagen fibrils in the mesangium and subendothelial space (see Chapter 29).

Patient Evaluation in Cases of
MPGN Pattern of Injury on Biopsy a

BOX 22.1

Immune Complex MPGN
Infection
- Viral serology for HBV, HCV, HIV, COVID-19
- Quantification of viral load
- Blood cultures
- Imaging studies for deep-seated abscesses and vegetations by echocardiogram
- QuantiFERON-Tb Gold
- Parasitic and fungal infections are investigated only in the appropriate clinical situation (history of recent travel to endemic regions, prolonged fever of unknown origin, atypical pulmonary infiltrates)

Autoimmune
- Antinuclear antibodies, anti-ds-DNA antibodies, extractable nuclear antigen antibodies (anti-ribonucleoprotein, anti-SSA, [Ro], anti-SSB, [La], antiSmith [Sm], Scl-70, Anti-Jo-1)

Monoclonal Immunoglobulin–Associated MPGN
Serum and urine protein electrophoresis and immunofixation
Serum M-protein isotype by mass spectrometry
Serum free light chains
Bone marrow biopsy
MPGN Without Immunoglobulin and Complement Deposition
Evaluate for thrombotic microangiopathy

aC3/C4, cryoglobulins, rheumatoid factor, C-reactive protein, serum albumin, urinalysis, quantified proteinuria and kidney function should be performed at baseline in all patients.

HBV, Hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MPGN, membranoproliferative glomerulonephritis.

Evaluation

The evaluation for MPGN should be guided by the suspected cause, based on clinical presentation and biopsy findings. A standard workup for MPGN is presented in Box 22.1. Low serum C3 and C4 are more typical of classic pathway activation, as in immune complex–mediated glomerulonephritis. A low C3 with a normal C4 suggests abnormalities of the alternative complement pathway. These findings, along with the biopsy results (particularly IF and EM), can guide further detailed evaluation.

Infections

Workup in the evaluation of infection-related MPGN depends on the suspected pathogen (see Chapter 57). In the case of viral infection–related MPGN, tests should include viral serology and quantification of viral load. The workup for parasitic infection–related MPGN should include blood tests for malaria, urine and stool tests for schistosomiasis, and serologic tests for schistosomiasis and leishmaniasis. Blood cultures, cultures of indwelling catheter tips, imaging studies for deep-seated abscesses, and transthoracic echocardiograms for valvular vegetations should be performed in the case of suspected fungal and bacterial infections.

Autoimmune Diseases

The diagnostic tests for autoimmune diseases should follow the established criteria, such as those of the American College of Rheumatology.

Monoclonal Gammopathy

The workup should include serum protein electrophoresis, urine protein electrophoresis, serum and urine immunofixation, and serum free light chain assays. Urine free light chains have no diagnostic utility and should not be assessed. Bone marrow evaluation should be performed to rule out an underlying plasma cell dyscrasia and/or lymphoproliferative disorder. In patients in whom a clone is identified (approximately 20%–30%), the underlying clonal process is plasmacytic in 50% of patients and derives from B-cell lymphocytes in the other 50%.33 In our experience, in the absence of a circulating monoclonal protein, the probability of finding an underlying plasma cell dyscrasia is limited.28

Treatment

Therapy should be directed to treatment of the underlying condition, such as chronic infection, autoimmune disease, and malignancy (e.g., myeloma, lymphoma, CLL). Treatment of monoclonal immunoglobulin–associated MPGN is complex and depends on the type of the immunoglobulin. In patients with IgM monoclonal proteins, we suggest employing a regimen used to treat Waldenström macroglobulinemia as initial therapy: rituximab 4 doses of 375 mg/m2, weekly for 4 weeks, with an identical regimen repeated 6 months later. More intense regimens include bendamustine plus rituximab; bortezomib, dexamethasone, and rituximab; or bortezomib plus rituximab with or without dexamethasone.

For patients with non-IgM monoclonal proteins, conservative and immunosuppressive therapy with the use of corticosteroids (alone or in combination with an alkylating agent), thalidomide, and mycophenolate mofetil (MMF) have been used in a small number of patients with variable outcomes.34 A recent case series suggests that clone-directed therapy with the use of rituximab; bortezomib plus dexamethasone; or bortezomib, cyclophosphamide, and dexamethasone, similar to that used in myeloma, results in a good chance of partial or complete proteinuria remission.33 In nontransplant patients who were treated empirically with these regimens, the rate of complete or partial remission of proteinuria was 75%. These regimens are well tolerated and safe for use in kidney failure, with minimal dose adjustments needed. We typically treat patients for at least 6 months and then reassess. Some patients may also respond with disappearance of the moncolonal gammopathy after a 3- to 6-month combined course of prednisone and cyclophosphamide.

Daratumumab is an IgG1-kappa human monoclonal antibody that binds to the CD38 transmembrane glycoprotein on the surface of tumor cells and induces apoptosis. It has shown promise in the treatment of refractory multiple myeloma. In a phase II trial in patients with proliferative glomerulonephritis and monoclonal immune deposits (PGNMID), the overall response rate at 12 months was 100% (60% partial and 40% complete remission of proteinuria).35 Autologous stem cell transplantation has been reported to be successful in MGRS and light chain proximal tubulopathy, but little information is available on its use regarding monoclonal immunoglobulin–associated MPGN.36

There is no strong evidence to guide treatment in patients with “idiopathic” MPGN.37 Corticosteroids have been widely used as monotherapy and/or in combination with other immunosuppressives. In a randomized trial, 80 children with nephrotic-range proteinuria and preserved estimated glomerular filtration rate (eGFR) were assigned to either prednisone or lactose 40 mg/m2 every other day for a mean duration of 41 months.38 Prednisone therapy had a significantly lower rate of treatment failure (40% vs. 55%) but was associated with significant toxicity, particularly hypertension, and it is uncertain whether the findings (published in 1992) are applicable to contemporary practice. No randomized studies with corticosteroids have been performed in adults with idiopathic MPGN.

Cytotoxic agents have been tried, with unimpressive results and significant side effects. Calcineurin inhibitors have also been used in

TABLE 22.2

Cryoglobulin Classification and Associated Diseases

Cryoglobulin Type	Immunoglobulin Class	Associated Diseases
I. Monoclonal immunoglobulins	M > G > A > BJP	Myeloma, CLL, Waldenström macroglobulinemia
II. Mixed cryoglobulins with monoclonal immunoglobulins	M/G ⪢ G/G	Infection (hepatitis C), Sjögren syndrome, CLL, lymphoma
III. Mixed polyclonal immunoglobulins	M/G	Infection (hepatitis B/C), SLE, RA, vasculitis, neoplasia

BJP, Bence Jones protein (light chains); CLL, chronic lymphocytic leukemia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

uncontrolled studies, suggesting a modest decline of proteinuria in patients with MPGN not otherwise characterized.

Data on the use of MMF in patients with MPGN are limited.[39–41] An observational study compared five adults treated with MMF and oral prednisolone to six patients on no immunosuppressive agents.[39] At 18 months, proteinuria had declined and GFR was preserved or improved in the MMF group, compared with no change in proteinuria and a 40% decline in GFR in patients who were not treated. Whether the benefit was derived from MMF or prednisone cannot be ascertained from the study.

Our experience with rituximab (1 g on days 1 and 15) in four patients with idiopathic MPGN showed a 65% reduction in proteinuria and preserved GFR over 1 year.[42]

The KDIGO 2021 Clinical Practice Guideline on Glomerular Diseases recognized difficulties in interpreting previous information because, in many instances, historical controls were used, studies antedated the use of angiotensin II blockade, statistical significance was marginal, or the power to detect substantial differences was small.[37] More importantly, in these studies, the underlying pathogenic processes that lead to MPGN were not taken into account. It also recognizes that truly “idiopathic” MPGN is an exceptional condition in adults. As such, KDIGO 2021 only provides practice points based on very low-quality evidence, clinical experience, and expert opinion. We have taken a pragmatic approach based on our clinical experience, as follows:

- Patients with normal kidney function, no active urinary sediment, and nonnephrotic range proteinuria can be treated conservatively as outlined in Chapter 82 because the long-term outcome is relatively benign in this setting. Frequent follow-up is required initially to detect early deterioration in kidney function. If there is no disease progression, follow-up every 6 months should suffice.

✓•✓ Patients with nephrotic syndrome and preserved kidney function could be treated with a regimen similar to that used in primary (permeability factor-related) focal segmental glomerulosclerosis, such as prednisone 1 mg/kg/day (maximum dose 60–80 mg/day) for 12 to 16 weeks (see Chapter 19). If the patient responds, prednisone is gradually tapered to alternate-day therapy over 6 to 8 months. If there is less than a 30% reduction in proteinuria after 12 to 16 weeks, we recommend tapering and discontinuing the prednisone. Calcineurin inhibitors may be considered in patients who do not respond to or tolerate glucocorticoids.

✓•✓ Patients who present with impaired kidney function (eGFR < 60 mL/min/1.73m2), with or without nephrotic syndrome, but without crescents or severe tubulointerstitial fibrosis on kidney biopsy, and an active urinary sediment (arbitrarily defined as >10 red blood cells per high-power field) can also be considered for treatment with corticosteroids, as mentioned previously. For patients who cannot or do not wish to receive high-dose glucocorticoids, treatment with MMF, with or without low-dose prednisone (10 mg/day), for 6 to 12 months is a reasonable alternative. If there is no improvement in GFR, proteinuria, or hematuria after 6 to 12 months of therapy, we discontinue these agents and consider repeating a kidney biopsy to reevaluate disease activity and chronicity. If the repeat kidney biopsy shows mainly chronic damage without mesangial proliferation and/or endocapillary hypercellularity, we do not give additional immunosuppressive therapy because it is unlikely to be beneficial. If the repeat kidney biopsy shows evidence of ongoing active glomerulonephritis, rituximab (1 g on day 1 and 1 g on day 15) or cyclophosphamide 2 mg/kg/day (reduced to 1.5 mg/kg/day in patients with a serum creatinine >2.5 mg/dL or age >60 years) for 3 to 6 months could be added, realizing that the efficacy of rituximab or cyclophosphamide in these patients is unknown. Patients who do not respond to treatment with either cyclophosphamide or rituximab are considered to have resistant disease and we recommend stopping immunosuppressive therapy, continuing general supportive measures, and referring them for kidney transplantation when appropriate.

✓•✓ Patients presenting with rapidly progressive disease and crescents on biopsy can be treated as in other forms of crescentic glomerulonephritis with pulse methylprednisolone followed by oral corticosteroids and cyclophosphamide (see Chapter 26).

✓•✓ Patients who present with eGFR less than 30 mL/min/1.73m2 and severe tubulointerstitial fibrosis on kidney biopsy are unlikely to benefit from immunosuppressive therapy.

Transplantation

Recurrent MPGN after kidney transplantation is discussed in Chapter 113

CRYOGLOBULINEMIC GLOMERULONEPHRITIS

Definition

Cryoglobulins are immunoglobulins that precipitate at cold temperatures and dissolve when rewarmed. Cryoglobulins usually present in the setting of infections, autoimmune diseases, and monoclonal gammopathy, but, in rare instances, they can be idiopathic. All of the aforementioned causes can present with an MPGN pattern of injury with intraluminal deposits (immune microthrombi) suggestive of cryoglobulins.

Cryoglobulins are often divided into three types (Table 22.2). Type I cryoglobulinemia is characterized by the presence of a single monoclonal immunoglobulin, most often resulting from an underlying B-cell hematologic malignancy, typically Waldenström macroglobulinemia or multiple myeloma. In the absence of overt malignancy, the diagnosis of MGRS should be established. The cryoglobulins are usually IgM or IgG, but IgA and monoclonal free light chains also may occur.

In type II mixed cryoglobulinemia, there is a mixture of monoclonal IgM with rheumatoid factor activity directed against a polyclonal IgG. It is most commonly caused by chronic infections, generally HCV, but also HBV and HIV. It can also occur in the context of autoimmune diseases, particularly Sjögren syndrome. In patients with HCV infection, cryoglobulinemia may be the first manifestation of liver disease.6 43

In type III mixed cryoglobulinemia, the IgG and IgM are polyclonal. Type III cryoglobulinemia is most commonly seen in HCV

B

A

Fig. 22.4 Purpura in a Patient with Hepatitis C Virus–associated Cryoglobulinemia. (A) Palpable nonpruritic purpura affecting the lower extremities in a patient with hepatitis C virus infection and cryoglobulinemia. Raised purpuric lesions are present on the legs. Differential diagnosis for patients with dermatorenal syndromes includes IgA vasculitis and antineutrophil cytoplasmic antibody–associated vasculitis. (B) Purpuric lesions are present on the patient’s buttocks and thigh. Note the purpuric lesions along the superior and inferior elastic border of the undergarment line.

infection, in chronic inflammatory and autoimmune disease (e.g., SLE and Sjögren syndrome), and in lymphoproliferative malignancies. Thus, there is a significant overlap between the underlying causes of type II and III cryoglobulins.

Clinical Presentation

The syndrome of cryoglobulinemia is caused by deposition of antigenantibody complexes in capillaries and small arterioles and occasionally in small arteries.44 Most cases are associated with HCV. In the majority of patients with HCV infection, the immune complexes consist of HCV, anti-HCV IgG, and monoclonal IgM anti-IgG (with rheumatoid factor activity) (type II mixed cryoglobulinemia). Clinical presentation of mixed cryoglobulinemia includes weakness, palpable nonpruritic purpura (Fig. 22.4), symmetric arthralgias (arthritis is rare), peripheral neuropathy, and kidney involvement.45 The purpura is usually painless and mainly localized to the extremities and buttocks, similar to patients with IgA vasculitis (see Chapter 24). Other manifestations include digital necrosis (Fig. 22.5), congestive heart failure, pulmonary infiltrates, and mesenteric ischemia. The clinical syndrome and dominant symptoms may evolve over time.

On the other hand, patients with type I cryoglobulinemia are usually asymptomatic. Kidney disease occurs in approximately 20% to 60% of the patients, ranging from microscopic hematuria with lowgrade proteinuria to a full-blown nephrotic or nephritic syndrome or both. Hypertension is common and can be severe. Kidney disease is a major determinant of long-term prognosis and substantially increases mortality.

Evaluation

Laboratory data suggestive of a cryoglobulin are low C4 levels (and normal or mildly decreased C3 levels) and a positive rheumatoid factor. It is crucial that blood is drawn into collection tubes that have been prewarmed to 37°C without anticoagulants because anticoagulants can produce false-positive results due to cryofibrinogen or heparinprecipitable complexes. However, in as many as 40% of patients with type II and in occasional patients with type III mixed cryoglobulinemia, circulating cryoglobulins may not be detected. In some cases, kidney disease presents in the absence of detectable cryoglobulins or other manifestations of mixed cryoglobulinemia such as purpura or arthritis. There is a poor correlation between the clinical manifestations and the cryocrit.

Fig. 22.5 Necrosis of the fingertips in a patient with cryoglobulinemia.

On kidney biopsy, an MPGN lesion is seen in more than 80% of cases (Fig. 22.6). Light microscopy findings that point toward a cryoglobulinemic

MPGN include a greater number of macrophages than seen in other forms of proliferative glomerulonephritis and the presence of intraluminal thrombi composed of precipitated cryoglobulins. On IF, there is diffuse IgM deposition in capillary loops, and EM may show subendothelial deposits that often have a characteristic “fingerprint” pattern of cryoprecipitates. MPGN with features of cryoglobulins should prompt evaluation for infections (especially HCV),

A

B

C

D

E

F

G

H

I

Fig. 22.6 Membranoproliferative Glomerulonephritis and Cryoglobulins Associated With Sjögren Syndrome. (A–B) Light microscopy showing a membranoproliferative glomerulonephritis pattern of injury. Immunofluorescence microscopy showing bright granular staining for immunoglobulin (Ig) G (C), IgM (D), C3 (E), kappa chains (F), and lambda light chains (G). (H–I) Electron microscopy showing numerous intraluminal deposits (arrowheads in H); subendothelial deposits and double contours (double arrow in I) are also present. Black arrows point to intraluminal deposits representing cryoglobulins. (A, PAS, ×40. B, Masson trichrome stain, ×40. H and I, ×2900.)

autoimmune diseases (especially Sjögren syndrome), and monoclonal gammopathies. Features that suggest glomerulonephritis because of monoclonal immunoglobulin–associated cryoglobulins (type I cryoglobulins) include intraluminal periodic acid–Schiff (PAS) positive (hyaline-like) deposits on light microscopy, intraluminal monoclonal immunoglobulin on IF microscopy, and substructures (microtubules, fibrillary, fingerprints) on EM.

Treatment

Patients with mixed cryoglobulinemia who have mild disease (i.e., petechial rash without necrotizing lesions, mild sensory neuropathy, arthralgias) typically do not require immunosuppressive therapy, and management of such patients should focus on treating the underlying disease. Patients with a rapidly progressive, organthreatening, or life-threatening cryoglobulinemic syndrome such as rapidly progressive glomerulonephritis, severe digital ischemia, gastrointestinal vasculitis, rapidly progressive neuropathy, central nervous system vasculitis, and heart failure should be treated with immunosuppressive therapy, regardless of the cause of the mixed cryoglobulinemia.[46] This typically involves a short course of corticosteroids combined with rituximab. If rituximab is unavailable, fails to produce a response, or is not tolerated, cyclophosphamide can be used instead. In patients with life-threatening disease (e.g., acute respiratory failure with pulmonary hemorrhage); cryoglobulinemia-associated hyperviscosity syndrome; severe, refractory skin ulcers because of cutaneous vasculitis; or a high cryocrit level (i.e., ≥10%), we suggest adding plasmapheresis to immunosuppressive therapy. We typically perform daily plasma exchange for 10 to 14 sessions or three exchanges per week for 2 to 3 weeks. After disease stabilization, therapy should be directed at the underlying disease. Patients with HCV infection (without decompensated cirrhosis) and mixed cryoglobulinemia should receive antiviral therapy as per current guidelines.[47]

Patients with severe manifestations of cryoglobulinemic vasculitis associated with HCV infection and not yet treated with antiviral therapy should receive immunosuppression first, with antiviral therapy delayed for 1 to 4 months.[44] The rationale is based on the fact that immunosuppression can rapidly improve inflammation and resolve target-organ damage, although no randomized trials have evaluated immediate versus delayed timing of antiviral therapy. However, in patients with cryoglobulinemic vasculitis associated with infection with HIV or HBV, antiviral therapy should always be initiated before or concurrently with immunosuppressive therapy because these patients are at high risk for enhanced viral replication as a result of rituximab or cyclophosphamide therapy.

The specific antiviral drugs and therapy schemes depend on the HCV genotype, kidney function, prior treatment response, type of

antiviral agent used, tolerance to treatment, and clinical and laboratory response to treatment.

Patients with a lymphoproliferative disorder should receive diseasespecific therapy.

Patients treated with immunosuppressive therapy should receive opportunistic infection (i.e., Pneumocystis jirovecii) prophylaxis. The frequency of monitoring is determined by the severity of disease.

SELF-ASSESSMENT QUESTIONS

1. A 50-year-old woman is referred for sudden onset of edema and hypertension. Past medical history is unremarkable. Apart from a blood pressure of 155/95 mm Hg and 2+ edema, the physical examination is unremarkable. Serum creatinine is 1.8 mg/dL and proteinuria is 3.2 g/24 h. Urinalysis shows 50 to 100 red blood cells per high-power field, of which more than 25% are dysmorphic. C3/C4 complement levels, antineutrophil cytoplasmic antibody, antinuclear antibody, and anti-GBM are all normal or negative. A kidney biopsy is performed. Light microscopy shows an MPGN pattern of injury on immunofluorescence (IF) IgG (+++), IgM (+), IgA (–) C3 (+++), C1q (–), kappa (+++), lambda (–) chains, and EM duplication of the GBM with subendothelial deposits. The most likely diagnosis is:

A. MPGN secondary to monoclonal gammopathy
B. MPGN secondary to underlying infection
C. MPGN secondary to abnormalities in the alternative pathway of complement
D. MPGN type I (idiopathic)

2. A 65-year-old man undergoes orthotopic liver transplantation for liver failure secondary to HCV infection. The immediate posttransplantation course is uneventful. However, 1 year later he presents with recurrence of HCV infection, blood pressure of 150/90 mm Hg, proteinuria of 3 g/24 h, a rising serum creatinine up to 1.8 mg/dL, and a serum albumin of 3.9 g/dL. Urinalysis shows 40 to 50 red blood cells per high-power field, of which more than 25% are dysmorphic. C3 complement is 101 mg/dL (normal 75–115 mg/dL), C4 complement is 2 mg/dL (normal 10–40 mg/dL), and rheumatoid factor is positive. In this patient, a kidney biopsy is most likely to show:

A. Focal segmental glomerulosclerosis
B. Minimal change disease
C. Membranous nephropathy
D. Cryoglobulinemic glomerulonephritis

3. Which of the following causes of glomerulonephritis is typically associated with low serum complement C4?

A. Mixed cryoglobulinemia
B. Henoch-Schönlein purpura nephritis
C. Anti-GBM disease
D. Poststreptococcal glomerulonephritis

4. A 52-year-old woman with a long history of rheumatoid arthritis and Sjögren syndrome is evaluated for new onset of a skin rash on the lower extremities and impaired kidney function. Blood pressure is 150/90 mm Hg. Serum creatinine is 1.8 mg/dL. Urinalysis shows more than 50% red blood cells per high-power field, of which more than 25% are dysmorphic. Proteinuria is 2.8 g/24 h. C3 complement is 82 mg/dL

(normal 75–115 mg/dL), and C4 complement is less than 5 mg/dL (normal 10–40 mg/dL). Antineutrophil cytoplasmic antibody, antinuclear antibody, and anti-GBM serologic results are all negative. In this patient a kidney biopsy is most likely to show:

A. MPGN with IgA (+++), C3 (++), IgG (+), kappa (+), lambda (++).
B. MPGN with linear IgG.
C. MPGN with C3 (+++), IgG (neg), IgM (neg), IgA (neg).
D. MPGN with IgG (++), IgM (+++), IgA (+), C3 (++), kappa (++), lambda (++).

REFERENCES

1. Sethi S, Haas M, Markowitz GS, et al. Mayo clinic/renal pathology society consensus report on pathologic classification, diagnosis, and reporting of GN. J Am Soc Nephrol. 2016;27(5):1278–1287.
2. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. Semin Nephrol. 2011;31:341–348.
3. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: a new look at an old entity. N Engl J Med. 2012;366:1119–1131.
4. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011;26:414–430.
5. Rennke HG. Secondary membranoproliferative glomerulonephritis. Kidney Int. 1995;47:643–656.
6. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med. 1993;328:465–470.
7. Wörnle M, Schmid H, Banas B, et al. Novel role of toll-like receptor 3 in hepatitis C-associated glomerulonephritis. Am J Pathol. 2006;168:370–385.
8. Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. Kidney Int. 1990;37:663–676.
9. Mustonen J, Mäkelä S, Helin H, et al. Mesangiocapillary glomerulonephritis caused by Puumala hantavirus infection. Nephron. 2001;89:402–407.
10. Marini G, et al. Membranoproliferative glomerulonephritis associated with infected ventriculoatrial shunt. report of two cases recovered after removal of the shunt. Mod Probl Paediatr. 1976;18:207–210.
11. Okada M, Sato M, Ogura M, et al. Central venous catheter infectionrelated glomerulonephritis under long-term parenteral nutrition: a report of two cases. BMC Res Notes. 2016;9:196.
12. Elmaci I, Senday D, Silav G, et al. Nocardial cerebral abscess associated with mycetoma, pneumonia, and membranoproliferative glomerulonephritis. J Clin Microbiol. 2007;45:2072–2074.
13. Ram R, Sandeep P, Sridhar AV, et al. Membranoproliferative glomerulonephritis and Pott’s disease. Clin Kidney J. 2014;7:391–393.
14. Date A, Neela P, Shastry JC. Membranoproliferative glomerulonephritis in a tropical environment. Ann Trop Med Parasitol. 1983;77:279–285.
15. Sethi S, Fervenza FC, Siddiqui A, et al. Leishmaniasis-associated membranoproliferative glomerulonephritis with massive complement deposition. Kidney Int Rep. 2016;1:125–130.
16. Zand L, Fervenza FC, Nasr SH, Sethi S. Membranoproliferative glomerulonephritis associated with autoimmune diseases. J Nephrol. 2014;27:165–171.
17. Cortez MS, Sturgill BC, Bolton WK. Membranoproliferative glomerulonephritis with primary Sjögren’s syndrome. Am J Kidney Dis. 1995;25:632–636.
18. Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjögren’s syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009;4:1423–1431.
19. Anand A, Krishna GG, Sibley RK, Kambham N. Sjögren syndrome and cryoglobulinemic glomerulonephritis. Am J Kidney Dis. 2015;66:532–535.
20. Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/exostosin 2-associated membranous nephropathy. J Am Soc Nephrol. 2019;30(6):1123–1136.
21. Sethi S, Fervenza FC, Zhang Y, et al. Proliferative glomerulonephritis secondary to dysfunction of the alternative pathway of complement. Clin J Am Soc Nephrol. 2011;6:1009–1017.
22. Nasr SH, Markowitz GS, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009;20:2055–2064.
23. Leung N, Bridoux F, Colin A, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012;120:4292–4295.
24. Sethi S, Fervenza FC, Rajkumar SV. Spectrum of manifestations of monoclonal gammopathy-associated renal lesions. Curr Opin Nephrol

Hypertens. 2016;25:127–137.

25. Sethi S, Zand L, Leung N, et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. Clin J Am Soc Nephrol. 2010;5:770–782.
26. Sethi S, Rajkumar SV. Monoclonal gammopathy-associated proliferative glomerulonephritis. Mayo Clin Proc. 2013;88:1284–1293.
27. Nasr SH, Larsen CP, Sirac C, et al. Light chain only variant of proliferative
glomerulonephritis with monoclonal immunoglobulin deposits is associated with a high detection rate of the pathogenic plasma cell clone. Kidney Int. 2020;97(3):589–601.
28. Bhutani G, et al. Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. Mayo Clin Proc. 2015;90:587–596.
29. Larsen CP, Messias MC, Walker PD, et al. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. Kidney Int. 2015;88:867–873.
30. Sethi S, Hernandez LH, Alexander MP, Fervenza FC. C4d as a marker for masked immune deposits. Kidney Int. 2016;90:223–224.
31. Sethi S, Nasr SH, De Vriese AS, Fervenza FC. C4d as a diagnostic tool in proliferative GN. J Am Soc Nephrol. 2015;11:2609–2611.
32. Sethi S, Sullivan A, Smith RJ. C4 dense-deposit disease. N Engl J Med. 2014;370:784–786.
33. Gumber R, Cohen JB, Palmer MB, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Kidney Int. 2018;94(1):199–205.
34. Guiard E, Karras A, Plaiser E, et al. Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab. Clin J Am Soc Nephrol. 2011;6:1609–1616.
35. Zand L, Rajkumar V, Sethi S, Leung N, El-Ters M, Fervenza FC. Safety and efficacy of daratumumab in treatment of patients with proliferative glomerulonephritis with monoclonal immune deposits. J Am Soc Nephrol. 2021 (in press).
36. Vignon M, Javaugue MP, Alexander K, et al. Current anti-myeloma therapies in renal manifestations of monoclonal light chain-associated Fanconi syndrome: a retrospective series of 49 patients. Leukemia. 2017;31:123–129.
37. The KDIGO 2021 clinical practice guideline on glomerular diseases. Kidney Int. 2021 (in press).
38. Tarshish P, Bernstein J, Tobin JN, Edelmann Jr CM. Treatment of mesangiocapillary glomerulonephritis with alternate-day prednisone: a report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1992;6:123–130.
39. Jones G, Juszczak M, Kingdon E, et al. Treatment of idiopathic membranoproliferative glomerulonephritis with mycophenolate mofetil and steroids. Nephrol Dial Transplant. 2004;19:3160–3164.
40. Choi MJ, Eustace JA, Gimenez LF, et al. Mycophenolate mofetil treatment for primary glomerular diseases [comment]. Kidney Int. 2002;61:1098–1114.
41. Bayazit AK, Noyan A, Cengiz N, Anarat A. Mycophenolate mofetil in children with multidrug-resistant nephrotic syndrome. Clin Nephrol. 2004;61:25–29.
42. Dillon JJ, Hladunewich M, Haley WE, et al. Rituximab therapy for Type I membranoproliferative glomerulonephritis. Clin Nephrol. 2012;77:290–295.
43. Yamabe H, Johnson RJ, Gretch DR, et al. Hepatitis C virus infection and membranoproliferative glomerulonephritis in Japan. J Am Soc Nephrol. 1995;6:220–223.
44. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinaemia. Nat Rev Dis Primers. 2018;4(1):11.
45. Fervenza F, Sethi S, Kyle R, Flamm S. Clinical Manifestations and Diagnosis of the Mixed Cryoglobulinemia Syndrome (Essential Mixed

Cryoglobulinemia). UpToDate; 2020.
46. Fervenza F, Leise M, Rocatello D, Kyle R. Treatment of Mixed Cryoglobulinemia Syndrome. UpToDate; 2020.
47. Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932–954.

23

Glomerulonephritis Associated With Complement Disorders

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Glomerular diseases associated with abnormalities of the complement system include thrombotic microangiopathy (see Chapter 30) and glomerulonephritides. Activation of complement in most cases of glomerulonephritis is secondary to deposition of immune complexes. Rarely, a genetic or acquired abnormality of the complement system itself causes glomerulonephritis. Deficiencies of early components of the classic pathway of complement are associated with autoimmunity and glomerulonephritis.[1] This is most clearly seen in the very rare individuals with C1q deficiency, almost all of whom have a lupuslike illness. This is thought to be because of the failure of clearance of immunogenic apoptotic bodies and other cellular debris in the absence of normal classic pathway complement activation. The largest group of patients with complement abnormalities and glomerulonephritis (C3 glomerulopathy) exhibits abnormal control of the alternative pathway of complement activation (Box 23.1).

C3 GLOMERULOPATHY

C3 glomerulopathy encompasses glomerular disease characterized by the predominant accumulation of complement component C3 in glomeruli particularly associated with abnormal control of the alternative pathway of complement activation (Fig. 23.1).[2] Glomeruli show strong staining for C3 with much less intense or absent staining for immunoglobulins or for components of the classic pathway of complement activation, C1q and C4. C3 glomerulopathy is distinct from atypical hemolytic uremic syndrome (aHUS; see Chapter 30), which is also associated with alternative pathway activation, because in aHUS, complement activation is on the kidney endothelium and is not associated with well-defined deposits on electron microscopy (EM). On light microscopy, C3 glomerulopathy may manifest with mesangial proliferation, a membranoproliferative pattern (see Chapter 22), endocapillary proliferation, and crescents. Many cases that were previously classified morphologically as membranoproliferative glomerulonephritis (MPGN) types I, II, or III are actually cases of C3 glomerulopathy. Indeed, it appears that most cases that have previously been called MPGN type III (see Chapter 22) are examples of C3 glomerulopathy. However, monoclonal gammopathy–associated MPGN also may be misclassified as C3 glomerulopathy if the glomerular immunoglobulin deposits are masked and only become detectable after protease digestion of the histologic section (see later and Chapter 22).

On EM, C3 glomerulopathy also may have a variety of appearances. Common is dense deposit disease (DDD), which is characterized by replacement of the glomerular basement membrane (GBM) by dense bands on EM (Fig. 23.2). In some cases, the light microscopic appearance in DDD shows a membranoproliferative pattern, which explains the older term MPGN type II (see Chapter 22). However, most cases of DDD do not have MPGN morphology on light microscopy.

Cases of C3 glomerulopathy that do not manifest as DDD may show a range of appearances on EM with deposits that may be mesangial, subendothelial, or subepithelial and may be more or less well defined (Fig. 23.3). The relevance of the site of the deposits has not been defined, although it is likely, by analogy with diseases such as lupus nephritis, that capillary wall deposits are associated with more glomerular inflammation and higher levels of proteinuria. These cases of non-DDD C3 glomerulopathy have been given the collective name of C3 glomerulonephritis (C3GN).[3,4]

Etiology and Pathogenesis

C3 glomerulopathy involves dysregulation of the alternative pathway of complement (see Fig. 23.1). In health, the alternative pathway is constantly activated at a very low rate. This means there is a constant generation of activated C3 (C3b), which allows the pathway to be rapidly amplified when needed. In the presence of pathogens, C3b amplification occurs through a positive feedback loop (C3b amplification loop) that generates millions of C3b molecules within minutes. Because amplification can progress rapidly, efficient systems are needed to prevent inappropriate activation. The most important regulator of the alternative pathway is factor H (CFH). CFH has three key functions: (1) to block the formation of alternative pathway C3 convertases by binding to C3b and inhibiting interaction between C3b and factor B, (2) to promote the spontaneous dissociation of these convertases, and (3) to work together with factor I to cleave C3b to iC3b. Mice genetically engineered to lack factor H have undetectable circulating C3 because C3 is constantly consumed by the uncontrolled alternative pathway.[5]

CFH is a glycoprotein predominantly made in the liver composed of protein subunits known as short consensus repeat (SCR) domains. The activity of CFH can be modulated by a group of closely related proteins called factor H–related (CFHR) proteins.[6] There are five CFHR proteins in humans (CFHR1–5) encoded by individual genes downstream from the CFH gene. The CFHR proteins, like CFH, are composed of SCR domains and share considerable sequence similarity with CFH. This has led to genomic rearrangements (i.e., polymorphisms and mutations) within the CFH-CFHR locus, most commonly a combined deletion of the CFHR1 and CFHR3 genes. This is present in homozygosity in 5% to 20% of healthy individuals depending on ethnic origin. It is now clear that some CFHR proteins are able to compete with the binding of CFH to C3b.[7] Unlike CFH, the CFHR proteins cannot inhibit complement activation. Furthermore, the CFHR-C3b interaction prevents CFH from negatively regulating C3b production. Consequently, the CFHR-C3b interaction promotes C3b amplification, termed CFH deregulation (Fig. 23.4).

In many cases of C3 glomerulopathy, the failure of CFH to control the activation of the alternative pathway in the circulation is associated with low circulating C3 because of uncontrolled consumption.

Up to 80% of patients with DDD and up to half of patients with C3GN have low serum C3.3 Many of these patients have a C3 nephritic factor (C3Nef). C3Nefs are autoantibodies that stabilize the alternative pathway C3 convertase, preventing CFH regulation. C3Nef likely plays an etiologic role in these patients. C3Nefs can be identified in 40% to 60% of cases of C3GN and 80% to 90% of cases of DDD.3 8 However, C3Nefs also may be found in patients with immune complex–associated MPGN, lupus nephritis, and poststreptococcal glomerulonephritis and even in healthy patients. Nephritic factors that stabilize the classical pathway C3 convertase (C4Nef) or the C5 convertase (nephritic factor of the terminal pathway, or Nft) have also been detected in some patients.9 In some patients, failure of alternative pathway control is associated with autoantibodies directed against factor H that target its regulatory domain.

In other cases, genetic mutations lead to failure of alternative pathway control. These cases include patients with complete CFH deficiency,10 11 mutations in CFH that interfere with its binding to C3b,12 13 and mutations in C3 that change its structure so that it cannot be inhibited by CFH.14 In cases of C3 glomerulopathy without activation of circulating C3, it can be assumed that there is a failure to control the alternative pathway locally within the glomerulus. This might be because of a failure to control activation or inappropriate handling of the fragments of C3 generated by alternative pathway activation.

There is a familial C3 glomerulopathy (now called CFHR5 nephropathy) without systemic C3 activation. This disease is endemic in Cyprus, and the mutation is a duplication of the first 2 exons of the CFHR5 gene.15 This leads to an abnormal protein that forms multimers that are able to deregulate the activity of CFH on surfaces.7 It appears that the abnormal protein interferes with the action of CFH locally within the glomerulus and enhances alternative pathway activation.

Several other mutations and polymorphisms in complement genes have been associated with C3 glomerulopathy, but their role is uncertain. Complement mutations are only detected in a minority of patients,16 and the frequency of rare variants in complement genes was

BOX 23.1

Definitions

C3 glomerulopathy—A disease process secondary to abnormal control of complement activation, deposition, or degradation characterized by predominant glomerular C3 fragment deposition with electron-dense deposits on electron microscopy.

Dense deposit disease—A form of C3 glomerulopathy with a characteristic electron microscopy appearance of intensely osmiophilic transformation of the glomerular basement membrane.

C3 glomerulonephritis—C3 glomerulopathy without the characteristic appearances of dense deposit disease.

Glomerulonephritis with dominant C3—A morphologic term for cases of glomerulonephritis with dominant staining for C3c. Dominant is defined as C3c intensity 2 or more orders of magnitude more than any other immune reactant on a scale of 0 to 3 (including 0, trace, 1+, 2+, 3+). Many, but not all, of these will represent cases of C3 glomerulopathy.

Activation of Complement

Classical pathway

Mannose-binding lectin pathway

Alternative pathway

C1q binds to Fc portion of IgG or IgM

in an immune complex

MBL (similar structure to C1q)
binds to bacterial cell wall

Circulating autoactivated C3b
binds to activating surface

Immune complex

MBL

Bacterial polysaccharides
Injured cells
Aggregated IgA
Endotoxins

C3b

C1q

B

C4
C4 NeF

C2

Classical pathway C3
convertase C4b2b

D

Properdin
Alternative pathway C3
convertase C3bBb

C3

Classical pathway C5 convertase
C4b2b3b

C5a — chemotactic factor

C3 Nef

Properdin

C3a — anaphylatoxin
C3b — opsonins

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C3b

Alternative pathway C5 convertase
C3bBbP

C5
C6
C7
C8
C9

Nft

C5b-9
Membrane attack complex

Fig. 23.1 Mechanisms of Activation of the Complement Pathways. These activators include nephritic
factors (NeF, Nef). MBL, Mannose-binding lectin; Nft, Nephritic factor of the terminal pathway.

*

*

*

Fig. 23.3 Electron micrograph of a glomerulus in a case of C3 glomerulonephritis. There is a complex pattern of thickening of the glomerular basement membrane with intramembranous electron-dense material. Similar deposits are also seen in the mesangium (asterisks).

Fig. 23.2 Electron micrograph of a glomerulus showing typical appearances of dense deposit disease with very osmiophilic transformation of the basement membrane (arrows).

no higher in MPGN or C3G patients than in controls.[17] There appears to be an association between monoclonal gammopathy and C3 glomerulopathy, particularly in patients who are older than 50 years.[18–20] In some cases, the monoclonal immunoglobulin may act as a C3Nef, but this has only rarely been demonstrated.[21,22]

Epidemiology

DDD has been reported to have a prevalence of 2 to 3 per million population and to be primarily a disease of children and young adults. However, in a 2009 series from New York, 39% of the adult patients were older than 60 years.[23] Some, but not all, studies have shown a female DDD predominance. In a French series, the ratio of C3GN to DDD was approximately 2:1 and patients with C3GN were significantly older, with a mean age at diagnosis of 30 years.[3] In the United Kingdom and Ireland, the ratio was approximately 3:1 and the incidence of C3 glomerulopathy 1 to 2 per million population per year.[24] The apparent incidence of C3GN may increase as the entity becomes better recognized. There is no reliable information on geographic variation in incidence, with the notable exception of C3GN resulting from a specific mutation in CFHR5, apparently originating in Cyprus several hundred years ago.[15]

Clinical Manifestations

Dense Deposit Disease

At presentation, almost all patients have proteinuria, usually with hematuria. Nephrotic range proteinuria is present in two-thirds of patients[23,25] and frank nephrotic syndrome in 12% to 65% in different series. In 98 patients from North America,[26] about 20% of patients did not suspect a problem and kidney disease was detected as part of a routine examination. Many patients have initial signs and symptoms of acute nephritic syndrome. In some cases, there may be episodes of acute kidney injury that show complete clinical resolution.[27] Decreased kidney function is common at presentation, particularly in adults. Hypertension is commonly found either at presentation or in follow-up. In about half of patients, clinical onset of DDD is preceded by acute infection.

Patients with DDD may develop ocular drusen (Fig. 23.5), lipoproteinaceous deposits of complement-containing debris within the Bruch membrane beneath the retinal pigment epithelium. This pathology is similar to that in age-related macular degeneration (AMD), but, in contrast to AMD, drusen in DDD may be found as early as the second decade of life. Complete visual loss is rare, but in late disease both peripheral and central vision can be affected.[28] There is no correlation between the severity of the disease in the kidney and that in the eye. A small minority of patients with DDD have acquired partial lipodystrophy (APL), a condition with symmetric loss of adipose tissue from the face, arms, and upper portions of the trunk (see Fig. 23.5).

The overall long-term outcome in DDD is poor and 50% of the patients progress to end-stage kidney disease (ESKD) within 10 years of diagnosis; young women appear to be at especially high risk.26

C3 Glomerulonephritis

C3GN has only recently been recognized, and thus clinical manifestations are less well defined. In a French series, 27% of patients with C3GN had nephrotic syndrome, two-thirds had microhematuria, and one-third had hypertension at presentation.3 In that series, the rate of progression to ESKD was similar to that in the patients with DDD.

In CFHR5 nephropathy in Cyprus, the major clinical feature in young patients is microhematuria, which is present in 90%, and 20% of patients reported episodes of macrohematuria often associated with upper respiratory tract infection.29 Proteinuria became more common with increasing age and was seen in 80% of males and 20% of females over the age of 50 years. Impaired kidney function was more common with increasing age, particularly in men, and of 18 patients who reached ESKD, 78% were male.

C3 Activation Through the Alternative Pathway and Pathogenesis of
C3 Glomerulopathy
C3

Abnormal alternative pathway activation
in C3 glomerulopathy

Alternative pathway

Potentiate C3b amplification:

C3 activation

- C3 nephritic factor
- Gain-of-function C3 mutations

Impaired factor H function:

- Factor H deficiency

Factor H
C3b
C3b amplification

- Abnormal factor H–related proteins, e.g.,
CFHR5 nephropathy

B

Factor H–related proteins
C5

A

Fig. 23.4 C3 Activation through the Alternative Pathway and Pathogenesis of C3 Glomerulopathy. (A) Activation of C3 results in the formation of C3b and then C5 activation. C3b production is amplified through a positive feedback loop. Factor H inhibits this amplification (depicted). Some factor H–related proteins (e.g., complement factor H–related protein 5 [CFHR5]) interact with C3b and, unlike factor H, allow C3b amplification to proceed. In this way, they antagonize the actions of factor H in a process termed factor H deregulation. (B) C3 glomerulopathy is associated with abnormal (increased) activation of the alternative pathway. These include situations in which there is enhanced C3b amplification despite normal factor H function, such as in the presence of C3 nephritic factor, and where there is a defect in the ability of factor H to negatively regulate the alternative pathway. Examples include cases of factor H deficiency (extremely rare) and abnormal factor H–related proteins associated with familial C3 glomerulonephritis (e.g., CFHR5 nephropathy).

A

B

Fig. 23.5 Dense Deposit Disease. (A) Partial lipodystrophy. Note the absence of subcutaneous fat from the face. (B) Drusen bodies in the retina. (Courtesy Dr. C.D. Short, Manchester, UK.)

Laboratory Findings

Low levels of serum C3 are found in approximately 80% of patients with DDD and up to 50% of patients with C3GN. In C3GN secondary to CFHR5 nephropathy, serum C3 levels are typically normal. Serum levels of the early components of the classic pathway (C1q and C4) are usually normal. Most patients with DDD are positive for serum C3Nef, and in more than 50% of patients C3Nef persists throughout the clinical course.30 However, C3Nef is not a specific serologic marker (see earlier). C3Nef can be identified in 40% to 60% of cases of C3GN.3,8 However, methods for measuring C3Nef and the other nephritic factors are not standardized. Box 23.2 shows a list of investigations that may be helpful in C3 glomerulopathy.31,32 It is recommended that investigations in the

BOX 23.2

Serologic and Genetic Evaluation of C3 Glomerulopathy

Tests Recommended in All Patients With C3 Glomerulopathy

- Measurement of serum levels of C3 and C4
- Measurement of C3 nephritic factor
- CH50—classic pathway hemolytic assay, and AH50—alternative pathway hemolytic assay
- Measurement of factor H and factor I
- Serum paraprotein detection
- Testing for the genetic mutation of CFHR5 nephropathy
- Anti–factor H autoantibodies

Tests That Should Be Considered on a Case-by-Case Basis

- Measurement of serum factor B and C5
- Measurement of markers of C3 and C5 activation (e.g., C3d, Bb, soluble C5b9)
- Detection of autoantibodies to factor B
- Mutation testing of complement regulatory genes (e.g., CFH, CFI, CD46), activation protein genes (C3, CFB), and assessment of copy number variation across the CFH-CFHR locus

Fig. 23.6 Immunofluorescence for C3c in a case of dense deposit disease. There is widespread staining of capillary walls and focal granular mesangial staining.

second category be discussed with experts and performed in laboratories with experience in complement assays. Complement laboratories in Europe are listed on the European Complement Network website (www.ecomplement.org). Parameter selection should consider the clinical scenario. For example, in patients with C3 glomerulopathy and low serum C3 levels in the absence of C3Nef, it is important to test for anti-CFH autoantibodies. In familial cases of C3 glomerulopathy, a search for genetic mutations may be important. It is important to test for a circulating paraprotein in adult patients. C3 glomerulopathy patients who have a detectable paraprotein in the absence of an underlying malignancy are classified as having a monoclonal gammopathy of renal significance (MGRS).33

Pathology

The defining feature of C3 glomerulopathy is the presence of C3 (usually detected with an antibody to C3c) in glomeruli by immunohistology (Fig. 23.6). In most cases, C3 is seen on capillary walls and in the mesangium. In some cases, particularly in DDD, C3 also may be found on Bowman’s capsule or on tubular basement membranes.

The light microscopic appearances are quite variable. In both DDD and C3GN, membranoproliferative changes are common with increased glomerular lobulation, an increase in mesangial matrix and cells, and capillary wall thickening with double contour formation (Fig. 23.7). In patients with C3GN, 71% showed an MPGN pattern.3 Other cases may exhibit a mesangial proliferative pattern or endocapillary hypercellularity, in part as a result of influx of macrophages or neutrophils. Sometimes this endocapillary hypercellularity may affect almost all the glomeruli, giving an appearance of diffuse endocapillary proliferative glomerulonephritis similar to that typically seen with postinfectious glomerulonephritis (PIGN). Crescent formation may be sufficiently prominent to merit the designation of crescentic glomerulonephritis (>50% crescents). In DDD, the distribution of different histologic patterns was membranoproliferative (25%), mesangial proliferative (45%), crescentic (18%), and acute proliferative and exudative (12%).34

The EM appearances of C3 glomerulopathy are also variable, but in many cases the diagnosis of C3 glomerulopathy can be suspected from the EM changes. By definition, DDD shows the presence of osmiophilic dense transformation of the GBM (see Fig. 23.2), with similar

Fig. 23.7 C3 Glomerulonephritis. Light microscopy in a case of C3 glomerulonephritis. The glomerulus shows a membranoproliferative pattern of injury, with increased mesangium, capillary wall thickening, and segmental endocapillary hypercellularity (PAS stain).

features often seen in Bowman’s capsule and tubular basement membranes. These changes may be segmental within glomeruli, in some cases making it difficult to define DDD with certainty. In DDD, there are typically large electron densities in the mesangium.

In some cases of C3GN, electron-dense material expands the GBM, similar to the changes in DDD but without such marked electron density; the distinction between these cases and DDD may not be clear cut and are subjective (see Fig. 23.3).35 Other cases have more distinct subendothelial and mesangial electron-dense deposits reminiscent of those seen in immune complex MPGN. Some cases show a complex pattern of intramembranous deposits that was previously designated as a form of MPGN type III (see Fig. 23.3).

In both DDD and C3GN, subepithelial hump-shaped deposits, identical to those characteristically seen in PIGN, occur. Their significance is unclear, although they may be more common in infectious exacerbations of the disease.

In one study the presence of crescents was associated with adverse kidney outcomes.16 In that study, activity and chronicity scores (analogous to those used in lupus nephritis) also correlated with kidney disease progression.

Differential Diagnosis

The diagnosis of C3 glomerulopathy is relatively straightforward if there is isolated C3 deposition with typical deposits on EM. However, some patients have otherwise typical appearances of DDD or C3GN but also have small amounts of immunoglobulin in glomeruli, which presents a diagnostic challenge. The criterion with the best balance of sensitivity and specificity is the presence of dominant C3 staining with the intensity of C3 staining at least two orders of magnitude greater than any other immunoreactant (i.e., immunoglobulin [Ig] G, IgM, IgA, and C1q).31 36 This is referred to as glomerulonephritis with dominant C3 (see Box 23.1). Cleavage of C3c generates the C3d fragment, which remains bound within the glomerulus. Antibodies that detect C3d may be useful for diagnosing C3 glomerulopathy in biopsies where C3c deposits appear faint.37 In some cases, the initial kidney biopsy may not show C3-dominant GN, but it may appear in subsequent biopsies,36 38 39 suggesting that repeat biopsy may be useful in cases with an atypical clinical course.

Some patients with monoclonal gammopathies have glomerular immunoglobulin deposits that are not detected by standard immunofluorescence and only after tissue digestion with pronase.40 41 It is recommended that screening for monoclonal gammopathy be performed in all patients presenting with C3G.

Another problem is the distinction of C3 glomerulopathy from PIGN. PIGN may show markedly reduced serum C3, and glomeruli may stain for C3 without immunoglobulin. In some cases, the distinction from C3 glomerulonephritis may be possible only by following the patient for resolution of clinical glomerulonephritis.31 It has been suggested that PIGN could be considered a self-limiting form of C3 glomerulopathy. Some patients who have been diagnosed with atypical PIGN have C3 glomerulopathy.42 Cryoglobulinemia also should be considered in the differential diagnosis because cases may present with prominent C3 with only sparse IgG staining. Anti–Factor B autoantibodies are transiently detectable in a high proportion of children with acute PIGN.43 If validated, this may represent a means of distinguishing PIGN from C3G at presentation.

Treatment

The optimal treatment for C3 glomerulopathy remains undefined. In addition, in many studies DDD was grouped with forms of MPGN, which makes it difficult to make specific statements about DDD. Treatments that have been tried include renin angiotensin system blockade, corticosteroids and other immunosuppressants, anticoagulants, and plasma exchange.44 Several case series have found that mycophenolate mofetil (MMF) may be effective in C3 glomerulonephritis.45 46

Nephritic factors are a form of autoantibody, and patients with nephritic factors may be more likely to respond to treatment with immunosuppression than patients with genetic causes of complement dysregulation. Nevertheless, some patients with complement gene mutations still respond to treatment, and there are not yet any lab tests that can be used to select or exclude patients for treatment. A Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference31 recommended that all patients should receive optimal blood pressure control and patients with moderate disease—defined as urine protein greater than 500 mg/24 h despite supportive therapy, moderate inflammation on kidney biopsy, or recent rise in creatinine—should receive prednisone or MMF. In severe disease with proteinuria more than 2 g/24 h, severe disease on biopsy, or progressive creatinine increase, the KDIGO conference suggested the use of methylprednisolone pulse dosing and other immunosuppressants.31

In many cases of C3 glomerulopathy, the deposition of C3 in glomeruli leads to subsequent activation of C5, and there are a number of case series reporting on use of the anti-C5 antibody eculizumab to treat C3 glomerulopathy.47 48 Some, but not all, patients have shown clinical improvement, and in some there was reduction of glomerular inflammation on repeat biopsy. Patients with rapidly progressive disease and glomerular crescents may be more likely to respond to treatment.49 In the patients who underwent repeat biopsy, IgG-κ was found, consistent with binding of the monoclonal eculizumab to C5 in glomeruli.50 However, the KDIGO conference concluded, “Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease.”31 Rational treatment of C3 glomerulopathy would involve inhibition of C3 activation, and a number of drugs are in clinical trials that may achieve that and allow more targeted therapy in the future.

In patients with an underlying monoclonal gammopathy, treatment of the hematologic process with B-cell or plasma cell–directed therapies can lead to improvement of the kidney disease.51 Transplantation is a reasonable option for patients who progress to ESKD, particularly because so many of these patients are children. Disease recurrence is seen in the majority of patients, however, and recurrence of C3 glomerulopathy after transplantation is higher than recurrence of other causes of primary glomerulonephritis (see Chapter 113).52 53

SELF-ASSESSMENT QUESTIONS

1. Which of the following are not features of C3 glomerulopathy?
A. Subendothelial electron-dense deposits
B. Full house of immunoglobulins and complement on immunofluorescence
C. Subepithelial electron-dense humps
D. Mesangial C3 on immunofluorescence
E. Glomerular crescents
2. Which of the following best describes C3 nephritic factor?
A. A paraprotein
B. An autoantibody against ADAMTS13
C. An autoantibody against complement factor H
D. An abnormal factor H-related protein
E. An autoantibody against the alternative pathway C3 convertase
3. Which of the following best describes CFHR5 nephropathy?
A. C3 glomerulopathy associated with C3 nephritic factor

B. C3 glomerulopathy associated with complete absence of CFHR5
C. C3 glomerulopathy associated with intramembranous electrondense deposits
D. C3 glomerulopathy associated with heterozygous mutation of CFHR5
E. C3 glomerulopathy associated with autoantibodies against CFHR5
4. Which of the following is an evidence-based therapy for C3 glomerulopathy?
A. CFHR5 replacement
B. Alternate-day glucocorticoid treatment
C. Anti-C5 antibody therapy (eculizumab)
D. Ponticelli regimen
E. None of the above

REFERENCES

1. Ballanti E, Perricone C, Greco E, et al. Complement and autoimmunity. Immunol Res. 2013;56(2–3):477–491.
2. Fakhouri F, Fremeaux-Bacchi V, Noel LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. Nat Rev Nephrol. 2010;6(8):494–499.
3. Servais A, Noel LH, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012;82(4):454–464.
4. Sethi S, Fervenza FC, Zhang Y, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney Int. 2012;82(4):465–473.
5. Pickering MC, Cook HT, Warren J, et al. Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H. Nat Genet. 2002;31:424–428.
6. Jozsi M, Tortajada A, Uzonyi B, Goicoechea de Jorge E, Rodriguez de Cordoba S. Factor H-related proteins determine complement-activating surfaces. Trends Immunol. 2015;36(6):374–384.
7. Goicoechea de Jorge E, Caesar JJ, Malik TH, et al. Dimerization of complement factor H-related proteins modulates complement activation in vivo. Proc Natl Acad Sci U S A. 2013;110(12):4685–4690.
8. Iatropoulos P, Noris M, Mele C, et al. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. Mol Immunol. 2016;71:131–142.
9. Zhao F, Afonso S, Lindner S, et al. C3-Glomerulopathy autoantibodies mediate distinct effects on complement C3- and C5-convertases. Front Immunol. 2019;10:1030.
10. Levy M, Halbwachs-Mecarelli L, Gubler MC, et al. H deficiency in two brothers with atypical dense intramembranous deposit disease. Kidney Int. 1986;30(6):949–956.
11. Dragon-Durey MA, Fremeaux-Bacchi V, Loirat C, et al. Heterozygous and homozygous factor h deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. J Am Soc Nephrol. 2004;15(3):787–795.
12. Licht C, Heinen S, Jozsi M, et al. Deletion of Lys224 in regulatory domain 4 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II). Kidney Int. 2006;70(1):42–50.
13. Wong EK, Anderson HE, Herbert AP, et al. Characterization of a factor H mutation that perturbs the alternative pathway of complement in a family with membranoproliferative GN. J Am Soc Nephrol. 2014;25(11):2425–2433.
14. Martinez-Barricarte R, Heurich M, Valdes-Canedo F, et al. Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. J Clin Invest. 2010;120(10):3702–3712.
15. Gale DP, de Jorge EG, Cook HT, et al. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. Lancet. 2010;376(9743):794–801.
16. Bomback AS, Santoriello D, Avasare RS, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. Kidney Int. 2018;93(4):977–985.
17. Levine AP, Chan MMY, Sadeghi-Alavijeh O, et al. Large-scale wholegenome sequencing reveals the genetic architecture of primary membranoproliferative GN and C3 glomerulopathy. J Am Soc Nephrol. 2020;31(2):365–373.
18. Sethi S, Sukov WR, Zhang Y, et al. Dense deposit disease associated with monoclonal gammopathy of undetermined significance. Am J Kidney Dis. 2010;56(5):977–982.
19. Bridoux F, Desport E, Fremeaux-Bacchi V, et al. Glomerulonephritis with isolated C3 deposits and monoclonal gammopathy: a fortuitous association? Clin J Am Soc Nephrol. 2011;6(9):2165–2174.
20. Zand L, Kattah A, Fervenza FC, et al. C3 glomerulonephritis associated with monoclonal gammopathy: a case series. Am J Kidney Dis. 2013.

21. Jokiranta TS, Solomon A, Pangburn MK, Zipfel PF, Meri S. Nephritogenic lambda light chain dimer: a unique human miniautoantibody against complement factor H. J Immunol. 1999;163(8):4590–4596.

22. Meri S, Koistinen V, Miettinen A, Tornroth T, Seppala IJ. Activation of the alternative pathway of complement by monoclonal lambda light chains in membranoproliferative glomerulonephritis. J Exp Med. 1992;175(4):939–950.

23. Nasr SH, Valeri AM, Appel GB, et al. Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. Clin J Am Soc Nephrol. 2009;4(1):22–32.

24. Medjeral-Thomas NR, O’Shaughnessy MM, O’Regan JA, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol. 2014;9(1):46–53.

25. Little MA, Dupont P, Campbell E, Dorman A, Walshe JJ. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. Kidney Int. 2006;69(3):504–511.

26. Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJ. Clinical features and outcomes of 98 children and adults with dense deposit disease. Pediatr Nephrol. 2012;27(5):773–781.

27. Antoine B, Faye C. The clinical course associated with dense deposits in the kidney basement membranes. Kidney Int. 1972;1(6):420–427.

28. Savige J, Amos L, Ierino F, et al. Retinal disease in the C3 glomerulopathies and the risk of impaired vision. Ophthalmic Genet. 2016;37(4):369–376.

29. Athanasiou Y, Voskarides K, Gale DP, et al. Familial C3 glomerulopathy associated with CFHR5 mutations: clinical characteristics of 91 patients in 16 pedigrees. Clin J Am Soc Nephrol. 2011;6(6):1436–1446.

30. Schwertz R, Rother U, Anders D, Gretz N, Scharer K, Kirschfink M. Complement analysis in children with idiopathic membranoproliferative glomerulonephritis: a long-term follow-up. Pediatr Allergy Immunol. 2001;12(3):166–172.

31. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) controversies conference. Kidney Int. 2017;91(3):539–551.

32. Pickering MC, D’Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84(6):1079–1089.

33. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019;15(1):45–59.

34. Walker PD, Ferrario F, Joh K, Bonsib SM. Dense deposit disease is not a membranoproliferative glomerulonephritis. Mod Pathol. 2007;20(6):605–616.

35. Sethi S, Fervenza FC, Smith RJ, Haas M. Overlap of ultrastructural findings in C3 glomerulonephritis and dense deposit disease. Kidney Int. 2015;88(6):1449–1450.

36. Hou J, Markowitz GS, Bomback AS, et al. Toward a working definition of C3 glomerulopathy by immunofluorescence. Kidney Int. 2014;85(2):450–456.

37. Snijders MLH, van de Wall-Neecke BJ, Hesselink DA, Becker JU, Clahsenvan Groningen MC. Utility of immunohistochemistry with C3d in C3 glomerulopathy. Mod Pathol. 2020;33(3):431–439.

38. Kerns E, Rozansky D, Troxell ML. Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. Pediatr Nephrol. 2013;28(11):2227–2231.

39. Kersnik Levart T, Ferluga D, Vizjak A, Mraz J, Kojc N. Severe active C3 glomerulonephritis triggered by immune complexes and inactivated after eculizumab therapy. Diagn Pathol. 2016;11(1):94.

40. Larsen CP, Messias NC, Walker PD, et al. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. Kidney Int. 2015;88(4):867–873.

41. Cook HT. Evolving complexity of complement-related diseases: C3

glomerulopathy and atypical haemolytic uremic syndrome. Curr Opin Nephrol Hypertens. 2018;27(3):165–170.
42. Sethi S, Fervenza FC, Zhang Y, et al. Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement. Kidney Int. 2013;83(2):293–299.
43. Chauvet S, Berthaud R, Devriese M, et al. Anti-factor B antibodies and acute postinfectious GN in children. J Am Soc Nephrol. 2020;31(4):829–840.

References

44. Appel GB, Cook HT, Hageman G, et al. Membranoproliferative glomerulonephritis type II (dense deposit disease): an update. J Am Soc Nephrol. 2005;16(5):1392–1403.
45. Rabasco C, Cavero T, Roman E, et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney Int. 2015;88(5):1153–1160.
46. Caravaca-Fontan F, Diaz-Encarnacion MM, Lucientes L, et al. Mycophenolate mofetil in C3 glomerulopathy and pathogenic drivers of the disease. Clin J Am Soc Nephrol. 2020;15(9):1287–1298.
47. Bomback AS, Smith RJ, Barile GR, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol. 2012;7(5):748–756.
48. Ruggenenti P, Daina E, Gennarini A, et al. C5 Convertase blockade in membranoproliferative glomerulonephritis: a Single-Arm clinical trial. Am J Kidney Dis. 2019;74(2):224–238.

49. Le Quintrec M, Lapeyraque AL, Lionet A, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis. 2018;72(1):84–92.
50. Herlitz LC, Bomback AS, Markowitz GS, et al. Pathology after eculizumab in dense deposit disease and C3 GN. J Am Soc Nephrol. 2012;23(7):1229–1237.
51. Chauvet S, Fremeaux-Bacchi V, Petitprez F, et al. Treatment of Bcell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. Blood. 2017;129(11):1437–1447.
52. Regunathan-Shenk R, Avasare RS, Ahn W, et al. Kidney transplantation in C3 glomerulopathy: a case series. Am J Kidney Dis. 2019;73(3):316–323.
53. Ham YR, Song CH, Bae HJ, et al. Growth differentiation factor-15 as a predictor of idiopathic membranous nephropathy progression: a retrospective study. Dis Markers. 2018;2018:1463940.

24

Immunoglobulin A Nephropathy and Immunoglobulin A Vasculitis (Henoch-Schönlein Purpura)

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IgA NEPHROPATHY

Definition

Immunoglobulin A (IgA) nephropathy (IgAN) is a mesangial proliferative glomerulonephritis (GN) characterized by diffuse mesangial deposition of IgA. IgAN was first recognized in 1968 by Jean Berger when immunofluorescence (IF) techniques were introduced for the study of kidney biopsy specimens. IgAN is unique among glomerular diseases in being defined by the presence of an immune reactant rather than by any other morphologic feature on kidney biopsy, and the light microscopy changes are variable. IgAN is the most prevalent pattern of glomerular disease seen in most Western and Asian countries where kidney biopsy is widely practiced. It is likely that IgAN is not a single entity but rather a common response to various injurious mechanisms.

Etiology and Pathogenesis

Although there has been much recent progress in understanding the pathogenesis of IgAN, it is not certain that all subjects with IgAN share a single common process leading to mesangial IgA deposition. Fig. 24.1 summarizes some key elements involved in the pathogenesis of IgAN.[1]

IgA Immune System

IgA is the most abundant immunoglobulin in the body and is chiefly concerned with mucosal defense.[2] It has two subclasses, IgA1 and IgA2. Mucosal antigen challenge provokes polymeric IgA (pIgA) production by plasma cells of the mucosa-associated lymphoid tissue (MALT); the pIgA is then transported across epithelium into mucosal fluids, where it is released after coupling to secretory component as secretory IgA (sIgA). The function of circulating IgA is less clear; it is derived from bone marrow and mostly is monomeric IgA1 (mIgA1). Circulating IgA1 is cleared by the liver through hepatocyte asialoglycoprotein receptors and Kupffer cell Fcα receptors.

The regular recurrence of IgAN after kidney transplantation in patients with prior underlying IgAN implies an abnormality in the host IgA immune system (see Chapter 113). Serum IgA levels, both mIgA and pIgA, are increased in only one-third of patients with IgAN and not useful for diagnosing IgAN. However, high serum IgA itself is not sufficient to cause IgAN. High circulating levels of monoclonal IgA in myeloma or polyclonal IgA in acquired immunodeficiency syndrome (AIDS) only infrequently provoke mesangial IgA deposition and thus in IgAN, changes to the physicochemical properties of IgA, rather than the absolute amount in the circulation, probably cause mesangial deposition and glomerular injury.

has no hinge and carries no such sugars. There is good evidence that circulating IgA1 in IgAN is enriched for IgA1 O-glycoforms with reduced galactosylation of the IgA1 hinge region; these glycoforms are collectively named galactose-deficient IgA1 (gd-IgA1).[1] O-galactosylation of IgA1 has a clear genetic basis, but it is unclear whether these same genes are linked to the development of IgAN.[3] This enrichment of gd-IgA1 in the serum is because of an excess of mucosal IgA1 entering the systemic circulation, either directly from the MALT or after translocation of mucosal lymphocytes to the bone marrow. The latter is consistent with experiments in which immortalized lymphocytes from patients with IgAN continued to produce dimeric and polymeric IgA with altered galactosylation.[4]

Mesangial IgA1 in IgAN also has increased gd-IgA1.[5,6] IgA and IgG antibodies with specificity for gd-IgA1 have been identified in IgAN, promoting formation of circulating immune complexes.[7] Mesangial IgA1 may result from deposition of these circulating IgA1 immune complexes or of altered IgA1 interactions with matrix proteins and mesangial cell or monocyte Fc receptors. There also may be impaired clearance of gd-IgA1 through inhibition of its interactions with hepatic and circulating myeloid cell IgA receptors.

Increased serum gd-IgA1 is also found in the unaffected relatives of subjects with IgAN, suggesting that gd-IgA1 is necessary but not sufficient for the development of IgAN, which requires a “second hit,” such as an event that provokes induction of autoimmunity or an encounter with microbial pathogens that triggers a humoral immune response, resulting in IgA cross-reactive antibodies.

Origin of Mesangial IgA

Evidence supporting the importance of mucosal-derived IgA as a major source of mesangial IgA in IgAN includes the close association between mucosal inflammation and episodes of nephritis. In addition, mesangial IgA in IgAN is predominantly pIgA1. IgAN patients exhibit elevated serum levels of sIgA and levels of IgA antibodies specific for food antigens, mucosal vaccines, and gut-associated bacteria. Mucosal hyperresponsiveness to a variety of food antigens has been noted in patients with IgAN.1 2 Furthermore, the composition of the gut microbiome appears different in IgAN, and gut bacteria are capable of modulating IgA class switching, the amount of mucosal IgA production, and IgA1 O-galactosylation in the MALT. Genome-wide association studies have identified a number of risk alleles that are either directly associated with risk of inflammatory bowel disease, maintenance of the intestinal epithelial barrier, or response to mucosal pathogens and which converge on the intestinal immune network for IgA production.8 9

IgA Glycosylation

Role of Infection

A striking feature of IgAN is altered glycosylation of the hinge region of IgA1. IgA1 carries distinctive O-linked sugars at its hinge region; IgA2

The clinical association of visible hematuria with upper respiratory tract infection in IgAN indicates the mucosa may be a site of entry

Modifiers (genetic background, generic progression factors)

Pathogenesis of IgA Nephropathy

Increased occurrence of
IgA1 with poor galactosylation
(gd-IgA1) in the circulation

Generation of IgG or IgA antibodies
against gd-IgA1

locally in the glomerulus, leading to mesangial cell proliferation (M) and recruitment of inflammatory cells into the glomerulus (E), occasionally resulting in crescent formation (C). These mediators also cross the glomerular basement membrane (GBM) and directly influence podocyte function, altering podocyte gene expression and glomerular permeability, increasing filtration of pIgA, podocyte damage (glomerular cell crosstalk), and segmental glomerulosclerosis (S).[11] In addition to effects within the glomerulus, glomerular-derived cytokines, along with filtered pIgA, are capable of activating tubular epithelial cells (glomerulotubular crosstalk), driving tubulointerstitial inflammation and fibrosis (T) via generic biochemical pathways (see Chapter 81).

Animal Models of IgA Nephropathy

Mesangial deposition
and/or formation of IgG-IgA1 or
IgA-IgA1 immune complexes

IgA
receptors

Complement
activation

Animal IgA does not have the same characteristics as human IgA1, and some animals also have IgA clearance mechanisms distinct from those in humans. Therefore, animal models, even if they provoke mesangial IgA deposits, are not particularly informative about the mechanisms that underlie human mesangial pIgA1 deposition, although they have provided many insights into events after IgA deposits have developed.

Genetic Basis of IgA Nephropathy

Mesangial cell damage and activation
of secondary pathways

Glomerulosclerosis
Tubulointerstitial fibrosis

Fig. 24.1 Pathogenesis of Immunoglobulin A (IgA) Nephropathy. Proposed mechanisms leading to mesangial deposition of abnormally glycosylated IgA1 and mesangial injury. (Modified from Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis. 2011;58:992–1004.)

for foreign antigens or alternatively may be a site for nonspecific activation of the innate immune system that enhances kidney injury. There have been occasional reports of IgAN in association with infection, both bacterial (e.g., Campylobacter, Yersinia, Mycoplasma, Haemophilus) and viral (e.g., cytomegalovirus, adenovirus, coxsackievirus, Epstein-Barr virus). A severe form of IgAN has been reported in association with staphylococcal infection (see Chapter 57). However, no organism has been consistently implicated in typical cases of IgAN. It is likely that exposure to a variety of microbial pathogens can result in the development of IgA cross-reactive antibodies, which, in subjects with a propensity for high serum gd-IgA1 levels, results in IgA immune complex formation and mesangial IgA deposition.

Glomerular Injury After IgA Deposition

Polymeric IgA deposition in the mesangium is typically followed by mesangial proliferative GN. Co-deposition of IgG and complement are not necessary for development of GN, but when present have been associated with greater glomerular injury. Complement deposits are usually C3 without C1q. Complement activation occurs via both the mannose-binding lectin pathway and alternative pathway.

Once deposited, pIgA binds to and activates mesangial cells, leading to a cascade of molecular events that result in the histopathologic features making up the MEST-C classification (see later).[10] Importantly, each of these features independently associates with progressive disease. In brief, mesangial cell IgA binding triggers the release of proinflammatory and chemotactic mediators, which act

Urine abnormalities increase in frequency among the relatives of patients with IgAN, although IgAN is rarely found in multiple generations of the same pedigree. More than 90% of all cases of IgAN appear to be sporadic.

Large worldwide genome-wide association studies have identified genetic modulators that seem to affect the prevalence of sporadic IgAN and modulate its course.[8,9] Variations in major histocompatibility gene loci (HLA-DR, -DQ, -DP, and HLA-B) have consistently been identified. Other gene loci are less consistent and include inflammatory mediators (tumor necrosis factor and α-defensin), gene loci affecting complement factor H, innate immunity, IgA-regulating cytokines, and mucosal integrity.[8,9]

Other Modulators of the Course of IgA Nephropathy

Many cases of IgAN never come to medical attention, and among those in whom the diagnosis is obtained by kidney biopsy, only a minority develop end-stage kidney disease (ESKD). Thus, in addition to genetic factors, there must be potent further modulators of the course of IgAN, such as essential hypertension, obesity, or smoking (see Fig. 24.1; see also Natural History).

Epidemiology

IgA nephropathy is typically the most prevalent pattern of glomerular disease in countries where kidney biopsy is widely available. The incidence rate has been estimated at 2 to 10 per 100,000 person-years. The prevalence of IgAN is higher in Asian populations (45 cases per million population/year in Japan) than in Whites (31 cases per million population/year in France).[12,13] The geographic variation has been associated with the presence of particular gene alleles that protect from IgAN[8,9] (Fig. 24.2). This racial predisposition is maintained in other locations; in the United States, IgAN is less common in Blacks than in Whites of European origin. Perceived prevalence of IgAN also may be influenced by attitudes to the investigation of microhematuria. A country with an active program of routine urine testing will inevitably identify more individuals with urine abnormalities, but IgAN will be identified only if kidney biopsy is performed. Even then, the prevalence of IgAN will be underestimated; a study of kidney donors suggests that the prevalence of IgAN with mesangial proliferative changes and glomerular C3 deposits in the general population in Japan may be 1.6%.[14] This suggests that the vast majority of patients with IgAN never come to medical attention and spontaneously remit.

Geographic Variation in Genetic Risk for IgA Nephropathy

Fig. 24.2 Geographic Variation in Genetic Risk for Immunoglobulin A (IgA) Nephropathy. Genome-wide association studies indicate a geographic gradient of risk from green (low risk) to red (high risk). (From Kiryluk K, Li Y, Sanna-Cherchi S, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8:e1002765.)

Clinical Manifestations

The wide range of clinical presentations of IgAN varies in frequency with age (Fig. 24.3). No clinical pattern is pathognomonic of IgAN. In populations of White descent, IgAN is more common in males than females by a ratio of 2:1 or 3:1, whereas the ratio approaches 1:1 in most Asian populations.

Macroscopic Hematuria

In 40% to 50% of patients with IgAN, the clinical presentation is episodic macroscopic hematuria, most frequently in the second decade of life. The urine is usually brown rather than red, and clots are unusual. There may be loin pain caused by kidney capsular swelling. Hematuria usually follows intercurrent mucosal infection, typically in the upper respiratory tract (the term synpharyngitic hematuria has been used) or occasionally in the gastrointestinal (GI) tract. Hematuria is usually visible within 24 hours of the onset of the symptoms of infection, differentiating it from the 2- to 3-week delay between infection and subsequent hematuria in postinfectious (e.g., poststreptococcal) GN. The macroscopic hematuria resolves spontaneously over a few days. Microscopic hematuria persists between attacks. Most patients have only a few episodes of frank hematuria, which become less frequent and resolve over a few years or sooner. Such episodes may be associated with acute kidney injury (AKI) characterized by tubular injury that is usually reversible.

Asymptomatic Hematuria and Proteinuria

As many as 30% to 40% of cases of IgAN are identified by detection of microhematuria with or without albuminuria (usually <2 g/24 hours)

Clinical Presentations of IgA Nephropathy and IgA Vasculitis in Relation to Age

Number of cases

IgA Nephropathy

IgA vasculitis
Macroscopic hematuria
Asymptomatic urine abnormality
Nephrotic syndrome
Chronic renal impairment

10

20

30

40
50

60
70
80
Age (years)

Fig. 24.3 Age in Clinical Presentation of Immunoglobulin A Nephropathy (IgAN) and IgA Vasculitis (IgAV). IgAV is most common in childhood but may occur at any age. Macrohematuria is very uncommon after age 40 years. The importance of asymptomatic urine abnormality as the presentation of IgAN will depend on attitudes to routine urine testing and renal biopsy. It is unclear whether patients presenting late with chronic renal impairment have a disease distinct from that of those presenting younger with macrohematuria. (Data from patients presenting in Leicester, UK, 1980–1995.)

TABLE 24.1

Diseases Reported in Association With IgA Nephropathy

Disease Group

Common

Reported

Rare

Rheumatic and autoimmune disease

Ankylosing spondylitis
Rheumatoid arthritis
Reiter syndrome
Uveitis

Behçet syndrome,a Takayasu arteritis,b myasthenia gravis

Sicca syndrome

Gastrointestinal disease

Celiac disease

Ulcerative colitis

Crohn disease
Whipple disease

Hepatic disease

Alcoholic liver disease
Nonalcoholic cirrhosis
Schistosomal liver disease

Lung disease

Sarcoid

Skin disease

Dermatitis herpetiformis

Malignancy
Infection

HIV, hepatitis B (in endemic areas)

Miscellaneous

Pulmonary hemosiderosis
IgA monoclonal gammopathy

Bronchial carcinoma, renal carcinoma, laryngeal carcinoma, mycosis fungoides, Sézary syndrome

Brucellosis

Leprosy

Wiskott-Aldrich syndromec

Rare associations have been made in one or two reported cases only. In a disease as common as IgA nephropathy, it is therefore uncertain whether these are truly related.
aBehçet syndrome: systemic vasculitis typified by orogenital ulceration and chronic uveitis.
bTakayasu arteritis: systemic vasculitis involving the aorta and its major branches, most often found in young women.
cWiskott-Aldrich syndrome: X-linked disorder in which increased serum IgA is associated with the triad of recurrent pyogenic infection, eczema, and thrombocytopenia.
HIV, Human immunodeficiency virus; IgA, immunoglobulin A.

during routine urine testing among asymptomatic individuals. The number of patients identified in this way will depend on local attitudes to urine testing and on the use of kidney biopsy in patients with isolated microscopic hematuria. Most patients with IgAN are asymptomatic and would be identified only when the urine is tested. If such patients with very early or mild IgAN are identified by kidney biopsy, their 20-year prognosis for kidney survival is very good, but 5% will progress to chronic kidney disease (CKD) stages IV to V,15 stressing the need for very long-term follow-up.

Chronic Kidney Disease

Proteinuria and Nephrotic Syndrome

Mesangial IgA deposition, which does not necessarily equal IgAN, is a frequent finding in autopsy studies in chronic liver disease. Although particularly associated with alcoholic cirrhosis, mesangial IgA deposition can occur in other chronic liver diseases, including those caused by hepatitis B and schistosomiasis. It is thought to result from impaired clearance of IgA by the Kupffer cells, which express Fcα receptors, and hepatocytes, which express the asialoglycoprotein receptor. Secondary IgAN is described as a form of IgAN associated with other diseases (e.g., liver cirrhosis, human immunodeficiency virus [HIV], and inflammatory bowel disease). There are no established definitions or different histologic findings in secondary IgAN cases, so the basis for the term is questionable.17 Clinical evidence of kidney disease is more common than previously appreciated, but patients rarely develop ESKD.
A number of case reports have associated IgAN with HIV infection and AIDS. It is not clear whether the polyclonal increase in serum IgA, which is a feature of AIDS, is the predisposing factor.
There are case reports associating IgAN with many other conditions, particularly with a number of immune and inflammatory diseases (Table 24.1). Their relationship to abnormalities of the IgA immune system is not always clear, and some may represent the coincidental development of unrelated but relatively common conditions. In a Swedish population-based cohort study, it was observed that patients with IgAN had an increased risk of inflammatory bowel disease both before and after their nephropathy diagnosis; the presence of inflammatory bowel disease increased the risk of progression to ESKD.18

It is rare for proteinuria to occur without microscopic hematuria. Although nephrotic-range proteinuria may occur, in particular in the presence of uncontrolled hypertension or marked obesity, full-blown nephrotic syndrome is uncommon, occurring in only 5% of all patients with IgAN. Nephrotic syndrome may occur early in the course of the disease, with minimal glomerular change (in such cases, IgAN may coexist with minimal change disease [MCD]) or with active mesangial proliferative GN. Alternatively, it may occur as a late manifestation of advanced chronic glomerular scarring.

Acute Kidney Injury

Although AKI is uncommon in IgAN (<5% of all cases), one study reports that it may be the manifestation in up to 40% of patients older than 65 years.16 The proportion of patients who progressed to ESKD was significantly higher in those presenting with AKI than in patients presenting without AKI. AKI develops by three distinct mechanisms. There may be acute severe immune and inflammatory injury with necrotizing GN and crescent formation (crescentic IgAN); this may be the first presentation of IgAN, or it may be superimposed on established, less aggressive disease. Alternatively, AKI can occur with mild glomerular injury when heavy glomerular hematuria leads to tubule occlusion by red blood cells (RBCs). Third, especially in elderly patients, chronic IgAN will predispose to AKI from a variety of incidental kidney insults, including drug-induced acute tubulointerstitial nephritis (see Chapter 64).

Some patients already have kidney impairment and hypertension when they are first diagnosed with IgAN. These patients tend to be older, and they probably have longstanding disease that previously remained undiagnosed because the patient did not have frank hematuria or undergo routine urinalysis. Hypertension is common, as in other chronic glomerular disease; accelerated hypertension occurs in 5% of patients.

Clinical Associations With IgA Nephropathy

A

C

B

D

E

F

Fig. 24.4 Renal Pathology in IgA Nephropathy (IgAN). (A) Diffuse mesangial IgAN seen on indirect immunofluorescence with fluorescein isothiocyanate–anti-IgA (magnification ×3300). (B) Diffuse mesangial hypercellularity (M1, Oxford classification). (C) Endocapillary hypercellularity (E1). (D) Segmental sclerosis (S1). (E) Crescentic lesion. (B–E, Light microscopy with PAS reaction, ×3300.) (F) Mesangial electron-dense deposits (arrows) (electron micrograph, ×316,000). (B–D, Courtesy Professor I. Roberts. E, Courtesy Professor P. Boor.)

Pathology

Immune Deposits

Diffuse mesangial IgA is the defining hallmark of IgAN (Fig. 24.4A). C3 is co-deposited in up to 90% of cases. IgG in 40% and IgM in 40% of cases also may be found in the same distribution. IgA also may deposit along capillary loops, a pattern more common in IgA vasculitis (IgAV); in IgAN, this pattern is associated with a worse prognosis. Mesangial deposits of terminal pathway complement complex C5b-9 are commonly observed in IgAN. Evidence of classical pathway activation, such as C1q deposits, is usually lacking in kidney biopsy specimens of patients with IgAN. Properdin co-deposits with IgA and C3 in 75% to 100% of patients and factor H in 30% to 90% of patients, indicating alternative complement pathway activation. MBL co-deposits with IgA in 17% to 25% of IgAN biopsies, and glomerular and arteriolar C4d as an indicator of the lectin pathway activation has been associated with more severe kidney damage.[19] Disappearance of IgA deposits after prolonged clinical remission has been documented in both children and adults. About one-third of the patients also have deposits of sIgA in the mesangium and are characterized by more severe disease.[20]

Light Microscopy

Light microscopy changes are remarkably variable and do not correlate topographically with the IgA deposits. There can be almost normal glomerular architecture, mesangial hypercellularity that may be diffuse (see Fig. 24.4B) or segmental, or, in rare cases, focal segmental necrotizing GN with extracapillary proliferation. Typical cases are characterized by an increase in mesangial cells and mesangial matrix with normal-appearing capillary loops, although endocapillary hypercellularity can occur (see Fig. 24.4C). Focal segmental or global glomerular sclerosis indicates that the disease has been ongoing for some time (see Fig. 24.4D). In addition to glomerular changes, the preglomerular arterial vessels often exhibit wall hyalinosis and subintimal fibrosis even in patients with only mild arterial hypertension. In longstanding disease, tubulointerstitial inflammation leads to interstitial fibrosis and tubular atrophy in a pattern no different from that of other progressive glomerular diseases. On occasion, IgAN and minimal change nephrotic syndrome coincide (see Differential Diagnosis), in which case light microscopy is normal but there are mesangial IgA deposits.

Morphology helps to predict prognosis in patients with slowly progressive disease. The Oxford (MEST-C) classification of IgAN is now widely accepted.10 This classification identifies five features of prognostic value and can be easily scored on light microscopy: mesangial hypercellularity (M1 when present, M0 when absent), endocapillary hypercellularity (E1), segmental sclerosis (S1), three degrees of tubular atrophy and interstitial fibrosis (T0, T1, T2), and three degrees of cellular and/or fibrocellular crescents (C0, C1, C2). Examples of these glomerular features are shown in Fig. 24.4

Histologic patterns of injury in AKI include tubular occlusion by RBCs with acute tubular epithelial injury in AKI associated with macroscopic hematuria (Fig. 24.5) or necrotizing GN and cellular crescent formation. Such crescentic IgAN may develop on a histologic background of established chronic kidney injury caused by IgAN or may be the first presentation of IgAN. Small numbers of crescents may be seen in hypertensive patients with stable kidney function and no other pathologic evidence of severe glomerular inflammation; the term crescentic IgAN should not be used for such patients, in whom the prognosis is often favorable.

Electron Microscopy

Electron-dense deposits correspond to the mesangial (or capillary loop) IgA (see Fig. 24.4E). Typically, electron-dense deposits are confined to mesangial and paramesangial areas, although subepithelial and subendothelial deposits also can be seen. Up to one-third of patients will have some focal thinning of the GBM. On occasion, there

BOX 24.1

Differential Diagnosis of Immunoglobulin A (IgA) Nephropathy: Conditions Associated With Mesangial IgA Deposition

- IgA nephropathy
- IgA vasculitis
- Lupus nephritisa
- Alcoholic liver disease
- IgA monoclonal gammopathy
- Schistosomal nephropathy
- IgA-dominant Staphylococcus-associated glomerulonephritis (more common in diabetics)

Fig. 24.5 Acute Kidney Injury in Immunoglobulin A Nephropathy. Tubular occlusion by red blood cells. This appearance may be associated with only minor glomerular changes. (H&E, ×300.)

will be extensive GBM thinning, suggesting a coincident diagnosis of thin basement membrane nephropathy (see Chapter 48).

Differential Diagnosis

The diagnosis of IgAN or IgAV nephritis requires identification of mesangial IgA in the glomeruli. Therefore, it cannot be made without a kidney biopsy, no matter how suggestive the clinical presentation. Serum IgA is often increased, and there may be IgA in cutaneous blood vessels in IgAN and in both affected and unaffected skin in IgAV. Neither finding, however, is reliable enough to support the diagnosis without a kidney biopsy. Serum complement components are normal in most patients.

Mesangial IgA occurs in other conditions and can usually be differentiated by clinical, serologic, and histologic criteria (Box 24.1). The light microscopic features alone are not diagnostic of IgAN.

An important differential diagnosis is IgA-dominant acute postinfectious GN (APIGN), in which IgA is the dominant immunoglobulin in glomerular deposits (see Chapter 57). It usually occurs in association with staphylococcal infections. Diabetes is a key risk factor. Compared with IgAN, patients with IgA-dominant APIGN are more likely to be older and have AKI, documented staphylococcal infection, hypocomplementemia, diffuse glomerular endocapillary hypercellularity with prominent neutrophil infiltration on light microscopy, stronger IF staining for C3 than IgA, and the presence of subepithelial humps on electron microscopy (EM).21 This entity has a poor prognosis.

Hematuria

Nonglomerular causes of hematuria, particularly stones and neoplasia, must be excluded by appropriate investigations (see Chapter 63). In its most characteristic clinical setting—recurrent macroscopic hematuria coinciding with mucosal infection in a man in the second or third decade of life—the diagnosis can be strongly suspected. Such a diagnosis, however, cannot be made without a biopsy because recurrent macroscopic hematuria also occurs in other glomerular diseases (e.g., Alport syndrome and membranoproliferative GN), particularly in children and young adults. In young adults, thin basement membrane nephropathy is the most important differential diagnosis for isolated microhematuria.

Nephrotic Syndrome

Patients with IgAN occasionally develop nephrotic syndrome, which is indistinguishable from that in MCD. There is a sudden onset of nephrosis, with biopsy evidence of glomerular epithelial cell foot process effacement and a prompt complete remission of proteinuria in response to corticosteroids. Only hematuria and mesangial IgA

a Distinguishing lupus nephritis (especially International Society of Nephrology/Renal Pathology Society classes II and III) may cause difficulty. The finding of C1q deposition is useful. It indicates classical pathway involvement found in lupus nephritis but not in IgAN.

deposits persist after treatment. This pattern occurs particularly in children. These patients are usually regarded as having two separate common glomerular diseases: IgAN and MCD.

Other patients with IgAN may develop nephrotic syndrome with more structural glomerular damage and lack the response to corticosteroids. The clinical differential diagnosis includes common causes of nephrotic syndrome appropriate for the age of the patient (see Chapter 16).

Chronic Kidney Disease: Hypertension, Proteinuria, Kidney Impairment

In this context, IgAN is clinically indistinguishable from many forms of CKD. The kidney biopsy may be diagnostic by identifying mesangial IgA, even when structural damage is so advanced on light microscopy that it has the nonspecific features of ESKD.

Acute Kidney Injury

When AKI occurs in a patient known to have IgAN, kidney biopsy should be performed unless there is rapid improvement in kidney function, after at least 5 days from the onset of kidney function worsening, in response to supportive care and vigorous hydration. Kidney biopsy may be required to differentiate the tubular occlusion and acute tubular necrosis that occasionally follow heavy glomerular hematuria from crescentic IgAN or other coincidental causes of AKI (see Fig. 24.5).

Natural History

IgA Nephropathy

The overall prognosis of IgAN differs based on the clinical presentation. If diagnosed very early, only about 5% will develop CKD stages 4 to 5 after 20 years.15 In the more typical clinical presentation, where many patients already exhibit some degree of GFR decline, at 20 years later one-fourth of patients will have ESKD and a further 20% will have progressive impairment of kidney function.22 23 A Swedish study suggested that patients with IgAN died 6 years earlier than people without the disease; most deaths were from cardiovascular causes.24

Although active investigation of microhematuria will increase the size of the cohort of patients found to have IgAN, it will include more with a good prognosis,15 thus altering the perceived risk for disease progression.

Episodes of macrohematuria do not confer a worse prognosis. This may indicate that such episodes occur only early in the natural history of the disease and patients doing less well from the point of diagnosis in fact were identified at a later stage in their disease. This is also suggested by the adverse prognosis associated with older age at diagnosis.

The risk for ESKD is not uniform. As in any chronic glomerular disease, hypertension, proteinuria, and reduced glomerular filtration rate

Prognostic Markers Used to Calculate the Risk of Progressive GFR Loss in Immunoglobulin A Nephropathy

BOX 24.2

- Estimated GFR at biopsy (mL/min/1.73 m^2)
- Systolic blood pressure at biopsy (mm Hg)
- Diastolic blood pressure at biopsy (mm Hg)
- Proteinuria at biopsy (g/day)
- Age at biopsy (years)
- Race
  - White
  - Chinese
  - Japanese
  - Other
- Use of ACE Inhibitor or ARB at Time of Biopsy
  - No
  - Yes
- MEST M-Score
  - 0
  - 1
- MEST E-Score
  - 0
  - 1
- MEST S-Score
  - 0
  - 1
- MEST T-Score
  - 0
  - 1
  - 2
- Immunosuppression Use at or Before Biopsy
  - No
  - Yes

Using clinical and histologic data at biopsy users can determine a 50% decline in eGFR or kidney failure at selected time intervals. The tool is not validated for use with data obtained remotely from the time of biopsy.

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

Modified from Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. JAMA Intern Med. 2019;179:942–952.

(GFR) at presentation, as well as histologic evidence of glomerular and interstitial fibrosis, are all associated with worse prognosis (Box 24.2). Hyperuricemia, smoking, and increased body mass index are also independent risk factors for progression. However, during follow-up, only hypertension and proteinuria, in particular time-averaged proteinuria, are reliable predictors of risk for progression. Risk for progression is low when proteinuria remains below approximately 0.2 g per 24 hours with normal blood pressure.[15,22,23,25,26] Another risk predictor for kidney disease progression is persistent hematuria, whereas hematuria remission was associated with improved kidney outcomes in IgAN among patients with persistent proteinuria.[27]

If a kidney biopsy documents IgAN in patients with mild disease (i.e., those manifesting with isolated microhematuria, little or no proteinuria, normotension, and normal GFR), the 7- to 10-year prognosis is mostly good.15 25 26 However, up to 40% of patients will develop increasing proteinuria and up to 5% will lose GFR over this period, implying the need for regular follow-up in such patients. Large studies with long-term follow-up indicate a slow attrition.

Pathologic findings and clinical findings together inform prognosis.28 The MEST-C classification of IgAN identified mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy and interstitial fibrosis, as well as crescents, as adding prognostic information even when adverse clinical features (proteinuria, hypertension, GFR) are known at presentation and during follow-up.10

The International IgAN Prediction Tool (available at www.qxmd.com) includes two validated Cox survival models that predict a 50% decline in estimated GFR (eGFR) or ESKD using clinical risk factors and Oxford MEST histology scores.29

Transplantation

Recurrent IgA Nephropathy

Patients with IgA nephropathy are ideal candidates for kidney transplant because they are often relatively young and with few comorbidities. Transplant registry data show that transplant outcome is not affected for the first 10 years if IgAN is the patient’s primary kidney disease; thereafter, however, recurrent disease may lead to accelerated graft loss (see Chapter 113). Mesangial IgA deposits recur in the donor transplant kidney in up to 60% of patients with IgAN.30 They may occur within days or weeks, but the risk increases with the duration of the transplant. The deposits seem benign in the short term and are not often associated initially with light microscopy changes. In pooled series, recurrent IgAN is 30% in living related transplants versus 23% in cadaveric grafts, but this does affect graft survival only beyond 10 years after transplantation.30 Living related donation should not be discouraged. However, any urinary abnormality in a potential related donor requires thorough evaluation, including kidney biopsy if necessary. Recurrence of crescentic IgAN with rapid graft failure occurs infrequently and is generally resistant to treatment.

In a few unwitting experiments, cadaver kidneys with IgA deposits have been transplanted into recipients without IgAN. In all cases, the IgA rapidly disappeared, supporting the concept that abnormalities in IgAN lie in the IgA immune system and not in the kidney.

Treatment

Although specific early treatment intervention might influence the IgA immune system abnormalities that underlie IgAN, the mechanisms of chronic disease progression are unlikely to be unique. Therefore, studies of such patients with IgAN may provide information applicable to many forms of chronic GN for which IgAN is the paradigm.

The balance of risk to benefit for immunosuppressive therapy is often unfavorable in patients with IgAN, except in the unusual circumstance of crescentic IgAN.

Fig. 24.6 provides a treatment algorithm for IgAN that is based on the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.30a The approach distinguishes among the following31:

✓ • ✓ The “low-risk” patient, with minor urinary abnormalities, normal GFR, and normotension, who needs only sporadic follow-up for a prolonged period (>10 years)

✓ • ✓ The “intermediate-risk” patient, with significant proteinuria, hypertension, and slow reduction of GFR, who particularly benefits from comprehensive supportive care

Treatment Recommendations for IgA Nephropathy

Low risk
(isolated microhematuria ± proteinuria
<0.5 g/d, GFR normal, no hypertension)

Annual or biannual monitoring
for at least 10 years

Intermediate risk
(no nephrotic syndrome, no AKI, no RPGN course)
Proteinuria >1 g/24 h despite at least 3 months of optimized
supportive care including blood pressure management,
maximum RAS blockade, lifestyle modification, and
management of cardiovascular risk

High risk
(acute or rapid loss of GFR)

Nephrotic syndrome
or
crescentic IgAN
with RPGN course

AKI due to
macrohematuria
or other common
cause

Continue
supportive therapy

Supportive therapy

Consider enrollment in a clinical trial

eGFR <30 mL/min per 1.73 m^2

eGFR >30 mL/min per 1.73 m^2

Toxicity risk stratification
- Advanced age
- eGFR <50 mL/min per 1.73 m^2
- Metabolic syndrome, morbid obesity
- Latent infection (TB, HIV, HBV, HCV)
- Acute peptic ulceration
- Uncontrolled psychiatric illness
- Severe osteoporosis

Continue maximum
supportive care

+ Add immunosuppression
(see text)

Discuss individual risk/benefit
profile of corticosteroids

Fig. 24.6 Treatment Recommendations for Immunoglobulin A Nephropathy (IgAN). AKI, Acute kidney

injury; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RPGN, rapidly progressive glomerulonephritis; TB, tuberculosis. (Modified from Floege J, Feehally J. Treatment of IgA nephropathy and Henoch-Schonlein nephritis. Nat Rev Nephrol. 2013;9:320–327.)

✓ • ✓ The “high-risk” patient, with rapid loss of GFR, who may require more aggressive immunosuppression

Slowly Progressive IgA Nephropathy (Intermediate Prognosis)

Minimal evidence exists to suggest the events of progressive glomerular injury are unique to IgAN. Comprehensive supportive therapy following the strategies outlined in Chapter 82 therefore remains central in the therapeutic approach to patients at risk for progressive IgAN (see Fig. 24.6).

Antihypertensives and proteinuria-lowering drugs. There is compelling evidence for the benefit of lowering blood pressure (BP) in the treatment of chronic progressive glomerular disease such as IgAN. In patients with IgAN, there is also evidence that casual clinic BP readings underestimate BP load, as judged by ambulatory monitoring and echocardiographic evidence of increased left ventricular mass.[32]

Two controlled trials strongly support the use of angiotensinconverting enzyme (ACE) inhibitors in patients with IgAN as firstchoice hypotensive agents to lower BP.[33,34] In a randomized study of IgAN, achieving a mean BP of 129/70 mm Hg prevented the decrease in kidney function over 3 years seen in patients achieving mean BPs of 136/76 mm Hg.[35]

Observational studies indicate that the risk for progression in IgAN decreases significantly if proteinuria can be reduced to less than 1 g/day by any therapeutic maneuver.[23] Another compelling indication for the role of lowering proteinuria in IgAN is based on the superior effectiveness of ACE inhibitors over other antihypertensive agents.[33,34] There is no good evidence to recommend dual renin-angiotensin system (RAS) blockade with ACE inhibitors plus angiotensin receptor blockers over monotherapy with either agent alone.[36]

Fish oil. The favorable effects of omega-3 fatty acids in the form of fish oil include reductions in eicosanoid and cytokine production, changes in membrane fluidity and rheology, reduced platelet aggregability, and reduced proliferation of kidney cells in response to platelet-derived growth factors (PDGF). The evidence for a benefit of fish oil in IgAN is weak; the 2021 KDIGO guidelines no longer support its use.[30a] However, fish oil is safe except for a decrease in blood coagulability, which is not usually a practical problem, and an unpleasant taste, with flatulence, which may make compliance difficult. Some fish oil preparations contain significant amounts of cholesterol.

Dipyridamole and warfarin. Two randomized controlled trials (RCTs) with dipyridamole and warfarin showed mutually inconsistent results. There was no benefit in one and preserved kidney function in the other. Neither drug is currently recommended in IgAN patients.[30a]

Newer nonimmunosuppressant approaches. A major reduction in renal endpoints (40% GFR loss, dialysis, death) was observed in IgAN patients treated with dapagliflozin.[30b] It is likely that inhibition of sodium glucose transporter-2 (SGLT-2) will become standard of care after RAS-blockade has been optimized in highrisk patients with IgAN. Empagliflozin is currently being evaluated in IgAN as well (EMPA-Kidney trial). A Chinese RCT suggested that hydrochloroquine (100–400 mg/day depending on GFR) may be useful to reduce albuminuria, potentially related to the mild antiinflammatory actions of the drug.[37] Various other novel treatment approaches, including dual angiotensin plus endothelin receptor blockade (PROTECT trial), endothelin A receptor blockade on top of RAS blockade (ALIGN trial), and various approaches to complement inhibition (e.g., the narsoplimab ARTEMIS or iptacopan APPLAUSE trials) are currently in phase II to III testing.

Immunosuppressive Regimens

Corticosteroids. A meta-analysis and retrospective data suggest that corticosteroids are beneficial in IgAN, in particular in adults with proteinuria exceeding 3 g/day.[38,39] However, several trials have failed to demonstrate benefit from corticosteroids, and dosage was somewhat lower in two of the three negative trials versus the positive trials.[31] Several trials did not optimize supportive therapy, in particular RAS blockers, or required that such drugs be temporarily halted before the trial.[31]

The role of corticosteroid therapy has been investigated in two large prospective trials of oral corticosteroids in IgAN added to optimized supportive care (STOP-IgAN and TESTING). In the German STOP-IgAN trial, an extensive 6-month optimization of supportive measures abolished any subsequent short- or long-term benefit from high-dose corticosteroids in adult patients with IgAN with an average baseline GFR of 60 mL/min/1.73 m^2 and baseline proteinuria around 1.7 g/d.[40,41] The largely Southeast Asia–based TESTING trial on highdose corticosteroids in adults with a baseline GFR of 58 mL/min and a baseline proteinuria of approximately 2 g/day was terminated early after an excess of severe, sometimes fatal infections was noted in the corticosteroid arm.[42] The trial was continued using a 50% lower corticosteroid dosage and demonstrated a considerable yet transient benefit on kidney function, but at the expense of more serious adverse events in the steroid arm.[42a] These two trials strongly emphasize the value of comprehensively optimizing supportive measures in high-risk patients with IgAN and suggest that corticosteroids may slow loss of renal function, particularly high-risk Asian IgAN patients.

Accordingly, the 2021 KDIGO guidelines suggest that corticosteroids should be initiated in high-risk patients only if proteinuria remains greater than 1 g/day after supportive care has been optimized for 3 to 6 months and only after a thorough discussion of potential adverse events with patients.[30a] At present, no evidence supports combined intravenous (IV) and oral corticosteroid therapy over a purely oral prednisolone regimen, starting with 1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day per month or low dose at 0.4 mg/kg/day methylprednisolone with tapering over 6 months.[31,42a] KDIGO also points out that corticosteroids should be used very restrictively or be avoided in obese patients (body mass index > 30 kg/m^2) or in patients with a GFR of less than 30 to 50 mL/min/1.73 m^2, diabetes mellitus, latent infection, secondary IgAN, active peptic ulcers, or psychiatric illness.[30a]

Full-blown nephrotic syndrome may occur when MCD and IgAN coincide, in which case the nephrotic syndrome will be fully and promptly corticosteroid responsive. A trial of high-dose corticosteroid therapy analogous to that used in MCD (see Chapter 18) is therefore justified in patients with IgAN who have nephrotic syndrome associated with minimal glomerular injury.

An alternative approach to corticosteroid dosing has been evaluated. An enteric release corticosteroid (budesonide) preparation administered to patients with intermediate-risk IgAN led to a reduction in proteinuria and better preservation of kidney function in the treated patients.[43] Based on the phase III NEFIGARD trial, enteric release budesonide has now obtained a conditional approval for use in high-risk IgAN patients in some countries.

Cyclophosphamide and azathioprine. Cyclophosphamide has been used in combination with warfarin and dipyridamole in two RCTs, with inconsistent results. Both showed modest reduction in proteinuria, but only one preserved kidney function. Cyclophosphamide followed by azathioprine combined with prednisolone preserved kidney function in patients with poor prognosis, although BP control was suboptimal.44 The same regimen, however, was ineffective in the STOP-IgAN trial and led to a death from pulmonary sepsis.45 In another recent study, adding azathioprine to corticosteroids in patients with proteinuric IgAN with GFR greater than 50 mL/min/1.73 m2 had no added benefit and only increased side effects.46 Neither agent is therefore recommended by the 2021 KDIGO guidelines in patients with intermediate-risk IgAN.30a

Other immunosuppressive approaches. Mycophenolate mofetil (MMF) has been used in several RCTs in high-risk patients. Three trials in White patients failed to demonstrate a benefit, whereas studies in Chinese patients noted reduced proteinuria and preserved GFR.31,47,48 Whether ethnic differences underlie these discrepant results remains to be clarified. In another Chinese trial, 4 of 32 patients with IgAN receiving MMF plus corticosteroids died of Pneumocystis pneumonia.49 MMF is not recommended by the 2021 KDIGO guidelines in nonChinese patients with intermediate-risk IgAN.30a

Cyclosporine has been used in one RCT in IgAN.50 Patients showed a reversible decrease in proteinuria along with a decrease in creatinine clearance, suggesting the changes were a hemodynamic effect of cyclosporine rather than an immunomodulating effect.

Rituximab (two infusions of 1 g) failed to reduce levels of undergalactosylated IgA and autoantibodies against this IgA in a small openlabel trial in adult patients with high-risk IgAN and did not affect proteinuria over the course of 1 year.51

Pooled human immunoglobulin has yielded encouraging preliminary results in patients with IgAN who have an aggressive clinical course. Proteinuria was reduced, deterioration of GFR slowed, and histologic activity lessened on repeated kidney biopsies.52 No RCT is available for this approach.

Newer immunosuppressive approaches targeting B-cell activation (e.g., B-cell activating factor [BAFF] and/or a proliferation-inducing ligand [APRIL] or using BAFF/APRIL inhibitors such as atacicept) are being studied in patients with IgAN.

Rapidly Progressive IgA Nephropathy (Poor Prognosis)

In this uncommon situation of rapidly progressive kidney failure associated with crescentic IgAN (i.e., not crescentic IgAN associated with stable GFR), the risk-to-benefit ratio most strongly favors intensive immunosuppressive therapy because untreated patients will rapidly progress to ESKD. Treatment has often combined plasma exchange with prednisolone and cyclophosphamide.53 Early clinical response is favorable, as in other crescentic nephritis. Medium-term results, however, are disappointing; kidney survival at 5 years was only 30% and not different in immunosuppressed and nonimmunosuppressed patients.54

A subset of patients with circulating IgG-antineutrophil cytoplasmic antibody (ANCA) may have a more favorable response to immunosuppressive therapy similar to that seen in other ANCA-positive crescentic nephritis.55 With no RCTs of treatment, it is impossible to be certain which elements of the regimen (corticosteroids, cyclophosphamide, or plasma exchange) are mandatory.

Other Therapeutic Approaches to Progressive IgA Nephropathy

Reduction of IgA production. Tonsillectomy reduces the frequency of episodic hematuria when tonsillitis is the provoking infection. In all other patients with IgAN, tonsillectomy is not routinely recommended30a; there is no role for prophylactic antibiotics. Dietary gluten restriction, used to reduce mucosal antigen challenge, has not been shown to preserve kidney function.2

Prevention and removal of IgA deposits. The ideal treatment of patients with IgAN would remove IgA from the glomerulus and prevent further IgA deposition. This remains a remote prospect while the pathogenesis remains incompletely understood.

Transplant recurrence. There is no evidence that newer immunosuppressive agents have modified the frequency of recurrent

IgA deposits or are of value in recurrent disease. There is, however, registry evidence that transplant outcome is improved if corticosteroids are continued long term and if the immunosuppression includes MMF.56 57 In patients with established IgAN recurrence, most clinicians merely optimize supportive care. When crescentic IgAN recurs with rapidly deteriorating graft function, treatment as for primary crescentic IgAN has been used, although evidence of its success is sparse.

IgA VASCULITIS

Definition

IgAV, previously termed Henoch-Schönlein purpura, is a smallvessel vasculitis that predominantly affects children and affects the skin, joints, gut, and kidneys. It is defined by tissue deposition of IgA. Typically, there is clinical involvement in the skin, gut, and kidneys. The nephritis associated with IgAV is characterized by diffuse mesangial IgA deposition. Indeed, the kidney histologic features of IgAV are indistinguishable from those of IgAN.

Epidemiology

In children, IgAV is usually diagnosed on clinical grounds without biopsy confirmation of tissue IgA deposition. Transient urine abnormalities are common in the acute phase. However, only those with persistent urine abnormalities or with more overt kidney disease will come to kidney biopsy. Therefore, the incidence of IgAV is almost certainly underestimated, with many unidentified mild and transient cases. There is no information on geographic variations in IgAV. Despite some differences in age at onset and natural history of IgAN and IgAV,58 there is much evidence to support a close link between the two conditions. Monozygotic twins who developed IgAN and IgAV, respectively, at the same time have been described. The evolution of IgAN into IgAV in the same patient is described in both adults and children, and patients with IgAV and ESKD receiving a kidney transplant may experience recurrent disease in the form of IgAN.

Pathogenesis

Many of the abnormalities of IgA production and handling reported in IgAN are also detected in IgAV, including circulating IgA-rheumatoid factors in 55% of cases, and increased serum gd-IgA1, which is found in IgAV when there is nephritis, but it is not clear whether gd-IgA1 is also predictive of extrarenal manifestations of IgAV. No studies have investigated whether gd-IgA1 is in mesangial deposits in IgAV. There is no animal model for IgAV to facilitate studies of pathogenesis. Although infection precedes IgAV in up to 50% of cases, no evidence indicates a role for any specific antigen.

Genetics

Subjects with IgAV have been excluded from recent large-scale genome-wide association studies in IgAN, and the genetic background to IgAV has not been systematically studied.

Clinical Manifestations

Although most prevalent in the first decade of life, IgAV may occur at any age. A palpable purpuric rash, which may be recurrent, occurs on extensor surfaces (Fig. 24.7). There may be polyarthralgia (usually without joint swelling) and abdominal pain caused by gut vasculitis. This may be severe, with bloody diarrhea if intussusception develops. In practice, the diagnosis is made by clinical criteria in the great majority of children, in whom IgAV is often a self-limiting illness. In adults, clinical features include purpura, arthritis, and GI symptoms in 95%, 60%, and 50% of patients, respectively.59 Kidney involvement in adults with IgAV does not differ from that in isolated IgAN. Tissue

Fig. 24.7 Immunoglobulin A Vasculitis. The rash is a palpable purpuric vasculitis on the lower limbs spreading on extensor surfaces to the buttocks and occasionally to the upper limbs. Histology shows leukocytoclastic vasculitis with immunoglobulin A deposits in blood vessel walls.

Treatment Recommendations for Nephritis in IgA Vasculitis

BOX 24.3

Crescentic nephritis: regimen is as for crescentic lgA nephropathy (see Fig. 24.6).
All other nephritis in IgA vasculitis (including nephrotic syndrome): regimen as for IgA nephropathy (see Fig. 24.6).
Hypertension: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are agents of first choice; target blood pressure: 130/80 mm Hg if proteinuria is <1 g/24 h, 125/75 mm Hg if proteinuria is >1 g/24 h.
Transplantation: Cadaveric donor may be preferable to living-related donor in children (controversial).

confirmation of IgA deposition by kidney or skin biopsy is necessary to establish the diagnosis of IgAV.
Much kidney involvement in IgAV is transient. Urine abnormalities are noted during the acute presentation but may disappear. Of those referred to a nephrologist, asymptomatic urine abnormality is still the most frequent clinical manifestation. Nephrotic syndrome occurs in 20% to 30% of patients. AKI may develop as a result of crescentic GN.

Pathology

The kidney histopathologic findings in IgAN and IgAV nephritis may be indistinguishable (see Fig. 24.4). The predictive value of the MEST score has not been shown for IgAV with kidney involvement.

Differential Diagnosis

In children, the diagnosis of IgAV is usually made on the basis of clinical criteria; not all patients have a kidney biopsy to confirm tissue IgA deposition. In adults, the differential diagnosis is much wider and includes other forms of systemic vasculitis, requiring diagnosis by clinical, serologic, and histologic characteristics (see Chapter 26).

Natural History

The natural history for IgAV is less clear than for IgAN. Observations are restricted to patients referred for kidney biopsy, which excludes the majority of patients with minor transient kidney involvement, who have an excellent prognosis. The kidney prognosis is worse in adults than in children with IgAV. In adults, up to 40% will have CKD or

ESKD 15 years after biopsy. One series reports an increased mortality from lung and GI malignancy.59

Transplantation

IgAV can recur as isolated IgA deposits in the graft (~50% of transplants), as full-blown yet isolated IgAN, or, rarely, as a full recurrence of systemic involvement, including a rash. The clinical and pathologic characteristics of kidney recurrence are similar to those of recurrent IgAN.30 Delay of transplantation after initiation of dialysis does not reduce the risk for IgAV recurrence.

Treatment

Many patients have transient nephritis during the early phase of IgAV, which spontaneously remits and requires no treatment. No RCTs guide the treatment of IgAV. Most therapeutic studies of IgAN exclude those with IgAV, so it is unclear whether the potential treatments for IgAN have a role in IgAV.30a Commonly used treatments for IgAV are shown in Box 24.3

Rapidly Progressive Chronic Kidney Disease Caused by Crescentic Nephritis

Crescentic nephritis is more common in IgAV than in IgAN, particularly early in the course of the disease. There is little specific information on treatment in adults or children, but regimens based on those for other forms of systemic vasculitis are widely used. These include corticosteroids and cyclophosphamide, with the addition of plasma exchange or pulse methylprednisolone in some cases. However, a French RCT in adults with severe IgAV failed to detect a benefit of cyclophosphamide plus steroids over steroids alone.60

Active IgA Vasculitis Without Kidney Failure

There is little information about less aggressive IgAV. Corticosteroids alone, although often considered more effective than in IgAN, have never been shown to be beneficial for prevention or treatment of kidney involvement in IgAV, although are apparently beneficial for extrarenal manifestations.30a Promising findings with combination therapy of corticosteroids, cyclophosphamide, and antiplatelet agents have been reported in only small, nonrandomized studies.30a A nonrandomized study reported that prednisolone and azathioprine preserved kidney function and improved histologic appearances, but it relied on historical controls.61

Slowly Progressive Chronic Kidney Disease

Although the kidney histology and clinical course of slowly progressive IgAV and IgAN may be indistinguishable, patients with IgAV have not been included in studies of slowly progressive IgAN. Therefore, there is no evidence that fish oil is beneficial in IgAV. Tight BP control with ACE inhibitors or angiotensin receptor blockers (ARBs) is recommended for proteinuric IgAV as for IgAN. The 2021 KDIGO guidelines recommend a similar indication for corticosteroids in slowly progressive IgAV as in patients with intermediate-risk IgAN.30a

Transplant Recurrence

No treatment is known to reduce the risk for recurrence. There is some evidence that recurrence is more common and more likely to lead to graft loss in children receiving kidneys from living rather than deceased donors, although this is not confirmed in adults.62 63 If crescentic IgAV recurs, intensive immunosuppression may be justified as for primary disease. This, however, has not been thoroughly evaluated.

SELF-ASSESSMENT QUESTIONS

1. Based on the 2021 KDIGO guidelines, which treatment is recommended for all patients at risk for progressive loss of GFR?
A. Fish oil
B. Mycophenolate mofetil
C. Prednisolone
D. Renin angiotensin aldosterone system inhibitor
E. Tonsillectomy

2. The Oxford (MEST-C) classification includes pathologic features predictive of outcome. Which of the following is not one of the predictive features?
A. Endocapillary hypercellularity
B. Capillary vascular changes (nephrosclerosis)
C. Mesangial hypercellularity
D. Segmental glomerulosclerosis
E. Tubulointerstitial damage and fibrosis

3. Which of the following statements for IgA nephropathy is true?
A. IgAN is more common in Europe than any other part of the world.

B. Measurement of abnormally glycosylated serum IgA is a diagnostic test for IgAN.
C. The renal pathologic features can be identical to those in IgA vasculitis.
D. Acute kidney injury with macrohematuria in IgA nephropathy is almost always caused by crescentic IgAN.
E. The risk for recurrence after kidney transplantation is reduced when MMF is part of the immunosuppressive regimen.

4. In IgA vasculitis, which of the following statements is true?
A. IgA vasculitis never occurs after age 40 years.
B. There is altered glycosylation of serum IgA1.
C. Delay in transplantation reduces the risk for recurrence.
D. Cyclophosphamide is of proven benefit for slowly progressive IgA vasculitis.
E. Corticosteroids given at the onset of the rash reduce the risk for subsequent nephritis.

REFERENCES

1. Yeo SC, Cheung CK, Barratt J. New insights into the pathogenesis of IgA nephropathy. Pediatr Nephrol. 2018;33:763–777.
2. Floege J, Feehally J. The mucosa-kidney axis in IgA nephropathy. Nat Rev Nephrol. 2016;12:147–156.
3. Gale DP, Molyneux K, Wimbury D, et al. Galactosylation of IgA1 is associated with common variation in C1GALT1. J Am Soc Nephrol. 2017;28:2158–2166.
4. Suzuki H, Moldoveanu Z, Hall S, et al. IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. J Clin Invest. 2008;118:629–639.
5. Allen AC, Bailey EM, Brenchley PE, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: observations in three patients. Kidney Int. 2001;60:969–973.
6. Hiki Y, Odani H, Takahashi M, et al. Mass spectrometry proves underO-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int. 2001;59:1077–1085.
7. Suzuki H, Fan R, Zhang Z, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest. 2009;119:1668–1677.
8. Li M, Yu XQ. Genetic determinants of IgA nephropathy: eastern perspective. Semin Nephrol. 2018;38:455–460.
9. Neugut YD, Kiryluk K. Genetic determinants of iga nephropathy: western perspective. Semin Nephrol. 2018;38:443–454.
10. Trimarchi H, Barratt J, Cattran DC, et al. Oxford classification of IgA nephropathy 2016: an update from the IgA nephropathy classification working group. Kidney Int. 2017;91:1014–1021.
11. Leung JCK, Lai KN, Tang SCW. Role of mesangial-podocytic-tubular cross-talk in IgA nephropathy. Semin Nephrol. 2018;38:485–495.
12. Schena FP, Nistor I. Epidemiology of IgA nephropathy: a global perspective. Semin Nephrol. 2018;38:435–442.
13. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011;26:414–430.
14. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. Kidney Int. 2003;63:2286–2294.
15. Knoop T, Vikse BE, Mwakimonga A, Leh S, Bjorneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrol Dial Transplant. 2017;32:1841–1850.
16. Sevillano AM, Diaz M, Caravaca-Fontan F, et al. IgA nephropathy in elderly patients. Clin J Am Soc Nephrol. 2019;14:1183–1192.
17. Saha MK, Julian BA, Novak J, Rizk DV. Secondary IgA nephropathy. Kidney Int. 2018;94:674–681.
18. Rehnberg J, Symreng A, Ludvigsson JF, Emilsson L. Inflammatory bowel disease is more common in patients with IgA nephropathy and predicts progression of ESKD: a Swedish population-based cohort study. J Am Soc Nephrol. 2021;32:411–442.
19. Rizk DV, Maillard N, Julian BA, et al. The emerging role of complement proteins as a target for therapy of IgA nephropathy. Front Immunol. 2019;10:504.
20. Oortwijn BD, Eijgenraam JW, Rastaldi MP, Roos A, Daha MR, van Kooten C. The role of secretory IgA and complement in IgA nephropathy. Semin Nephrol. 2008;28:58–65.
21. Nasr SH, D’Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. Nephron Clin Pract. 2011;119:c18–c25. discussion c6.
22. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 2011;22:752–761.
23. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis R. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–3183.
24. Jarrick S, Lundberg S, Welander A, et al. Mortality in IgA nephropathy: a nationwide population-based cohort study. J Am Soc Nephrol. 2019;30:866–876.

25. Szeto CC, Lai FM, To KF, et al. The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. Am J Med. 2001;110:434–437.

26. Gutierrez E, Zamora I, Ballarin JA, et al. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol. 2012;23:1753–1760.
27. Yu GZ, Guo L, Dong JF, et al. Persistent hematuria and kidney disease progression in IgA nephropathy: a cohort study. Am J Kidney Dis. 2020;76:90–99.
28. Barbour SJ, Espino-Hernandez G, Reich HN, et al. The MEST score provides earlier risk prediction in lgA nephropathy. Kidney Int. 2016;89:167–175.
29. Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. JAMA Intern Med. 2019;179:942–952.
30. Floege J, Grone HJ. Recurrent IgA nephropathy in the renal allograft: not a benign condition. Nephrol Dial Transplant. 2013;28:1070–1073.
30a. Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int. 2021;100:S1–S276.
30b. Wheeler DC, Toto RD, Stefansson BV, et al. DAPA-CKD Trial Committees and Investigators. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. Kidney Int. 2021;100:215–224.
31. Floege J, Feehally J. Treatment of IgA nephropathy and henochschonlein nephritis. Nat Rev Nephrol. 2013;9:320–327.
32. Stefanski A, Schmidt KG, Waldherr R, Ritz E. Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. Kidney Int. 1996;50:1321–1326.
33. Praga M, Gutierrez E, Gonzalez E, Morales E, Hernandez E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. J Am Soc Nephrol. 2003;14:1578–1583.
34. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol. 2007;18:1880–1888.
35. Kanno Y, Okada H, Saruta T, Suzuki H. Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: a 3-year follow-up. Clin Nephrol. 2000;54:360–365.
36. Lennartz DP, Seikrit C, Wied S, et al. Single versus dual blockade of the renin-angiotensin system in patients with IgA nephropathy. J Nephrol. 2020;33:1231–1239.
37. Liu LJ, Yang YZ, Shi SF, et al. Effects of hydroxychloroquine on proteinuria in IgA nephropathy: a randomized controlled trial. Am J Kidney Dis. 2019;74:15–22.
38. Lv J, Xu D, Perkovic V, et al. Corticosteroid therapy in IgA nephropathy. J Am Soc Nephrol. 2012;23:1108–1116.
39. Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA nephropathy: a retrospective analysis from the valiga study. J Am Soc Nephrol. 2015;26:2248–2258.
40. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med. 2015;373:2225–2236.
41. Rauen T, Wied S, Fitzner C, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney Int. 2020;98:1044–1052.
42. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2017;318:432–442.
42a. Lv J, Wong MG, Hladunewich MA, et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2022;327:1888–1898.
43. Fellstrom BC, Barratt J, Cook H, et al. Targeted-release budesonide versus

placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017;389:2117–2127.
44. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J Am Soc Nephrol. 2002;13:142–148.
45. Rauen T, Fitzner C, Eitner F, et al. Effects of two immunosuppressive treatment protocols for IgA nephropathy. J Am Soc Nephrol. 2018;29:317–325.

References

46. Pozzi C, Andrulli S, Pani A, et al. Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. J Am Soc Nephrol. 2010;21:1783–1790.
47. Hogg RJ, Bay RC, Jennette JC, et al. Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy. Am J Kidney Dis. 2015;66:783–791.
48. Hou JH, Le WB, Chen N, et al. Mycophenolate mofetil combined with prednisone versus full-dose prednisone in IgA nephropathy with active proliferative lesions: a randomized controlled trial. Am J Kidney Dis. 2017;69:788–795.
49. Lv J, Zhang H, Cui Z, Su T, Zhang Y, Wang H. Delayed severe pneumonia in mycophenolate mofetil-treated patients with IgA nephropathy. Nephrol Dial Transplant. 2008;23:2868–2872.
50. Lai KN, Mac-Moune Lai F, Vallance-Owen J. A short-term controlled trial of cyclosporine A in IgA nephropathy. Transplant Proc. 1988;20:297–303.
51. Lafayette RA, Canetta PA, Rovin BH, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. J Am Soc Nephrol. 2017;28:1306–1313.
52. Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. High-dose immunoglobulin therapy for severe IgA nephropathy and HenochSchonlein purpura. Ann Intern Med. 1994;120:476–484.
53. Roccatello D, Ferro M, Cesano G, et al. Steroid and cyclophosphamide in IgA nephropathy. Nephrol Dial Transplant. 2000;15:833–835.
54. Lv J, Yang Y, Zhang H, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol. 2013;24:2118–2125.
55. Haas M, Jafri J, Bartosh SM, Karp SL, Adler SG, Meehan SM. ANCAassociated crescentic glomerulonephritis with mesangial IgA deposits. Am J Kidney Dis. 2000;36:709–718.

56. Clayton P, McDonald S, Chadban S. Steroids and recurrent IgA nephropathy after kidney transplantation. Am J Transplant. 2011;11: 1645–1649.
57. Von Visger JR, Gunay Y, Andreoni KA, et al. The risk of recurrent IgA nephropathy in a steroid-free protocol and other modifying immunosuppression. Clin Transplant. 2014;28:845–854.
58. Davin JC, Ten Berge IJ, Weening JJ. What is the difference between IgA nephropathy and Henoch-Schonlein purpura nephritis? Kidney Int. 2001;59:823–834.
59. Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. HenochSchonlein Purpura in adults: outcome and prognostic factors. J Am Soc Nephrol. 2002;13:1271–1278.
60. Pillebout E, Alberti C, Guillevin L, Ouslimani A, Thervet E, group C. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schonlein Purpura. Kidney Int. 2010;78:495–502.
61. Foster BJ, Bernard C, Drummond KN, Sharma AK. Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. J Pediatr. 2000;136: 370–375.
62. Hasegawa A, Kawamura T, Ito H, et al. Fate of renal grafts with recurrent Henoch-Schonlein purpura nephritis in children. Transplant Proc. 1989;21:2130–2133.
63. Meulders Q, Pirson Y, Cosyns JP, Squifflet JP, van Ypersele de Strihou C. Course of Henoch-Schonlein nephritis after renal transplantation. Report on ten patients and review of the literature. Transplantation. 1994;58: 1179–1186.

25

Anti–Glomerular Basement Membrane Disease and Goodpasture Disease

Richard G. Phelps, A. Neil Turner

The syndrome of kidney failure and lung hemorrhage was associated with the name of Ernest Goodpasture by Stanton and Tange in their description of nine cases in 1958.[1,2] All nine patients presented with lung hemorrhage and acute kidney failure and died within hours or days. These features had been prominent in the case of a young man who died during the influenza pandemic of 1919, whose postmortem findings were memorably reported by Goodpasture[1]: “The lungs gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled” (Fig. 25.1).

Several diseases are now recognized as being associated with alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN). Nevertheless, this remains a striking clinical entity with relatively few causes and few pathogenetic mechanisms. Because the first recognized mechanism was anti–glomerular basement membrane (anti-GBM) antibody formation and deposition, Goodpasture’s name is firmly associated with anti-GBM disease (Goodpasture disease), even though this is responsible for only a proportion of patients with Goodpasture syndrome of lung hemorrhage and RPGN. The terminology used in this chapter is defined in Table 25.1.

ETIOLOGY AND PATHOGENESIS

Autoimmunity to a Component of Glomerular Basement Membrane

Goodpasture disease is caused by autoimmunity to the carboxyl terminal, noncollagenous (NC1) domain of a type IV collagen chain, α3(IV) NC1, also known as the Goodpasture antigen[3,4] (Fig. 25.2). Type IV collagen is an essential constituent of all basement membranes. In most tissues, it is composed of trimers including two α1 chains and one α2 chain, but there are also four tissue-specific chains, α3 through α6.[5,6] Three of these, α3 through α5, are found in GBM and in the basement membranes of the alveolus, the cochlea, parts of the eye (including corneal basement membrane and Bruch’s membrane), the choroid plexus of the brain, and some endocrine organs.

All patients with RPGN, lung hemorrhage, and anti-GBM antibodies have antibodies to α3(IV)NC1, usually binding predominantly to a single or a very restricted set of epitopes. Some patients also have antibodies to other basement membrane constituents, including other collagen IV chains, usually in low titer.

Predisposing Factors

Both environmental and genetic factors appear to be important in etiology. There are strong associations between Goodpasture disease and human leukocyte antigen (HLA) class II alleles, including DRB1*1501 and DR4 alleles, whereas DR1 and DR7 confer strong and dominant protection.[7] Some diseases and treatments predispose, as described in the following section.

Precipitating Factors

Theories of pathogenesis include precipitating factors that alter antigen processing to generate peptides that are usually destroyed or hidden, and to which tolerance is therefore deficient,[8,9] and molecular mimicry.[10] None of these is proved. Reports of temporal and geographic clustering of cases suggest an environmental trigger but no specific infectious agent has been consistently identified, leading to speculation that autoimmunity could be triggered (or amplified) by infection in general (or the response to infection), rather than the consequence of an aberrant immune response to a particular infectious agent.[11,12] Hydrocarbon exposure has been linked to disease onset in several striking case reports, but such exposure may simply trigger lung hemorrhage in patients who already have the disease. Furthermore, exposures of this kind are very common in the modern world. Similarly, cigarette smoking may precipitate lung hemorrhage in patients who already have circulating autoantibodies, but there is no evidence for a role in causation.

In several cases, kidney trauma or inflammation has preceded the development of the disease (Box 25.1). This may alter α3(IV)NC1 turnover and metabolism qualitatively or quantitatively, providing an opportunity for self-tolerance to be broken. Qualitative changes in the basement membrane epitopes presented to T cells could be a result of overloading of the usual or recruitment of alternative processing pathways, such as extracellular processing by proteases released into inflamed glomeruli. The quantity of α3(IV)NC1 presented to T cells may be greater where there has been damage to the basement membrane, as occurs in small-vessel vasculitis (see Chapter 26). Some features suggest that an anti-GBM response may be a secondary phenomenon in some patients with vasculitis.[13,14] The association with membranous nephropathy (MN) is interesting because the thickened GBM in that disease contains increased amounts of the tissue-specific type IV collagen chains, including the Goodpasture antigen. The same could apply to a possible association with long-standing type 1 diabetes mellitus.[15]

Mechanisms of Kidney Injury

The α3(IV)NC1 autoantibodies are central in the pathogenesis of Goodpasture disease[16,17] (Fig. 25.3). Antibodies eluted from the kidneys of patients who had died of Goodpasture disease rapidly bind to the GBM and cause glomerulonephritis (GN) when they are injected into monkeys.[18] The deposited antibodies are predominantly immunoglobulin G1 (IgG1). Contributions to kidney injury mediated by such antibodies come from complement and from neutrophil and macrophage infiltration. T cells are essential for driving autoantibody production by T cell–dependent B cells, and, in experimental kidney disease, they are critical in producing glomerular crescents,[16,19] which are a usual feature of Goodpasture disease. Moreover, in mice engineered to express the human susceptibility HLA allele DRB1*1501, α3(IV)NC1-specific CD4 T cells are sufficient to transfer disease between animals.20

Agents that downregulate inflammation by inhibiting interleukin-1 (IL-1) or tumor necrosis factor (TNF), or that inhibit recruitment of inflammatory cells by blockade of adhesion molecules or chemoattractants, suppress injury in experimental models of anti-GBM disease.

Evidence in humans and in experimental animals supports the severity of kidney injury being increased by proinflammatory cytokines or by stimuli likely to elicit them, such as bacteremia.19 Crescent formation is seen in aggressive inflammatory GN, as described in Chapter 17 (see Fig. 17.7).

Lung Hemorrhage

Lung hemorrhage in Goodpasture disease (but not in small-vessel vasculitis, the other major cause of Goodpasture syndrome) occurs only if there is an additional insult to the lung, which is usually cigarette smoke. However, infection, fluid overload, toxicity from inhaled vapors or other irritants, and the systemic effects of some cytokines are also possibilities. The higher risk of kidney disease compared with lung hemorrhage may be because alveolar capillary endothelial cells more effectively block circulating immunoglobulin from reaching the underlying basement membrane. In the glomerulus, antibodies have more direct access to the GBM via the diaphragm-free fenestrations of glomerular endothelium. Other sites at which the Goodpasture antigen is found are not involved in Goodpasture disease, except possibly the choroid plexus, where the endothelium is again fenestrated, and more rarely the eye.

EPIDEMIOLOGY

Goodpasture disease is rare, with an incidence in both White and Chinese populations approaching 1 case per 1 million population per year.15 The incidence in Black populations appears to be lower. The incidence in other racial groups is uncertain. There is a slight male predominance. Lung hemorrhage is more common in younger patients. Age incidence is bimodal, with peaks in third and sixth decades.15

CLINICAL MANIFESTATIONS

Between 50% and 75% of patients present with acute symptoms of lung hemorrhage and advanced kidney failure. Symptoms are usually confined to the preceding few weeks or months, but rapid progression (during days) or much slower progression (during many months) may occur. A lack of systemic symptoms, other than those related to anemia, is typical, although an apparently minor infection often triggers the clinical presentation.

Lung Hemorrhage

Lung hemorrhage may occur with kidney disease or in isolation. Presenting symptoms may include cough and hemoptysis, but lung hemorrhage may result in marked iron-deficiency anemia and exertional dyspnea, even in the absence of hemoptysis. Examination findings may include pallor, dry inspiratory crackles, signs of consolidation, or respiratory distress. Recent lung hemorrhage typically is shown on the radiograph as central shadowing that may traverse fissures and give rise to the appearance of an air bronchogram (Fig. 25.4). However, even lung hemorrhage sufficient to reduce the hemoglobin concentration may cause only minor or transient radiographic changes, and these cannot be distinguished radiologically from other causes of alveolar shadowing, notably edema or infection. The most sensitive indicator of recent lung hemorrhage is an increased uptake of inhaled carbon monoxide (Dlco). Patients with lung hemorrhage are usually current cigarette smokers.

In apparently isolated lung disease, progressive alveolar or fibrotic disease or pulmonary hemosiderosis may be suspected, although hematuria is usually found to be present if sought. This may continue for months or, in rare cases, recurrently for years before significant kidney disease occurs.

Glomerulonephritis

Fig. 25.1 Alveolar Hemorrhage. Open lung biopsy sample in a patient with Goodpasture disease shows alveolar hemorrhage. (Courtesy Dr. E. Mary Thompson, St Mary's Hospital, London.)

Patients with GN may notice dark or red urine, but progression to oliguria is sometimes so rapid that this phase, if it occurs, is missed. In a third to half of patients, GN occurs in the absence of lung hemorrhage.

TABLE 25.1 Definition of Terms Associated With Anti-GBM Disease and Goodpasture Syndrome

Term	Definition	
Pulmonary-renal syndrome	Kidney and respiratory failure	Many causes (see Box 25.3)
Goodpasture syndrome	RPGN and alveolar hemorrhage	Several causes (see Box 25.4)
Anti-GBM disease	Disease associated with antibodies specific for (any) components of GBM	Most important are Goodpasture disease and Alport syndrome posttransplant anti-GBM disease
Goodpasture disease	Disease associated with autoantibodies specific for α3(IV)NC1 May include RPGN, lung hemorrhage, or both	Autoimmunity to α3(IV)NC1
Alport syndrome posttransplant anti-GBM disease	Glomerulonephritis associated with anti-GBM antibodies developing after kidney transplantation in patients with Alport syndrome	Immunity to foreign collagen IV chains not expressed in patients with Alport syndrome, usually α3 or α5(IV)NC1

GBM, Glomerular basement membrane; RPGN, rapidly progressive glomerulonephritis.

Pathogenesis

Type IV Collagen Structure
α2-like

α1-like

A

B

α1

α2

α3

α4

α5

α6

C

D

α3:α4:α5 network

α5:α6 network

α1:α2 network

Fig. 25.2 Type IV Collagen Structure. (A) The type IV collagen network makes a "chicken wire" structure in the glomerular basement membrane (GBM). (B) Six paired type IV collagen genes, COL4A1 to COL4A6, encode type IV collagen monomers α1 to α6. (C) These associate in two or three defined monomer types per protomer (carboxyl terminal domains of α3:α4:α5) to form three recognized networks (D). α1:α2 is present in almost all basement membranes; α3:α4:α5 is the major constituent of GBM and is a significant component of alveolar basement membrane and other locations; and α5: α6 is found in Bowman's capsule, skin, esophagus, and other locations.

Predisposing Events Associated With the Presentation of Goodpasture Disease

BOX 25.1

Possibly Induce Autoimmune Response and Disease
- Systemic small-vessel vasculitis affecting glomeruli
- Membranous nephropathy
- Lithotripsy of kidney stones
- Urinary obstruction
- Alemtuzumab therapy for multiple sclerosis

Precipitate Pulmonary Hemorrhage
- Cigarette smoke
- Hydrocarbon exposure
- Pulmonary infection
- Fluid overload

In this subgroup, because systemic symptoms are generally not prominent, presentation is often late with kidney failure.

Whatever the early pattern of disease, once significant kidney impairment has occurred, further deterioration in kidney function is usually rapid. Presentation at or shortly after acceleration of the disease process is common, and patients may demonstrate very rapid loss of kidney function and life-threatening lung hemorrhage. Urinalysis always reveals hematuria (even in apparently isolated pulmonary disease), usually modest proteinuria, and dysmorphic red blood cells (RBCs) and RBC casts on microscopy. The kidneys are generally of normal size but may be enlarged. Hematuria may be substantial or associated with loin pain in acute disease.

Fig. 25.3 Autoantibodies to Goodpasture Antigen Bound to a Normal Glomerulus. Direct immunofluorescence of normal kidney with sera from a patient with Goodpasture disease shows the antigen in a patient with lung hemorrhage and hematuria. (Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)

PATHOLOGY

Kidney biopsy is essential because it provides diagnostic and prognostic information. Typical appearances are of diffuse proliferative GN with variable degrees of necrosis, crescent formation, glomerulosclerosis, and tubular loss (Fig. 25.5). The degree of crescent formation and tubular loss correlates with kidney prognosis. Characteristically, the crescents all appear to be of similar age and cellularity. When biopsy is performed earlier in the disease, changes may be limited to focal and segmental mesangial expansion, with or without necrosis.

A

B

Fig. 25.4 Lung Hemorrhage. (A) Patient with early pulmonary hemorrhage. The chest radiograph still appears normal. (B) Radiograph taken 4 days later shows the evolution of alveolar shadowing caused by lung hemorrhage.

A

B

Fig. 25.5 Kidney Biopsy in Goodpasture Disease. (A) Glomerulus from a patient with Goodpasture disease showing a recent, mostly cellular crescent. (B) Direct immunofluorescence study showing ribbon-like linear deposition of immunoglobulin G along the glomerular basement membrane. The glomerular tuft is slightly compressed by cellular proliferation (exhibiting no immunofluorescence), forming a crescent (arrows). (Courtesy Dr. Richard Herriot, Aberdeen Royal Infirmary, UK.)

This progresses to hypercellularity and then to more general changes, including fractures of the GBM and Bowman’s capsule, neutrophils in the glomeruli, and glomerular capillary thrombosis.21

Immunohistology

In the presence of severe glomerular inflammation, linear deposition of Ig along the GBM is pathognomonic. The immunoglobulin is usually IgG, sometimes with IgA or IgM (10%–15%), but IgA alone is rarely detected. Linear deposition of C3 is detectable in about 75% of biopsies. Linear immunofluorescence (IF) with anti-immunoglobulin reagents is occasionally seen in other conditions, usually without glomerular inflammation (Box 25.2). In most such cases, the deposited immunoglobulin is less abundant than in Goodpasture disease and is either nonspecifically deposited or bound to GBM components other than type IV collagen chains.

Circulating IgG anti-GBM antibodies are almost invariably present and may be detected and quantified by use of immobilized Goodpasture antigen in an immunoassay. The titer of anti-GBM antibody at presentation correlates with the severity of nephritis, but sometimes is at a very low level despite significant disease; interpretation may require knowledge of the local laboratory’s approach to classifying assay results. Treatment and relapse are often mirrored by changes in titer.

Conditions Associated With Linear Binding of Immunoglobulin to the GBM

BOX 25.2

Specific Binding to GBM
- Goodpasture syndrome
- Alport syndrome after kidney transplantation

Nonspecific Binding to GBM
- Diabetes
- Cadaver kidneys
- Light chain disease
- Fibrillary glomerulopathy

- Systemic lupus erythematosus (possibly specific but not considered directly pathogenic)

GBM, Glomerular basement membrane.

Pathology in Other Tissues

Pathologic changes in lung tissue can be difficult to interpret because the changes, including Ig deposition, are often patchy and may be missed.

Fig. 25.6 Immunoglobulin G (IgG) Binding to Choroid Plexus. Direct immunofluorescence study showing binding of IgG to the choroid plexus of a patient who died of Goodpasture disease. (Courtesy Dr. Stephen Cashman, Imperial College, London.)

Frequently, the only findings are mild, chronic inflammation and hemosiderin-laden macrophages, which are consistent with other more common pathologic diagnoses. This makes negative bronchoscopic or open-lung biopsy findings unhelpful in excluding the diagnosis.

Other tissues in which α3(IV)NC1 is expressed are rarely available for pathologic analysis, but even if antibody is deposited in these other sites, it is rarely associated with clinical disease. A number of case reports describe neurologic syndromes, particularly seizures, that may be related to antibody deposition in the choroid plexus but may have other explanations in patients with acute kidney injury (Fig. 25.6). Other reports have described retinal detachment, in one case with antibody deposition, but again, this is rare. Placental tissue also contains the Goodpasture antigen and has been reported in a single case to act as a “sink” that binds anti-GBM antibody during pregnancy, resulting in exacerbation of GN after delivery.

DIFFERENTIAL DIAGNOSIS

Diagnosis of Goodpasture disease in patients who present with Goodpasture syndrome does not usually present difficulties once the possibility has been raised, although the urgency is often not appreciated. Direct IF on kidney tissue and assay for circulating anti-GBM antibodies are the most rapid techniques, and kidney biopsy is always indicated. Diagnosis is often delayed when patients present with subacute disease affecting the lung or the kidney in isolation. Patients with subacute lung hemorrhage may not report hemoptysis and may present with diffuse lung disease, which has many causes. Dipstick testing for hematuria is important.

Detection of Anti–Glomerular Basement Membrane Antibodies

Direct immunohistology is very sensitive for detection of anti-GBM antibody production because the GBM selectively adsorbs and concentrates low levels of circulating antibody. However, in some circumstances, GBM may also adsorb antibody nonspecifically (see Box 25.2).

Detection of anti-GBM antibodies in serum requires immunoassays based on preparations of human or animal GBM or recombinant antigen. The performance of these assays is variable. False negatives may be encountered with low titers of antibody (typically in apparently isolated pulmonary disease) and, rarely, with antibodies targeting unusual epitopes or unusual types (e.g., IgA or monoclonal

proteins). Confirmation of the specificity of anti-GBM antibodies may be obtained by Western blotting of serum onto solubilized human GBM or recombinant α3(IV)NC1, usually at a reference laboratory.

Indirect immunohistology (putting patient serum onto normal kidney sections) is too insensitive for reliable diagnostic use.

False-positive results may be encountered in sera from patients with inflammatory diseases that often exhibit increased nonspecific binding. This places greater emphasis on the purity of antigen used for antiGBM assays. False-negative results are usually encountered in patients with low titers of antibodies in association with isolated lung disease or with very early or subacute kidney disease. Low titers also may be associated with anti-GBM disease that occurs after kidney transplantation in patients with Alport syndrome (see later discussion).

In very advanced disease, linear antibody deposition may not be seen because of extensive destruction of GBM structure. Otherwise, deposited Ig remains detectable for some months after immunoassays have become negative.

Patients With Anti-GBM Antibodies and Other Diseases

Antineutrophil Cytoplasmic Antibody and Systemic SmallVessel Vasculitis

Anti-GBM antibodies are sometimes detected in patients with antineutrophil cytoplasmic antibodies (ANCAs), especially ANCAs with specificity for myeloperoxidase (see Chapter 26). Such “doublepositive” patients may have a clinical course and response to treatment more typical of vasculitis than of Goodpasture disease and have possibly developed anti-GBM antibodies secondary to vasculitic glomerular damage.[8–11] Anti-GBM titers tend to be lower in ANCA-positive anti-GBM antibody–positive patients than in patients with anti-GBM antibodies alone. Recovery of kidney function may be more likely if ANCAs are present, even if patients are dialysis dependent when treatment is started, although newer series have failed to detect the differences described in early reports.

Membranous Nephropathy

Anti-GBM antibodies are occasionally identified in patients with MN, usually coincident with an accelerated decline in kidney function and the formation of glomerular crescents.[5 15 22] About two-thirds of studies report evidence of evolution from preexisting nephrotic syndrome, and about half report that a previous kidney biopsy showed typical MN. Progression to end-stage kidney disease (ESKD) has usually been rapid, but the diagnosis has rarely been made at a stage early enough to expect intensive treatment to be successful. Three patients with Goodpasture disease later developed typical MN.

Alemtuzumab Treatment

Treatment of multiple sclerosis (MS) with alemtuzumab, a monoclonal antibody targeting CD52 on B and T cells, is associated with the development of new autoimmunity in approximately 30% of patients, including rare cases of anti-GBM disease, sometimes as late as 4 years after treatment.[23] It remains to be established whether carriage of DRB1*1501, which is overrepresented in MS, influences the risk for developing anti-GBM disease after alemtuzumab therapy.

Pulmonary-Renal Syndromes

A wide variety of conditions may cause simultaneous pulmonary and kidney disease. The term pulmonary-renal syndrome implies failure of both organs, the most common cause being fluid overload in a patient with kidney failure of any cause (Box 25.3). Then there are diseases associated with pulmonary hemorrhage and RPGN, sometimes called Goodpasture syndrome (Box 25.4).

Nonimmune Causes of Pulmonary-Renal Syndrome

BOX 25.3

With Pulmonary Edema
- Acute kidney injury with hypervolemia
- Severe cardiac failure

Infective
- Severe bacterial pneumonia (e.g., Legionella) with kidney failure
- Hantavirus infection
- Opportunistic infections in the immunocompromised patient

Other
- Acute respiratory distress syndrome with kidney failure in multiorgan failure
- Paraquat poisoning
- Renal vein/inferior vena cava thrombosis with pulmonary emboli

Causes of Lung Hemorrhage and Rapidly Progressive Glomerulonephritis

BOX 25.4

Diseases Associated With Antibodies to the GBM (20%–40% of Cases)
- Goodpasture disease (spontaneous anti-GBM disease)

Diseases Associated With Systemic Vasculitis (60%–80% of Cases)
- Granulomatosis with polyangiitis (common)
- Microscopic polyangiitis
- Systemic lupus erythematosus
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- IgA vasculitis (Henoch-Schönlein purpura)
- Henoch-Schönlein purpura
- Behçet syndrome
- Essential mixed cryoglobulinemia
- Rheumatoid vasculitis
- Drugs: Penicillamine, hydralazine, propylthiouracil

there is a much narrower window of opportunity for effective treatment than when other diseases cause the syndrome.

Although a severe exacerbation of lung disease usually coincides with deterioration of kidney function, the natural history of isolated lung disease critically depends on continued exposure to pulmonary irritants.

TREATMENT

Immunosuppressive Regimens

Before the introduction of immunosuppressive treatment, most patients died shortly after the development of renal impairment or lung hemorrhage.19 Lung hemorrhage now usually can be arrested within days. Kidney function can be protected if impairment is mild, and even severe kidney impairment can be reversed in some patients. However, dialysis-dependent patients rarely recover kidney function despite immunosuppression and should probably be immunosuppressed only if lung hemorrhage occurs.

Fig. 25.7 shows a chart recording the treatment of a patient with Goodpasture disease. Treatment recommendations for acute severe disease were devised to reduce levels of circulating pathogenic antibodies as rapidly as possible and to lessen their contribution to rapid glomerular destruction (Table 25.2). However, this regimen is almost certainly effective through a much broader range of mechanisms, including T-cell depletion. Once the disease is controlled, immunosuppression usually can be tapered off over 3 months, and subsequent relapse is uncommon. The immune response is self-limited in the absence of immunosuppression, with antibodies disappearing over 1 to 2 years. Spontaneous remissions and effectiveness of relatively brief periods of immunosuppression are in striking contrast to the more prolonged immunosuppression generally required to prevent relapse of vasculitis and suggest a greater capacity for restoration of usual tolerance to α3(IV)NC125 than to targets in vasculitis (see Chapter 26).

Response to Immunosuppressive Treatment
in a Patient with Goodpasture Disease

GBM, Glomerular basement membrane; IgA, immunoglobulin A.

NATURAL HISTORY

There is some variability in the pattern of early disease. Most patients present acutely with lung hemorrhage or advanced kidney failure and report that the illness developed over weeks or a few months. However, there are several reports of patients presenting with mild respiratory symptoms or incidental microhematuria, with disease progressing much more slowly during months or years; some have abruptly developed the full acute syndrome. Microhematuria preceded kidney failure in all the patients who developed anti-GBM disease while being monitored after alemtuzumab treatment of MS. A study of US veterans showed a similarly long delay between first appearance of antibodies and clinical presentation.24

Once RPGN has developed, kidney function is rapidly and often irretrievably lost. Progression is often much more rapid than in RPGN occurring in other contexts, such as microscopic polyangiitis, perhaps because more glomeruli are simultaneously affected. Consequently,

100
Anti-GBM antibody titer

The two classes of disease in Box 25.4 can sometimes be differentiated clinically, but serology and kidney biopsy are usually required. Kidney biopsy also provides valuable prognostic information.

Prednisolone
Cyclophosphamide
Plasma exchange × 23
Dialysis

80

9

7

60
4.5
40
2.2

20
0

Creatinine (mg/dL)

290

0
3

4
5
6
7
8
Time (months)

Fig. 25.7 Response to Immunosuppressive Treatment in Goodpasture Disease. The patient required dialysis but had no lung hemorrhage.
The good response to treatment was unusual but not unique. The kidney biopsy showed that 85% of glomeruli contained recent (mostly cellular) crescents, suggesting very acute disease, which may be indicative of a more favorable response to treatment. GBM, Glomerular basement membrane.

0

1

2

TABLE 25.2
Treatment Regimen for Acute Goodpasture Disease

Therapy	Recommendation
Prednisolone	1 mg/kg/24 hr orally. Reduce at weekly intervals to achieve one-sixth of this dose by 8 wk. For a starting daily dose of 60 mg, use weekly reductions to 45, 30, 25, 20, and 15 mg; then alternate weekly reductions to 12.5 and 10 mg. Maintain this dose to 3 months; then taper to stop by 4 months.
Cyclophosphamide	3 mg/kg/24 h orally, rounded down to the nearest 50 mg. Patients >55 years receive a reduced dose of 2.5 mg/kg. Discontinue after 3 months.
Plasma exchange	Daily exchange of 1 volume of plasma for 5% human albumin for 14 days or until the circulating antibody is suppressed. In the presence of pulmonary hemorrhage or within 48 hours of invasive procedure, 300–400 mL of fresh-frozen plasma is given at end of each treatment or according to coagulation tests.
Monitoring	Daily blood count during plasma exchange and while antibody titer remains elevated. At least twice weekly during first month, weekly thereafter. If white blood cell count decreases to <3.5 × 109/L, stop cyclophosphamide until the count recovers. Resume at lower dose if cessation has been necessary. Baseline Dlco, with further measurements as indicated. Daily coagulation tests during plasma exchange to monitor for significant depletion of clotting factors. Initially, daily checks of kidney and hepatic function and glucose.
Prophylaxis against complications of treatment	Oral antifungal lozenges or rinse; proton pump inhibitor. Cotrimoxazole prophylaxis against Pneumocystis jirovecii. Avoid nonessential lines and catheters.

Dlco, Diffusing capacity of lung for carbon monoxide.

In RPGN with no evidence of an infective cause, immunosuppressive therapy should be started immediately, sometimes before the kidney biopsy findings are available. If therapy is stopped after a few days, the patient will have incurred minimal risk (as long as pulse high-dose corticosteroids are avoided) but may have much to gain from earlier treatment.

Plasma Exchange and Immunosuppression

The regimen described in Table 25.2 dramatically improved the outlook for patients when it was introduced in the 1970s. An early randomized trial suggested some additional benefit of plasma exchange, but the interpretation was complicated by the recipient group's less severe disease at presentation.26 It showed that milder disease can be effectively treated with corticosteroids and cyclophosphamide alone, although the overall outcomes for all patients were not as good as described with more intensive regimens.26 Historical evidence suggests that treatment with corticosteroids alone, or corticosteroids with azathioprine, is less effective. Plasma exchange is of value only if it is accompanied by adjunctive immunosuppressive therapy.

Plasma exchange is likely to benefit kidney outcome by removing circulating auto-antibody so there is interest in new treatments that are more specific or more potent in their capacity to remove autoantibody. More specific is immunoadsorption to protein A, which also lowers anti-GBM antibodies rapidly and does not deplete complement

components or clotting factors: A few reports suggest that it is as effective as plasma exchange. More effective is treatment with IdeS, a bacterial IgGase, which has been shown to rapidly and profoundly deplete circulating IgG anti-GBM autoantibody in patients with refractory anti-GBM disease.27 The place of IdeS in therapy is yet to be worked out, but on current understanding of the immunopathogenesis of anti-GBM disease, it could well replace plasma exchange offering more rapid, more complete, and more selective depletion of circulating antiGBM IgG and possibly reducing the deleterious effects of autoantibody that is already bound to the GBM. 28

Information is lacking on the effectiveness of newer immunosuppressive agents such as mycophenolate mofetil (MMF) or anti–B cell antibodies, which tend to have only a slow effect on antibody production but may affect antigen presentation. Therefore, it is difficult to justify their use over proven therapy in the acute phase of this often rapidly progressive disease, but there may be a role in particular circumstances. Rituximab has anecdotally led to reductions in antibody titer in patients with autoimmune responses persisting or relapsing after usual therapy.29

Lung hemorrhage occurring alone tends to be relapsing and remitting, so there have been many reports of treatments (e.g., bilateral nephrectomy) that may help. Pulse methylprednisolone has been advocated, but high doses of corticosteroids fail to alter the underlying pathogenetic immune response and put the patient at increased risk for infectious and other complications. We recommend treating seriously ill patients with moderate doses of corticosteroids plus plasma exchange and cyclophosphamide. In contrast to advanced kidney failure, in which treatment is unlikely to lead to recovery of kidney function, even severe lung hemorrhage is likely to respond to treatment with full or almost full recovery of lung function.

In other acute severe diseases, daily administration of cyclophosphamide often has been superseded by pulse administration. We still prefer to use daily oral administration because it is known to work and requires only 3 months of therapy. Patients unable to take the drug orally can be given daily intravenous therapy at the usual oral dose. Dose does not need to be reduced in severe kidney failure, provided the white blood cell (WBC) count is monitored closely, but reductions for older patients are important (see Table 25.2) and close monitoring of leukocyte counts is imperative in all patients. If pulsed therapy were chosen, the CYCLOPS (Randomised Trial of Daily Oral Versus Pulse Cyclophosphamide as Therapy for ANCA-Associated Systemic Vasculitis) regimen would be a reasonable, if untested, option (see Chapter 26).

Results from all series show that recovery of kidney function is unlikely if, at initiation of treatment, the patient is oliguric, has a very high proportion of glomeruli with circumferential crescents, or has a serum creatinine level greater than 5.5 to 6.5 mg/dL (~500–600 µmol/L).30 This is a notably different experience from that encountered in systemic vasculitis or idiopathic RPGN (see Chapter 26), in which kidney disease of apparently similar severity (using histology and serum creatinine) can be salvaged by similar treatment protocols.31 This has led to the suggestion that immunosuppressive treatment should be withheld from patients with only slight chance of recovery (Table 25.3).

Supportive Treatment

The most likely cause of death in the first few days is respiratory failure caused by lung hemorrhage. Lung hemorrhage may be precipitated or exacerbated by the following:

✓ • ✓ Fluid overload
✓ • ✓ Smoking and other pulmonary irritants, possibly including high inspired oxygen concentration (Fio2)
✓ • ✓ Local or distant infection

TABLE 25.3 Factors to Consider in Aggressive Treatment of Goodpasture Disease

	Factors Favoring	Factors Against
Pulmonary hemorrhage	Present	Absent
Oliguria	Absent	Present
Creatinine	<5.5 mg/dL (~500 µmol/L)	>5.5–6.5 mg/dL (~500–600 µmol/L) and ANCA negative
Other factors	Creatinine >5.5–6.5 mg/dL (~500–600 µmol/L) but rapid and recent progression ANCA positive Glomerular damage less severe than expected Crescents recent, nonfibrous Early kidney transplantation desired	Severe damage on kidney biopsy No desire for early kidney transplantation
Associated disease	Absent	

Monitoring of anti-GBM titers during, and particularly 24 hours after, the last planned plasma exchange treatment is useful for confirming effective suppression of autoantibodies. They should be undetectable within 8 weeks, but even without treatment, autoantibodies generally become undetectable by an average of 14 months.

Duration of Treatment and Relapses

Corticosteroid treatment may be gradually reduced and cyclophosphamide discontinued at 3 months. In contrast to treatment of smallvessel vasculitis, immunosuppression longer than this is usually not necessary. Longer treatment is appropriate for patients who are positive for both anti-GBM antibody and ANCA (see later discussion).

Late increases in anti-GBM level may predict clinical relapse, although antibodies are generally permanently suppressed in patients who have completed the immunosuppressive regimen. If there is recurrence, success has been achieved by treating as at first presentation.

Electing Not to Treat

Unusually high risk from
immunosuppression

ANCA, Antineutrophil cytoplasmic antibody.

✓ • ✓ Anticoagulation used during dialysis or plasma exchange
✓ • ✓ Thrombocytopenia, defibrination, and depletion of clotting factors as a consequence of plasma exchange

It is therefore advisable to ensure correct fluid balance, to prohibit smoking, to use the lowest fractional Fio2 that gives adequate oxygenation, and to minimize the use of heparin.

Plasma exchange (see Table 25.2) should be monitored by daily blood counts, calcium concentration (if regional citrate anticoagulation is used), and coagulation tests. Diminished clotting factor levels should be replenished by administration of fresh-frozen plasma or clotting factor preparations at the end of each plasma exchange session, as required.

After the first few days, the major cause of morbidity and mortality is infection. Infection carries the added risk for potentiating glomerular and lung inflammation and injury, so precautions to reduce risk, such as minimizing indwelling cannulas, are important. If leukopenia less than 3.5 × 109/L or neutropenia develops, cyclophosphamide should be discontinued and resumed at a lower dose when the neutrophil count recovers, if necessary with the assistance of granulocyte colony-stimulating factor.

Monitoring Effect of Treatment on Disease Activity

The effect of treatment on the kidney disease is monitored by following serum creatinine values. Indicators of recent lung hemorrhage include hemoptysis, decreases in hemoglobin concentration, chest radiograph changes, and increases in the Dlco, with the last being the most sensitive. Any worsening of symptoms during treatment may indicate inadequate immunosuppression, but it is frequently a consequence of intercurrent infection exaggerating immunologic injury or fluid overload or other factors precipitating lung hemorrhage.

Advanced kidney failure, frequently already established at presentation, is generally not salvaged by any current treatment.30 32 33 Furthermore, the immunosuppressive regimen outlined carries significant risks and careful monitoring is required. For these reasons, it may be reasonable not to initiate immunosuppression in patients who present with advanced kidney failure without lung hemorrhage. The decision not to treat is strengthened if the kidney biopsy specimen shows widespread glomerulosclerosis and tubular loss and the patient is dialysis dependent at presentation (see Table 25.3). The risk for development of late lung hemorrhage in these patients seems to be low but warrants particular care to avoid the major precipitating factors, smoking and pulmonary edema, in at least the first few months. However, patients who are dialysis dependent usually should be treated if the kidney histopathologic changes are unexpectedly mild or very recent (highly cellular crescents, even if 100% of glomeruli are involved, or acute tubular necrosis). Several reports describe good outcomes in these patients even after prolonged oliguria.

Treatment of Double-Positive Patients

Patients with both ANCA and anti-GBM antibodies may have other extrarenal disease requiring treatment (see Table 25.3). There is conflicting evidence as to whether their kidney prognosis is the same as or better than that of other patients with anti-GBM antibodies. Earlier series suggested a better prognosis, but this was not confirmed in two later reports.13 14 Because of the risk for serious disease in other organs, double-positive patients should usually receive an immunosuppressive regimen similar to that given for small-vessel vasculitis, with continuing immunosuppression with azathioprine after 3 months of cyclophosphamide (see Chapter 26).

TRANSPLANTATION

Kidney transplantation in patients who have had Goodpasture disease carries the additional risk for disease recurrence. Recurrence with consequent loss of the graft has been reported and appears more likely when circulating anti-GBM antibodies are still detectable at transplantation. Therefore, it is reasonable to delay transplantation until circulating anti-GBM antibodies have been undetectable for 6 months and to monitor graft function, urinary sediment, and circulating anti-GBM antibody levels to detect recurrent disease (see Chapter 113). Biopsy samples of well-functioning grafts sometimes show linear deposition of Ig on the GBM without clinical or histologic disease or apparently an adverse prognosis.

ALPORT SYNDROME POSTTRANSPLANT ANTI–GLOMERULAR BASEMENT MEMBRANE DISEASE

Patients with Alport syndrome have mutations in a gene encoding one of the tissue-specific type IV collagen chains, usually α5. Because these chains assemble with each other during biosynthesis, the resulting phenotype in the case of most mutations often has all the tissue-specific chains (α3–α5) missing from the basement membranes, where they are normally coexpressed. Altered expression may lead to absent or inadequate immunologic tolerance to these proteins and to preservation of the capacity to mount a powerful (allo)immune response to the type IV collagen chains expressed in a normal donor kidney after kidney transplantation. Most patients with Alport syndrome accommodate kidney transplants with conventional immunosuppression without development of anti-GBM nephritis. However, development of low titers of anti-GBM antibodies is shown by many such patients having linear deposition of IgG on the GBM of the transplanted kidney on direct IF, without disease. This alone does not justify treatment. Up to 2% of patients with Alport syndrome have been reported to develop RPGN in the transplanted kidney, although anecdotally this is much less common than historically. It is clinically indistinguishable from spontaneous anti-GBM disease but without lung

hemorrhage. This is more likely if the patient has a large gene deletion causing the disease rather than a point mutation, with the inference that the immune system has never been exposed to the mature protein. Typically, graft function is lost despite treatment for presumed acute rejection. Disease is usually encountered some months or longer after a first kidney transplant, after weeks in a second, and after days in a third.32 However, regrafting has been successful in two cases known to us and in two further cases in the literature. If the disease is recognized early, there are sound theoretical reasons for treating with the regimen recommended for Goodpasture disease, but there are few data on its effectiveness.34

In contrast to spontaneous Goodpasture disease, the specificity of anti-GBM antibodies in Alport syndrome posttransplant anti-GBM disease is not always to α3(IV)NC1. In many patients, possibly in most, the autoantibodies are specific for α5(IV)NC1, encoded by the COL4A5 gene usually implicated in causation of the disease.35 This is important because immunoassays for anti-GBM antibodies are optimized for detection of the anti-α3(IV)NC1 antibodies of spontaneous Goodpasture disease, and they may have low sensitivity for antiα5(IV)NC1 antibodies. In the absence of widely available assays for these uncommon antibodies, kidney biopsy with immunohistology is the only reliable method of diagnosis.

SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presenting with acute kidney failure and pulmonary hemorrhage was diagnosed after appropriate investigation as having Goodpasture disease and was treated with plasma exchange (10 × 4 L over 2 weeks), oral cyclophosphamide (150 mg/day), and prednisolone (week 1: 60 mg/day; week 2: 45 mg/day; week 3: 30 mg/day; week 4: 25 mg/day; week 5: 20 mg/day; week 6: 15 mg/day; weeks 7–8: 20 mg alternate days). Cyclophosphamide (CYP) had to be omitted for 5 days, then restarted at 100 mg/day in week 4 because of neutropenia. At review 3 months after treatment commenced, the patient is entirely well with estimated glomerular filtration rate of 36 mL/min, hemoglobin of 110 g/L, and white blood cell count of 2.4 × 103 per µL. Anti-GBM antibodies remain detectable just above the reporting threshold of the local assay. How should his immunosuppression be managed?

A. Replace CYP with azathioprine or MMF and maintain with steroids to at least 1 year.
B. Discontinue CYP and steroids with close outpatient monitoring.
C. Continue CYP at a reduced dose with prednisolone (10 mg/day) or equivalent to at least 1 year.
D. Reinstitute plasmapheresis.

2. A 45-year-old nonsmoking executive collapses at a meeting and in the emergency department is found to have a serum creatinine of 1800 μmol/L, hemoglobin of 90 g/L, potassium of 7.2 mmol/L, blood pressure (BP) 165/92 mm Hg, and normal-sized unobstructed kidneys on ultrasound scan. After appropriate acute dialysis and BP control, a kidney biopsy sample is taken, which shows

severe crescentic GN affecting 32/32 sampled glomeruli. On silver staining, breaks could be seen in multiple capillary loops and in Bowman’s capsule of most glomeruli. Linear deposition of IgG along the residual GBM and strong positivity for serum anti-GBM antibodies establishes a diagnosis of Goodpasture disease. ANCA testing is negative, and there is no evidence of lung hemorrhage. What treatment would you recommend for this patient with Goodpasture disease?
A. Plasma exchange, CYP, and oral prednisolone for at least 3 months
B. Plasma exchange, CYP, and oral prednisolone with plan for early discontinuation in the event of continuing dependence on dialysis
C. Close monitoring with a goal of avoiding immunosuppression
D. CYP and oral prednisolone for at least 3 months

3. A 26-year-old man has a deceased donor renal transplant after 10 months on hemodialysis. His kidney failure is of unknown cause. Eight months posttransplant, kidney function is found to have deteriorated dramatically, with creatinine rising from 130 to 800 μmol/L at routine clinic visits 3 weeks apart. A biopsy shows 100% crescentic nephritis with strong linear binding of IgG to the GBM. Serum anti-GBM titers are negative. The most likely diagnosis is:
A. Anti-GBM (Goodpasture) disease
B. Alport anti-GBM disease
C. Antibody-mediated rejection
D. Polyomavirus infection

REFERENCES

1. Goodpasture EW. The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci. 1919;158:863–870.
2. Stanton MC, Tange JD. Goodpasture’s syndrome (pulmonary haemorrhage associated with glomerulonephritis). Aust NZ J Med. 1958;7:132–144.
3. Saus J, Wieslander J, Langeveld J, et al. Identification of the goodpasture antigen as the α3(IV) chain of collagen IV. J Biol Chem. 1988;263:13374–13380.
4. Turner N, Mason PJ, Brown R, et al. Molecular cloning of the human goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen. J Clin Invest. 1992;89:592–601.
5. Kashtan CE, Michael AF. Alport syndrome. Kidney Int. 1996;50:1445–1463.
6. Aumailley M. Structure and supramolecular organization of basement membranes. Kidney Int. 1995;49:S4–S7.
7. Phelps RG, Rees AJ. The HLA complex in goodpasture’s disease: a model for analyzing susceptibility to autoimmunity. Kidney Int. 1999;56:1638–1654.
8. Zou J, Henderson L, Thomas V, et al. Presentation of the goodpasture autoantigen requires proteolytic unlocking steps that destroy prominent T cell epitopes. J Am Soc Nephrol. 2007;18:771–779.
9. Pedchenko V, Bondar O, Fogo AB, et al. Molecular architecture of the goodpasture autoantigen in anti-GBM nephritis. N Engl J Med. 2010;363:343–354.
10. Arends J, Wu J, Borillo J, et al. T cell epitope mimicry in antiglomerular basement membrane disease. J Immunol. 2006;176:1252–1258.
11. Canney M, O’Hara PV, Caitriona M, et al. Spatial and temporal clustering of anti-glomerular basement membrane disease. Clin J Am Soc Nephrol. 2016;11:1392–1399.
12. Prendecki M, Clarke C, Cairns T, et al. Anti-glomerular basement membrane disease during the COVID-19 pandemic. Kidney Int. 2020;98:780–781.
13. Rutgers A, Slot M, van Paassen P, et al. Coexistence of anti–glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. Am J Kidney Dis. 2005;46:253–262.
14. Levy JB, Hammad T, Coulthart A, et al. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. Kidney Int. 2004;66:1535–1540.
15. Cui Z, Turner AN, Zhao MH. Antiglomerular basement membrane disease: Overview, clinical features and diagnosis, treatment and outcomes. In: Turner AN, et al., ed. Oxford Textbook of Nephrology. 4th ed. Oxford: Oxford University Press; 2015:598–608.
16. Ooi JD, Holdsworth SR, Kitching AR. Advances in the pathogenesis of Goodpasture’s disease: From epitopes to autoantibodies to effector T cells. J Autoimmun. 2008;31:295–300.
17. Phelps RG, Turner AN. Goodpasture’s syndrome: new insights into pathogenesis and clinical picture. J Nephrol. 1996;9:111–117.
18. Lerner R, Glassock R, Dixon F. The role of anti–glomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. J Exp Med. 1967;126:989–1004.

19. Cui Z, Turner AN, Zhao MH. Antiglomerular basement membrane disease: Pathogenesis. In: Turner AN, et al., ed. Oxford Textbook of Nephrology. 4th ed. Oxford: Oxford University Press; 2015:609–618.
20. Ooi JD, Chang J, O’Sullivan KM, et al. The HLA-DRB1*15:01–restricted Goodpasture’s T cell epitope induces GN. J Am Soc Nephrol. 2013;24:419–431.
21. Heptinstall RH. Schönlein-Henoch syndrome: Lung hemorrhage and glomerulonephritis. In: Heptinstall RH, ed. Pathology of the Kidney. Boston: Little, Brown; 1983:761–791.
22. Thitiarchakul S, Lal SM, Luger A, Ross G. Goodpasture’s syndrome superimposed on membranous nephropathy. A case report. Int J Artif Organs. 1995;18:763–765.

23. Phelps R, Winston JA, Wynn D, et al. Incidence, management, and outcomes of autoimmune nephropathies following alemtuzumab treatment in patients with multiple sclerosis. Mult Scler. 2019;9:1273–1288.
24. Olson SW, Arbogast CB, Baker TP, et al. Asyptomatic autoantibodies associate with future anti-glomerular basement membrane disease. J Am Soc Nephrol. 2011;22:1946–1952.
25. Cairns LS, Phelps RG, Bowie L, et al. The fine specificity and cytokine profile of T helper cells responsive to a glomerular autoantigen in Goodpasture’s disease. J Am Soc Nephrol. 2003;14:2801–2812.
26. Johnson JP, Moore JJ, Austin HA, et al. Therapy of anti–glomerular basement membrane antibody disease: Analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine (Baltimore). 1985;64:219–227.
27. Soveri I, Molne J, Uhlin F, et al. The IgG-degrading enzyme of Streptococcus pyogenes causes rapid clearance of anti-glomerular basement membrane antibodies in patients with refractory anti-glomerular basement membrane disease. Kidney Int. 2019;96(5):1234–1238.
28. Raftat C, Luque Y. IdeS in anti-glomerular basement membrane disease: Is this the new deal? Kidney Int. 2019;96:1068–1070.
29. Uematsu-Uchida M, Ohira T, Tomita S, Satonaka H, Tojo A, Ishimitsu T. Rituximab in treatment of anti-GBM antibody glomerulonephritis: A case report and literature review. Medicine (Baltimore). 2019;98(44):e17801.
30. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti–glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001;134:1033–1042.
31. Hind CRK, Paraskevakou H, Lockwood CM, et al. Prognosis after immunosuppression of patients with crescentic nephritis requiring dialysis. Lancet. 1983;1:263–265.
32. Turner AN, Rees AJ. Anti–glomerular basement membrane antibody disease. In: Brady HR, Wilcox N, eds. Therapy in Nephrology and Hypertension: A Companion to Brenner and Rector’s The Kidney. 3rd ed. Philadelphia: Saunders; 2008:197–204.
33. Flores JC, Taube D, Savage COS, et al. Clinical and immunological evolution of oliguric anti-GBM nephritis treated by haemodialysis. Lancet. 1986;1:5–8.
34. Browne G, Brown PA, Tomson CR, et al. Retransplantation in Alport post-transplant anti-GBM disease. Kidney Int. 2004;65:675–681.
35. Brainwood D, Kashtan C, Gubler MC, Turner AN. Targets of alloantibodies in Alport anti–glomerular basement membrane disease after renal transplantation. Kidney Int. 1998;53:762–766.

26

Renal and Systemic Vasculitis

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DEFINITION

The large number and variety of kidney vessels make the kidneys targets for a variety of systemic vasculitides, especially those affecting small vessels.1–4 Vasculitis involving the kidneys produces a variety of clinical manifestations, depending on the type of kidney vessel affected. Vasculitides are categorized as large-, medium-, and small-vessel vasculitis (Figs. 26.1 and 26.2). The 2012 Chapel Hill Consensus Conference definitions are used throughout this chapter (Table 26.1).4

Several vasculitides in Fig. 26.2 are reviewed in other chapters and are discussed here only in the context of differential diagnosis. Nephrologists often encounter patients with small-vessel vasculitides because these frequently cause glomerulonephritis (GN). Therefore, small-vessel vasculitis (SVV) is the primary focus of this chapter.

Small-Vessel Vasculitis

SVV is necrotizing vasculitis affecting predominantly vessels that are smaller than arteries, including capillaries, venules, and arterioles; however, small arteries can be involved.4 The most common renal target for SVV is glomerular capillaries and the most common kidney clinical manifestation is GN.

Medium-Vessel Vasculitis

Medium-vessel vasculitis is necrotizing arteritis affecting predominantly major visceral arteries.4 In the kidneys, interlobar arteries and arcuate arteries are most affected, although any arteries from the main renal artery to the smallest interlobular arteries may be affected. Arterial inflammation and necrosis may result in thrombosis or rupture, causing kidney infarction and hemorrhage, respectively.

Large-Vessel Vasculitis

Large-vessel vasculitis is chronic granulomatous arteritis affecting the aorta and its major branches more often than other forms of vasculitis.4 With kidney involvement, the ostia of the renal arteries and the main renal arteries are most often affected. The most common clinical kidney manifestation is renovascular hypertension.

SMALL-VESSEL PAUCI-IMMUNE VASCULITIS

SVV can be divided into immune complex SVV with moderate to marked vessel wall deposits of immunoglobulin and pauci-immune SVV with few or no immune deposits in vessel walls.4 Pauci-immune SVV often is associated with circulating antineutrophil cytoplasmic autoantibodies (ANCAs).1 The ANCA-associated vasculitides share an indistinguishable form of necrotizing SVV that affects capillaries, venules, arterioles, and small arteries.1–5 Some patients with ANCAassociated vasculitis (AAV) have no evidence of arterial involvement,

although they have involvement of glomerular capillaries, causing GN; pulmonary alveolar capillaries, causing pulmonary hemorrhage; or dermal venules, causing purpura. The clinicopathologic variants of pauci-immune SVV are categorized based on clinical, laboratory, and pathologic findings, as follows4:

✓ • ✓ Microscopic polyangiitis (MPA) is pauci-immune SVV in the absence of evidence for necrotizing granulomatous inflammation.

✓ • ✓ Granulomatosis with polyangiitis (GPA) is pauci-immune vasculitis associated with necrotizing granulomatous inflammation, most often affecting the respiratory tract.

✓ • ✓ Eosinophilic granulomatosis with polyangiitis (EGPA; formerly called Churg-Strauss syndrome) is pauci-immune vasculitis associated with asthma, eosinophilia, and necrotizing granulomatous inflammation.

MPA, GPA, and, less frequently, EGPA share an indistinguishable pattern of GN that is expressed as vasculitis in glomerular capillaries.1 In the acute phase, the GN usually has necrosis and crescents, an absence or paucity of immunoglobulin deposition, and is designated pauci-immune crescentic glomerulonephritis. In the absence of systemic vasculitis, pauci-immune crescentic GN is sometimes referred to as renal-limited vasculitis.

Pathogenesis

MPA, GPA, EGPA, and renal-limited pauci-immune crescentic GN are all associated with ANCAs.4–6 The most common antigen targets of ANCAs are proteinase 3 (PR3) and myeloperoxidase (MPO).7,8

The association of ANCAs with this form of SVV suggests that ANCAs are involved in disease pathogenesis.4–6 Correlation of ANCA titers with disease activity in some individuals suggests a pathogenic role; however, this correlation is not strong and some patients with clinically and pathologically typical MPA, GPA, or renal-limited pauci-immune crescentic GN are negative using conventional serologic ANCA testing. MPO-ANCA epitope specificity determines the pathogenicity, detectability, and clinical predictive value of circulating MPO-ANCA.9 For example, ANCAs with certain epitope specificities occur only during active disease, whereas other MPO-ANCA epitope specificities occur regardless of disease status and in healthy controls (natural ANCAs), although at very low titers.10,11 Some patients with AAV who are negative by conventional serologic testing have MPOANCA with restricted epitope specificity that can be detected with unmasking techniques.10

The pathogenic potential of ANCAs is supported by the observation that certain drugs, such as propylthiouracil, hydralazine, and penicillamine, can induce AAV.12 Cocaine adulterated with levamisole can induce AAV with high titer MPO-ANCA, PR3-ANCA, and ANCA specific for elastase.12 Levamisole-induced vasculitis has frequent cutaneous leukocytoclastic angiitis and upper respiratory tract involvement but rarely kidney or lung involvement.

Renal Vascular Involvement in Vasculitides
Aorta

Renal
artery

Interlobar
artery

Arcuate
artery
Interlobular
artery
Arteriole
Glomerulus

Mediumvessel
vasculitis

Largevessel
vasculitis

Small-vessel
vasculitis

Granulomatous
arteritis in a
patient >50 years

Granulomatous
arteritis in a
patient <50 years

Necrotizing arteritis without
mucocutaneous lymph
node (MCLN) syndrome

Necrotizing
arteritis with
MCLN syndrome

Giant cell
arteritis

Takayasu
arteritis

Polyarteritis
nodosa

Kawasaki
disease

Immune complexes in vessel walls
with immunofluorescent staining
for immunoglobulins

Circulating antineutrophil cytoplasmic
antibodies (ANCA) with paucity of
vascular immunoglobulin staining

Other sources
for immune
complexes

Cryoglobulins
in blood and
vessel walls

IgA-dominant
deposits in
vessel walls

Systemic lupus
erythematosus or
rheumatoid arthritis

No asthma or
granulomas

Granulomas
and no asthma

Eosinophilia,
asthma, and
granulomas

Other immune
complex vasculitis

Cryoglobulinemic
vasculitis

IgA vasculitis

Lupus/rheumatoid
vasculitis

Microscopic
polyangiitis

GPA

EGPA

Fig. 26.1 Renal Vasculitis. Predominant distribution of kidney vascular involvement by a variety of vasculitides. The heights of the trapezoids represent the relative frequency of involvement of different portions of the renal vasculature by the three major categories of vasculitis. EGPA, Eosinophilic granulomatous polyangiitis; IgA, immunoglobulin A.

In vitro observations suggest mechanisms by which ANCAs cause vascular injury.5 6 Cytokine priming causes neutrophils to increase expression of ANCA antigens on their surfaces where ANCAs can bind. Cytokine-primed neutrophils activated by ANCAs release lytic enzymes from granules, generate toxic oxygen metabolites, and kill cultured endothelial cells. ANCA-antigen complexes adsorb onto endothelial cells where they could participate in in situ immune complex formation. ANCA activation of neutrophils is mediated by F(ab)2 binding to neutrophils and to a greater degree by FcR engagement. These events cause vasculitis as a result of neutrophils adhering to, penetrating, and destroying vessel walls (Fig. 26.3).

The ability of ANCA to cause pauci-immune necrotizing and crescentic GN and vasculitis is demonstrated in animal models induced with MPO-ANCA. No widely accepted model of PR3-ANCA disease has been developed because of differences in murine PR3 expression and limited homology between mice and humans.6 Wild-type or immunodeficient mice intravenously (IV) injected with anti-MPO antibodies develop pauci-immune focal necrotizing crescentic GN.13

A rat model of pauci-immune necrotizing crescentic GN developed by immunizing rats with human MPO developed antibodies that crossreact with rat MPO.14 MPO-ANCA GN in mice is mediated by neutrophil activation, modulated by the FcγR repertoire, and is prevented by neutrophil depletion.6 13 Alternative complement pathway activation plays a role in amplifying ANCA-induced inflammation.15 ANCAactivated neutrophils release factors that activate the alternative complement pathway, resulting in C5a generation, which is chemotactic for neutrophils and primes for further activation by ANCAs.16 Patients with active AAV (as defined by the Birmingham Vasculitis Activity Score [BVAS]) have increased plasma levels of C3a, C5a, soluble C5b9, and Bb, and plasma levels of Bb correlated with percentage of cellular crescents in kidney biopsy samples and BVAS.17 Further studies concluded that complement cascade activation differs with disease activity and serotype.18
Clinical and experimental data indicate that ANCAs can activate neutrophils and cause vasculitis, especially if there are synergistic proinflammatory stimuli. The synergistic neutrophil-priming

Major Categories of Noninfectious Vasculitis
Vasculitis

Small-vessel
vasculitis

Circulating antineutrophil
cytoplasmic antibodies
(ANCA) associated
Microscopic polyangiitis (MPA)
GPA
EGPA
Drug-induced ANCA-associated
vasculitis

Medium-vessel
vasculitis
Polyarteritis nodosa
Kawasaki disease

Immune-complex associated
Cryoglobulinemic vasculitis
IgA vasculitis
Anti-GBM (glomerular basement
membrane) disease
Infection-induced immune
complex vasculitis
(e.g., hepatitis B and C)
Serum sickness vasculitis
Lupus vasculitis
Rheumatoid vasculitis
Hypocomplementemic
urticarial vasculitis
Behçet disease
Drug-induced immune-complex
vasculitis

Large-vessel
vasculitis
Giant cell arteritis
Takayasu arteritis

Paraneoplastic
Carcinoma-induced
vasculitis
Lymphoproliferative
neoplasm–induced
vasculitis
Myeloproliferative
neoplasm–induced
vasculitis

Inflammatory
bowel disease
vasculitis

Fig. 26.2 Major Categories of Noninfectious Vasculitis. Not included are vasculitides that are known to be caused by direct invasion of vessel walls by infectious pathogens, such as rickettsial vasculitis and neisserial

vasculitis. EGPA, Eosinophilic granulomatous polyangiitis; GPA, granulomatous polyangiitis.

inflammatory process may be reflected in the frequent association of AAV onset with an influenza-like syndrome.19

Initiation of the ANCA autoimmune response is less understood but involves human leukocyte antigen (HLA) with specific molecular recognition capabilities.20,21 Genome-wide association studies have identified associations between HLA alleles and AAV (HLA-DP for PR3-ANCA and HLA-DQ for MPO-ANCA).20–22

Because certain HLA have a greater predilection for binding autoantigenic peptides, it is logical that HLA associated with AAV has a higher propensity to bind MPO or PR3 peptides. Within the MPOANCA serotype, a small number of MPO peptides bind specific HLA, and T cells react to these same peptides.11 These autoreactive T cells are capable of shaping the B-cell response, leading to ANCA production.

Epidemiology

GPA, MPA, and EGPA occur at any age but usually begin during the fifth through seventh decades of life, with a peak incidence of 65 to 75 years. There is a slight male predominance. AAV has geographic and race/ethnicity differences in prevalence.23 In the United Kingdom, GPA (148 per 1 million) is more common than MPA (65 per million), and MPA is more common than EGPA (46 per 1 million). In France, AAV prevalence is twice as high in Europeans (105 per 1 million) compared with non-Europeans (53 per million). In the United States, the incidence is disproportionately greater in Whites than in Blacks, which may be caused by HLA differences.24

In the United Kingdom and northern Europe, PR3-ANCA (usually associated with GPA) is more common than MPO-ANCA; however, in Southern Europe, Asia, and India, MPO-ANCA and MPA are more common.23 In the United States, there is a similar trend with more PR3-ANCA and GPA in northern states and more MPO-ANCA and MPA in southern states. Geographic and racial differences may be related to HLA differences.20,21

Clinical Manifestations

Generalized nonspecific manifestations of systemic inflammatory disease (fever, malaise, anorexia, weight loss, myalgias, and arthralgias) often are present. Many patients trace the onset of their vasculitic disease to a flu-like illness.19

Clinical manifestations of GPA, MPA, and EGPA are extremely varied because they are influenced by the organs affected. The three categories of vasculitis share features caused by SVV, and patients with GPA and EGPA have additional defining features.4,25,26

Kidney involvement occurs often in GPA and MPA and is uncommon in EGPA (Table 26.2). Most common kidney manifestations are hematuria, proteinuria, and kidney failure. Kidney failure often has the characteristics of rapidly progressive glomerulonephritis (RPGN) in GPA and MPA but is less severe in EGPA. A cohort of more than 300 patients with pauciimmune crescentic GN evaluated at kidney biopsy had a mean age of 56 years (range, 2–92 years), male-to-female ratio of 1.0:0.9, mean serum creatinine concentration of 6.5 mg/dL (range, 0.8–22.1 mg/dL; 69–1900 µmol/L), and proteinuria of 1.9 g/day (range, 0.1–18g/day).27

TABLE 26.1

Names and Definitions of Vasculitis

Category/Name
Large-Vessel Vasculitis
Takayasu arteritis
Giant cell arteritis

Medium-Vessel Vasculitis
Polyarteritis nodosa
Kawasaki disease

Definition
Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 years.
Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with predilection for branches of carotid and vertebral arteries; often involves temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica.
Necrotizing arteritis of medium or small arteries without GN or vasculitis in arterioles, capillaries, or venules and not associated with ANCA.
Arteritis associated with mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries; coronary arteries are often involved; aorta and large arteries may be involved. Usually occurs in infants and young children.

Small-Vessel Vasculitis
ANCA-Associated Small-Vessel Vasculitis
Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles, small arteries), associated with MPOANCA or PR3-ANCA. Not all patients have ANCA. Add prefix indicating ANCA reactivity (e.g., PR3-ANCA, MPO-ANCA, ANCA-negative).
Microscopic polyangiitis (MPA)

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles).
Necrotizing arteritis involving small and medium arteries may be present. Necrotizing GN is common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

Granulomatosis with polyangiitis (GPA)

Necrotizing granulomatous inflammation usually involving upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels (capillaries, venules, arterioles, arteries, veins). Necrotizing GN is common.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia. ANCA is more common when GN is present.

Immune Complex Small-Vessel Vasculitis

Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (capillaries, venules, arterioles, small arteries). GN is common.

Anti–glomerular basement membrane (anti-GBM) disease

Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti–basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes GN with necrosis and crescents.

Cryoglobulinemic vasculitis

Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum. Skin, glomeruli, and peripheral nerves are often involved.

IgA vasculitis (IgAV)

Vasculitis with IgA1-dominant immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract and frequently causes arthritis. GN indistinguishable from IgA nephropathy may occur.

Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (capillaries, venules, arterioles) and associated with anti-C1q antibodies. GN, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

Adopted by the 2012 Chapel Hill consensus conference on the nomenclature of systemic vasculitis. Note that all three categories affect arteries, but only small-vessel vasculitis has a predilection for vessels smaller than arteries.

ANCA, Antineutrophil cytoplasmic antibody; GN, glomerulonephritis; IgA, immunoglobulin A.

Modified from Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: Results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77:1143–1149.

Cutaneous involvement, manifesting as purpura, occurs frequently in all types of SVV (Fig. 26.4). Purpura is most common on the lower extremities, tends to occur as recurrent crops, and may be accompanied by areas of ulceration. Nodular cutaneous lesions are more frequent in GPA and EGPA than MPA. Nodules can be caused by dermal or subcutaneous arteritis and granulomatous inflammation.

Upper respiratory tract involvement is most common in GPA and EGPA but also occurs in MPA.28 In all three categories, patients can have pulmonary hemorrhage caused by alveolar capillaritis. Patients with GPA, and to a lesser extent EGPA, can have pulmonary injury caused by necrotizing granulomatous inflammation, which may be detected radiographically as nodular or cavitating lesions. By definition, patients with MPA do not have granulomatous respiratory tract lesions.4

Manifestations of upper respiratory tract disease include subglottic stenosis, sinusitis, rhinitis, nasal septal collapse, otitis media, and ocular inflammation. The upper respiratory inflammation in MPA

is caused by angiitis alone, without granulomatous inflammation.
Destruction of bone, resulting in septal perforation and saddle nose, results from necrotizing granulomatous inflammation and does not occur in MPA.

Cardiac disease is identified in approximately 50% of patients with EGPA (usually myocarditis) but in less than 20% of patients with GPA or MPA. Cardiac manifestations in GPA and MPA are predominantly transient heart block and ventricular hypokinesis that respond to immunosuppressive treatment, although infarction, endocarditis, pericarditis, and severe life-threatening myocarditis may occur.

ANCA-Induced Vasculitis: A Possible Pathogenetic Path
Unstimulated
neutrophil

Cytokine stimulation: antigens move to cell
surface and microenvironment and bind ANCA

Fc and Fab'2 bind
ANCA-antigen
complexes or ANCA
causing neutrophil
activation

Activation of
alternative complement
pathway resulting in
amplification of
inflammation via C5a

Apoptosis and
necrosis of neutrophils
and endothelial cells

C5a

C5a
C5a
C5a

C5a

ANCA

Antigens binding ANCA

Cytokine

Cytokine receptor

Fc receptor

Adhesion molecule

Adhesion molecule receptor

Fig. 26.3 Vasculitis Induced by Antineutrophil Cytoplasmic Antibody (ANCA). Hypothetical sequence of pathogenetic events.

TABLE 26.2

Organ System Involvement in Small-Vessel Vasculitis
FREQUENCY OF INVOLVEMENT (%)

Organ System

Microscopic
Polyangiitis

GPA

EGPA

IgA Vasculitis

Cryoglobulinemic
Vasculitis

Kidney

90

80

20

50

55

Skin/cutaneous

40

40

40

90

90

Lungs

50

90

90

<5

<5

Ear, nose, throat

35

90

70

<5

<5

Musculoskeletal

60

60

50

75

70

Neurologic

30

50

40

10

40

Gastrointestinal

50

50

40

60

30

EGPA, Eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A.

Peripheral neuropathy, usually mononeuritis multiplex, is the most common neurologic manifestation. Central nervous system involvement is less common, most often resulting from vasculitis within the meninges. Gastrointestinal (GI) involvement typically causes abdominal pain and hematochezia, with mesenteric ischemia and rarely intestinal perforation. Vasculitis in the pancreas and liver can mimic pancreatitis and hepatitis symptomatically and cause elevated serum pancreatic and liver enzymes.

Antineutrophil Cytoplasmic Autoantibody

Serologic testing for ANCAs is useful for diagnosing SVV and pauciimmune crescentic GN but should be interpreted in the context of patient characteristics and performance qualities of the assay.29–32

Antigen specificity of ANCA for PR3 versus MPO is helpful for diagnosis and has predictive value in clinical course and outcome.8 32
Laboratory testing for ANCA should include indirect immunofluorescence microscopy assay (IFA) and enzyme immunoassay (EIA).31
IFA using normal human neutrophils as substrate produces two major staining patterns (Fig. 26.5): cytoplasmic (c-ANCA), and perinuclear (p-ANCA). By EIA, most c-ANCAs have specificity for proteinase 3 (PR3-ANCA) and most p-ANCAs have specificity for myeloperoxidase (MPO-ANCA). For diagnostic accuracy, serologic testing for ANCAs should include an immunochemical analysis for antigen specificity, such as an EIA.7 31 32 High-quality EIA can be used alone as a screening test for AAV.32 Although positive results are rare in healthy individuals, one-fourth of patients with other inflammatory kidney diseases

Antineutrophil Cytoplasmic Antibody in Small-Vessel Vasculitis

Fig. 26.4 Cutaneous Vasculitis. Ankle of a patient with small-vessel vasculitis, showing purpura and a few small ulcers.

A

B

Fig. 26.5 Antineutrophil Cytoplasmic Antibodies (ANCAs). Indirect immunofluorescence staining pattern of alcohol-fixed normal human neutrophils. (A) Cytoplasmic pattern caused by ANCAs with specificity for proteinase 3. (B) Perinuclear pattern caused by ANCAs with specificity for myeloperoxidase (anti–immunoglobulin G). (Original magnification, ×250.)

TABLE 26.3

	FREQUENCY (%)		
Disorder	Proteinase 3 (PR3, Usually c-ANCA)	Myeloperoxidase (MPO, Usually p-ANCA)	Negative
Granulomatosis with polyangiitis	70	25	5
Microscopic polyangiitis	40	50	10
Eosinophilic granulomatosis with polyangiitis	5	40	55
Renal-limited pauciimmune crescentic GN	20		

70

10

Approximate frequency of antibody in small-vessel vasculitis (ANCA) with specificity for proteinase 3 (PR3/c-ANCA) and for myeloperoxidase (MPO/p-ANCA) in patients with different categories of pauci-immune small-vessel vasculitis and crescentic glomerulonephritis.
GN, Glomerulonephritis.

(especially lupus) have a false-positive IFA result (usually p-ANCA) and approximately 5% have a false-positive EIA result (usually low titer).[31]

ANCA testing has good sensitivity for AAV (80%–90%). The specificity and predictive value depend on the patient population and the assay quality.[7] Although ANCAs are most frequent in patients with pauci-immune crescentic GN, one-fourth to one-third of patients with anti–glomerular basement membrane (GBM) crescentic GN and onefourth of those with idiopathic immune complex crescentic GN with 50% or more crescents are ANCA-positive.[27,33] Some patients have well-recognized types of immune complex GN complicated by ANCAs, such as membranous nephropathy and IgA nephropathy; others have non-lupus IgG-dominant immune complex disease that cannot be categorized further. Patients with concurrent ANCAs and anti-GBM antibodies have a worse prognosis than patients with ANCAs alone. This is complicated by antiperoxidasin antibodies in some patients with anti-GBM exhibiting pulmonary-renal syndrome.[34] Peroxidasin and MPO have antigenic overlap, which may be implicated in the autoimmune process. Anti-GBM antibodies typically disappear after treatment without recurrence, whereas ANCAs and associated vasculitis may recur.

Table 26.3 estimates the relative frequencies of PR3-ANCA/c-ANCA and MPO-ANCA/p-ANCA in the different clinical phenotypes of AAV, although this has geographic and racial influences.[5,23] PR3-ANCA/c-ANCA are most prevalent in GPA, and MPO-ANCA/p-ANCA are most prevalent in renal-limited pauci-immune crescentic GN and EGPA. Patients with MPA have a more equal distribution of PR3-ANCA/c-ANCA and MPO-ANCA/p-ANCA, although this varies geographically.[23] Patients with EGPA have the lowest overall frequency of ANCAs, but the frequency of ANCAs is much higher in EGPA patients with GN (75%) than in those without GN (26%).[35] ANCA specificity correlates with clinical symptoms, with PR3-ANCA having the highest frequency (~90% when ANCA present) in patients who have destructive upper respiratory tract disease, especially saddle nose.[28]

Fig. 26.6 Necrotizing Arteritis of Interlobular Artery in Patient with Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis. There is segmental fibrinoid necrosis with adjacent perivascular leukocyte infiltration. (H&E, ×50.)

Changes in ANCA titers over time may correlate with disease activity but are not dependable and must be interpreted with caution.[7,31,32,36] Titers generally decrease with treatment and increase before or at disease recurrence. Increased ANCA titers should prompt careful patient evaluation for corroborating evidence of exacerbation, but most physicians do not modify treatment based on increased titer without accompanying clinical signs. Epitope-specific assays may provide better correlation with and prediction of disease outcome.[10] MPO-ANCAs with certain epitope specificities occur only in patients with active disease, disappear with remission, and reappear during relapse.[10]

From 10% to 20% of patients with pauci-immune necrotizing and crescentic GN and SVV are ANCA negative. The clinicopathologic and outcome characteristics of these patients are indistinguishable from ANCA-positive patients.[37] In the epitope-specific assays previously mentioned, some patients with AAV who are negative by clinical assays have MPO-ANCA with restricted epitope specificity that can be detected with sensitive assays.[10]

ANCAs may be positive but not associated with vasculitis in inflammatory conditions other than vasculitis, including inflammatory bowel disease (IBD), rheumatoid disease, chronic inflammatory liver disease, bacterial endocarditis, and cystic fibrosis. In IBD, specificity of the ANCAs usually is not against PR3 or MPO but against other neutrophil antigens, including lactoferrin, cathepsin G, and anti–bactericidal/permeability-increasing protein (BPI).[31,32]

Pathology

The acute vascular lesion of pauci-immune SVV is segmental fibrinoid necrosis, often accompanied by leukocyte infiltration and leukocytoclasia[1,38–40] (Figs. 26.6 and 26.7). The earliest vasculitic lesions have infiltrating neutrophils quickly replaced by predominantly mononuclear leukocytes. The acute necrotizing lesions evolve into sclerotic lesions and may be complicated by thrombosis.

These focal necrotizing lesions can affect many different vessels, producing varied signs and symptoms. For example, involvement of glomerular capillaries causes nephritis; of alveolar capillaries, pulmonary hemorrhage; of dermal venules, purpura; of upper respiratory tract mucosal venules, rhinitis and sinusitis; of abdominal visceral arteries, abdominal pain; and of epineural arteries, mononeuritis multiplex.

Fig. 26.7 Necrotizing Arteritis of Interlobular Artery in Patient with Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis. The fibrinoid necrosis is indicated by the red staining. (Masson trichrome, ×100.)

Fig. 26.8 Segmental Glomerular Necrosis and Crescent Formation in Patient with Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis. The fibrinoid material is red. The uninvolved segments appear normal. (Masson trichrome, ×150.)

Pauci-immune SVVs present as necrotizing GN, usually with resultant crescent formation.[1,38–40] Early mild lesions have segmental fibrinoid necrosis with or without adjacent small crescent (Fig. 26.8). Severe acute lesions may have global necrosis with large circumferential crescents (Fig. 26.9). In a cohort of 181 kidney biopsy specimens from patients with ANCA-associated GN, 90% had glomerular crescents affecting 50% of glomeruli, with half having crescents in more than 50% of glomeruli.[27] Nonnecrotic segments within segmentally injured glomeruli (see Fig. 26.8) and glomeruli without necrosis have slight or no histologic abnormalities.

Approximately one-fourth of patients with anti-GBM crescentic GN and one-fourth of patients with immune complex–mediated crescentic GN are ANCA positive,[27] but less than 5% of patients with immune complex GN who do not have crescents are ANCA positive.

Even in patients with immune complex GN, the presence of ANCAs is associated with an increased incidence of crescents (and inflammation in vessels other than glomerular capillaries). A histopathologic classification has been proposed for AAV GN: sclerotic class (≥50% globally sclerotic glomeruli), focal class (≥50% normal glomeruli), crescentic class (≥50% of glomeruli with cellular crescents), or mixed class if none of these features predominated.[40] Kidney survival at 5 years was 93% for the focal class, 76% for crescentic class, 61% for mixed class, and 50% for sclerotic class.

In addition to GN, patients with AAV may have renal arteritis, most often affecting interlobular arteries (see Figs. 26.6 and 26.7), and medullary angiitis affecting the vasa recta (Fig. 26.10). Medullary angiitis rarely causes papillary necrosis.

Patients with GPA and EGPA have pathologic lesions in addition to necrotizing SVV.[1 3 4] The necrotizing granulomatous inflammation of GPA occurs most often in the respiratory tract, characterized by necrotic zones surrounded by infiltrates of neutrophils, lymphocytes, monocytes, and macrophages, including scattered multinucleated giant cells. In patients with GPA and EGPA, extravascular granulomatous inflammation is rare in kidney biopsy specimens. Varying numbers of eosinophils may be present in the lesions of GPA, but these are more conspicuous in the necrotizing granulomatous inflammation of EGPA. Eosinophils are typically conspicuous in the vasculitic lesions of EGPA, but this is not a pathognomonic observation because eosinophils may be present in the vasculitic lesions of GPA, MPA, polyarteritis nodosa (PAN), and other vasculitides.

Differential Diagnosis

Fig. 26.9 Global glomerular necrosis and circumferential crescent formation in a glomerulus from patient with antineutrophil cytoplasmic antibody–associated small-vessel vasculitis. (Masson trichrome, ×150.)

Fig. 26.10 Medullary leukocytoclastic angiitis involving vasa recta in a patient with granulomatosis with polyangiitis. (H&E, ×150.)

TABLE 26.4

AAV must be differentiated from other forms of SVV that can produce similar signs and symptoms.[1 3 4] An attempt should be made to distinguish MPA, GPA, and EGPA, although in some patients this cannot be accomplished conclusively and is not required for initiation of therapy. Patients should be categorized as MPO-ANCA, PR3-ANCA, or ANCA-negative because serotype has independent predictive value about clinical course and outcome.[5 8 28] Pathologic confirmation of the granulomatous inflammation in ANCA disease is difficult because biopsy specimens often show nonspecific acute and chronic inflammation and necrosis. Findings such as nodular or cavitating lung lesions observed radiographically or destructive bone lesions in the nasal septum often are markers of necrotizing granulomatous inflammation to categorize patients. Because of treatment toxicity, even in patients with substantial clinical and serologic evidence of ANCA disease, pathologic confirmation of vasculitis is warranted. This can be accomplished with biopsy of different involved sites, including skin, muscle, nerve, gut, and kidney. In patients with substantial kidney involvement, kidney biopsy findings can be useful for predicting treatment response and clinical outcome.[38–40]

All forms of SVV in Fig. 26.2 are capable of producing clinically indistinguishable overlapping features of disease, such as nephritis, purpura, peripheral neuropathy, myalgias, arthralgias, and abdominal pain. Table 26.4 lists features that help distinguish categories of SVV.[3] Accurate differentiation is important for proper patient management because the natural histories and treatments vary greatly. For example, a patient with nephritis, arthralgias, and abdominal pain could have IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), MPA, cryoglobulinemic vasculitis, or several other small-vessel vasculitides.

Serologic and pathologic observations are useful for reaching the correct diagnosis (see Table 26.4). A positive ANCA assay (confirmed by EIA to be MPO- or PR3-ANCA) supports a diagnosis of MPA or one of the other pauci-immune SVV. A negative ANCA assay and positive

Differential Diagnostic Features of Select Forms of Small-Vessel Vasculitis

Features

Microscopic Polyangiitis

GPA

EGPA

IgA Vasculitis

Cryoglobulinemic
Vasculitis

Vasculitic signs and symptoms[a]

+

+

+

+

+

IgA-dominant immune deposits

−

−

−

+

−

Cryoglobulins in blood and vessels

−

−

−

−

+

ANCAs in blood

+

+

+

–

–

Necrotizing granulomas

–

+

+

–

–

Asthma and eosinophilia

–

–

+

–

–

aThese

vasculitides can manifest any of the shared features of small-vessel vasculitides, such as nephritis, purpura, abdominal pain, peripheral neuropathy, myalgias, and arthralgias. Each is distinguished by the presence and, just as important, by the absence of certain specific features.
ANCAs, Antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis.
Modified from Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;337:1512–1523.

cryoglobulin assay (especially accompanied by hypocomplementemia and positive hepatitis C serology) support a diagnosis of cryoglobulinemic vasculitis. A negative ANCA assay, negative cryoglobulin assay, and normal complement levels support a diagnosis of IgAV, especially in a patient younger than 21 years. Patient age influences the likelihood of a specific diagnosis, so approximately 80% of children younger than 10 years who have purpura, nephritis, and arthralgias will have IgAV, but approximately 80% of adults older than 60 years with the same symptoms will have an AAV. However, each disease can occur at any age.

Drug exposures that may provoke AAV must be considered, including penicillamine, hydralazine, propylthiouracil,12 and cocaine adulterated with levamisole.12 Cholesterol embolization can mimic the clinical features of SVV with lower extremity rash or livedo reticularis, but ANCA assay is negative. The differential diagnosis of lung hemorrhage and nephritis includes anti-GBM disease, alone or with ANCA disease.

Natural History

Before the advent of immunosuppressive therapy, patient survival in MPA and GPA was poor, with most dying in less than 1 year. With adequate immunosuppressive therapy, 5-year kidney and patient survival is 65% to 75%.5,41,42 The success of long-term maintenance of kidney function is inversely correlated with the serum creatinine concentration when therapy begins, indicating the importance of early diagnosis and prompt therapeutic intervention. Patient survival increases with early treatment of pulmonary hemorrhage and sepsis and avoidance of overimmunosuppression leading to life-threatening infections. Adverse events from therapy, including infections, are the leading cause of death in the year after diagnosis.41 Older age, higher serum creatinine at presentation, pulmonary hemorrhage, and dialysis-dependent kidney failure correlate with an overall poor outcome; however, dialysis-dependent kidney failure may resolve with aggressive early therapy. Respiratory tract disease and PR3-ANCA are predictors of higher relapse rates.42 Pathologic features correlating with kidney outcome include histologically normal glomeruli, glomerular sclerosis, interstitial leukocyte infiltration, tubular necrosis, and tubular atrophy.40 Increased histologically normal glomeruli or glomeruli with cellular crescents correlate with a better prognosis than higher proportions of globally sclerotic glomeruli, suggesting that active inflammatory lesions may be suppressed if not reversed by treatment, whereas chronic injury at initiation of treatment may be irreversible.

When severe GN is present, the kidney prognosis is similar for patients with MPA, GPA, or EGPA, and renal-limited pauci-immune crescentic GN. Kidney involvement is less common and usually less severe in patients with EGPA. Cardiac involvement is the most frequent cause of death in patients with EGPA but rarely causes mortality in MPA or GPA. GPA has a broad spectrum of clinical manifestations, from localized indolent disease to fulminant multisystem disease. Some patients have disease limited to the upper respiratory tract or the upper and lower respiratory tract. Limited disease may have a more benign natural history than systemic disease with substantial kidney involvement and may warrant less aggressive treatment.

Patients with MPO-ANCA have a slightly better kidney outcome than those with PR3-ANCA, although they have more kidney impairment and more chronic kidney pathologic changes at presentation.

Patients with PR3-ANCA have more extrarenal organ manifestations (especially respiratory tract disease), more frequent relapse, and higher mortality than patients with MPO-ANCA. Regardless of the category of AAV, the best clinical predictor of kidney outcome is the glomerular filtration rate (GFR) at diagnosis.

Treatment

In patients with AAV affecting the kidneys, the goal is to avoid overtreating mild disease or undertreating severe disease. GN resulting in kidney impairment is an indication for immunosuppressive treatment in patients with GPA, MPA, EGPA, and renal-limited pauci-immune crescentic GN. Patients with AAV and concurrent immune complex disease should be treated similarly to patients with AAV alone. Patients with AAV and concurrent anti-GBM disease should be treated similarly to patients with anti-GBM disease alone. Treatment involves three phases: induction of remission, maintenance of remission, and treatment of relapse (Fig. 26.11).

Induction Therapy

Standard induction therapy for AAV combines corticosteroids with an immunomodulatory agent, usually cyclophosphamide or rituximab.5,42–55 Combined corticosteroid and cyclophosphamide induces remission in approximately 75% of patients at 3 months and 90% at 6 months. Combined induction regimens vary with respect to agents, doses, route of administration, and duration. One approach begins with methylprednisolone 7 mg/kg/day IV for 3 days, followed by oral prednisone 1 mg/kg/day, tapering to an alternate-day regimen and discontinuing within 3 to 6 months.44 Alternatively, corticosteroids can be administered as prednisolone 1 mg/kg/day tapered to 0.25 mg/kg/day by 3 months.48 Most trials used an IV methylprednisolone dose of 1 to 3 g followed by oral prednisone 1 mg/kg/day (max 80 mg).
Early steroid withdrawal is possible using combination therapy;
49 patients were successfully induced with a short course of oral glucocorticoids (1–2 weeks) while receiving combination cyclophosphamide (3 months) and rituximab (2 doses) therapy.56 The Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis (PEXIVAS) trial demonstrated noninferiority of reduced corticosteroid dosing (60% less exposure) compared with standard dosing in end-stage kidney disease (ESKD) and all-cause mortality.57 Novel complement-based strategies are being evaluated to reduce cumulative corticosteroid exposure. In a phase II trial, avacopan (CCX168; selective C5a receptor inhibitor) was as effective as prednisone in patients with newly diagnosed or relapsing vasculitis.58 The phase III Avacopan Development in Vasculitis to Obtain Corticosteroid Elimination and Therapeutic Efficacy (ADVOCATE) trial for safety and efficacy of avacopan compared with prednisone showed that 72.3% of patients achieved remission with avacopan compared with 70.1% with prednisone.59,60 Other complement-based trials are underway with IFX-1, an anti-C5a antibody (NCT03712345, NCT03895801).

Because of the morbidity with long-term corticosteroid use, a reduceddose corticosteroid regimen and discontinuation by 16 weeks in most patients is recommended. Utilization of cyclophosphamide or combination of cyclophosphamide and rituximab can help taper steroids faster. Corticosteroid treatment is combined with oral cyclophosphamide 2 mg/kg/day or cyclophosphamide at 0.35 to 0.5 g/m2 IV per month adjusted upward to 1 g/m2, based on the leukocyte count after 2 weeks, with a target nadir of 3000 cells/mm3. Oral cyclophosphamide dose can be reduced by 25 mg for patients older than 60 years. A comparison by the European Vasculitis Study Group (CYCLOPS trial) indicated that IV cyclophosphamide has similar remission rates as oral cyclophosphamide while reducing the total cyclophosphamide dose.52

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved rituximab for AAV induction therapy based on the results of two randomized controlled trials (RCTs), noting that rituximab-based cyclophosphamide-sparing strategies were comparable to traditional cyclophosphamide induction protocols.50,51 The Rituximab for ANCA-Associated Vasculitis

(RAVE) trial51 noted no difference in remission off all therapy in 6

Recommended Treatment of ANCA-Associated Vasculitis
ANCA glomerulonephritis

No life-threatening or
organ-threatening disease

Life-threatening or organthreatening disease

Rituximab with prednisone
6 months or cyclophosphamide
IV q month × 3 months,
prednisone × 16 weeks

Methylprednisolone and/or plasma
exchange, cyclophosphamide
IV q month × 3–6 months,
prednisone × 16 weeks

Remission following
rituximab

Treatment
resistance

Remission following
cyclophosphamide

Follow closely to detect
disease early relapse

Remission maintenance
with azathioprine

Relapse

Relapse

Rituximab with prednisone if relapse caught early
or cyclophosphamide IV q month with prednisone
for life/organ-threatening disease

Remission

Rituximab or oral
cyclophosphamide

After 12–18 months in remission,
maintenance immunosuppression may
be discontinued with close follow-up

Fig. 26.11 Recommended treatment for antineutrophil cytoplasmic antibody (ANCA)偃associated vasculitis.

months between patients treated with prednisone and four infusions of 375 mg/m2 rituximab versus oral cyclophosphamide (64% in rituximab arm, 55% in cyclophosphamide arm). The RITUXVAS trial61 62 compared 6 to 10 infusions of cyclophosphamide followed by azathioprine to 4 infusions of 375 mg/m2 rituximab in combination with 2 infusions of cyclophosphamide without maintenance therapy. There was no difference in remission rates at 12 months between the groups.

In RAVE and RITUXVAS, there were no significant differences in adverse events between rituximab and cyclophosphamide. Compared with cyclophosphamide, rituximab is more effective in PR3-ANCA disease.63 Our approach uses two 1-g doses 14 days apart.
Combination of cyclophosphamide-rituximab allows a rapid steroid taper and reduces mortality, relapses, and ESKD compared with propensity-matched patients from European Vasculitis Study Group (EUVAS) trials.64 We recommend combination IV cyclophosphamiderituximab in patients with severe kidney or pulmonary involvement to decrease cumulative cyclophosphamide exposure.
Plasma exchange (PLEX) has come under much scrutiny. Prior studies showed benefit in patients with life-threatening pulmonary hemorrhage53 and patients who have dialysis-dependent kidney failure at presentation.54 With pulmonary hemorrhage, 20 of 20 patients treated with early PLEX had resolution of pulmonary bleeding compared with a 50% mortality in historical controls.53 A EUVAS trial (MEPEX) evaluated the efficacy of IV methylprednisolone as induction therapy or PLEX in patients who had a serum creatinine of more than 500 µmol/L.54 Patient survival and adverse events were similar in patients who did or did not receive PLEX. PLEX was associated with a 24% reduced risk for progression to ESKD, from 43% to 19% at 1 year.54 Conversely, the PEXIVAS trial noted no reduction in mortality or ESKD with the use of PLEX in patients with severe AAV. The PEXIVAS trial enrolled 704 patients with severe AAV (an eGFR rate

of <50 mL/min/1.73 m2 or diffuse pulmonary hemorrhage). ESKD or death occurred in 28.4% patient in the PLEX group versus 31% patients in control group.57 One drawback of PEXIVAS was the lack of kidney biopsy data on interstitial fibrosis and tubular atrophy. PLEX had a trend for benefit in subgroup analyses of patients with pulmonary hemorrhage. Hence, we still consider PLEX in patients with acute kidney injury (estimated GFR [eGFR] < 30 mL/min/1.73 m2) without significant chronic changes of interstitial fibrosis. We also use PLEX in patients presenting with severe pulmonary hemorrhage requiring mechanical ventilation or supplemental oxygen.

Maintenance Therapy

Duration of induction therapy and intensity of maintenance therapy should be decreased as much as possible to reduce toxic side effects. This is difficult because of the tendency for AAV to recur. Various approaches to reduce the cyclophosphamide dose include using IV cyclophosphamide rather than oral, substituting a less toxic maintenance drug after 3 to 6 months, and discontinuing therapy earlier in patients with lower risk for relapse. IV cyclophosphamide regimens afford one-third to one-half the total dose of cyclophosphamide given in oral regimens. Long-term follow-up notes longer time to relapse in the oral cyclophosphamide treated group, at the cost of increased leukopenia.55 Azathioprine after 3 to 6 months of therapy can reduce cyclophosphamide dose.48 In another EUVAS trial (CYCAZAREM), cyclophosphamide was replaced with azathioprine 2 mg/kg/day after 3 to 6 months with no change in the relapse rate at the end of the study.48 When azathioprine 2 mg/kg/day was compared with mycophenolate mofetil (MMF) 2 g/day in a randomized control fashion, relapses were more common in the MMF group compared with the azathioprine group (unadjusted hazard ratio [HR] for MMF, 1.69; 95% confidence interval [CI] 1.06–2.70). Adverse events, disease activity score, GFR, and proteinuria did not differ between groups, but two instances of bladder cancer and three of skin cancer were noted in the azathioprine group compared with one instance of skin cancer in MMF group (HR, 0.25; 95% CI, 0.02–2.62).65

The French Vasculitis Study Group compared methotrexate with azathioprine as maintenance therapy in patients with GPA and MPA.66 Methotrexate was as effective as azathioprine for maintenance of remission, but methotrexate did not have fewer side effects. Methotrexate should not be used in patients with eGFR less than 30 mL/min/1.73 m2. Karras et al. compared 24 versus 48 months of azathioprine remission maintenance therapy. Although 48 months of azathioprine therapy had fewer relapses (22% vs. 63%), more severe adverse events were noted (9 vs. 3 events).67 An alternative is to stop all immunosuppressive therapy at 6 to 12 months if the patient is in full remission, especially if the patient is at lower risk for relapse.

Rituximab is another option for maintenance of remission.66 67 The MAINRITSAN trial compared rituximab with azathioprine for maintenance in patients with MPA and GPA in remission after induction treatment with cyclophosphamide and glucocorticoids. Rituximab was more effective than azathioprine for preventing relapse, including renal relapse,66 for up to 60 months.68 The rituximab versus azathioprine in remission maintenance (RITAZAREM) trial is evaluating patients with relapsing ANCA vasculitis after achieving remission with rituximab induction. Preliminary results suggest a lower relapse rate with rituximab as opposed to azathioprine (18% vs. 38%).69 70

Dose and frequency of rituximab infusion and duration of therapy have been controversial. Tailored rituximab dosing of 500 mg based on reappearance of CD19+B cells or ANCA or rise in ANCA titer had similar relapse rates compared with fixed 500 mg rituximab dose every 6 months in the MAINRITSAN2 study (17.3% vs. 9.9%, P = .22).71 The tailored group had fewer infusions of rituximab (median 3 vs. 5), suggesting that dose and frequency of rituximab infusion can be successfully modified. The MAINRITSAN3 trial treated patients in remission from MAINRITSAN2 with placebo versus rituximab 500 mg biannually. The rituximab group had more major relapse-free survival compared with placebo group (100% vs. 87%, P = .009).72 Although the adverse events were similar, the trial included patients who had previously tolerated rituximab.

Because rituximab is a biologic agent that has immunogenic mouse protein in its structure, many patients have become sensitized and some have developed serum sickness–like disease. If sensitivity develops during maintenance therapy, rituximab may not be an option for recurrent clinical disease. Fully humanized anti-CD20 antibodies, ofatumumab, obinutuzumab, and ocrelizumab may have a lower risk of sensitization but efficacy data is lacking. The expense of rituximab may be prohibitive for some patients. Because of these concerns and the risk of hypogammaglobulinemia, we suggest using a rituximab maintenance dose of 500 mg. Additionally, because of ease of reinduction,73 we recommend discontinuing rituximab if patients are in long-term remission (>2 years).

The role of antimicrobial agents such as trimethoprim-sulfamethoxazole (TMP-SMX) in maintenance of remission is controversial. Some studies suggest a benefit, but others do not because of an increased likelihood of relapse.74 TMP-SMX may be useful adjunct therapy, especially in patients with upper respiratory tract disease but should not be used in the absence of immunosuppressive drugs with more proven efficacy (e.g., cyclophosphamide, azathioprine) for induction or maintenance therapy for systemic vasculitis or GN. We often use TMP-SMX as prophylaxis in patients receiving prednisone at 20 mg or higher dose.

evidence of recurrent disease, not by increase in ANCA titer alone.36

Increase in ANCA titer does increase the likelihood of a relapse, and some advocate preemptive immunosuppressive therapy if the titer increases by at least fourfold.36 We prefer identifying clear-cut clinical or pathologic evidence of relapse before increasing or resuming immunosuppressive therapy.44

Observational data suggest that rituximab is the best treatment for relapses and is superior to cyclophosphamide.50 Reinstitution of treatment similar to an induction regimen is used most often, but less intensive or less toxic therapy may be adequate.44 Lifetime exposure to cyclophosphamide is a consideration when selecting treatment for relapses. In addition to rituximab or cyclophosphamide, other therapies can be used for treating relapse, including azathioprine, MMF, methotrexate, or combinations of these drugs tailored to the individual patient with recalcitrant disease.

The MAINRITSAN and RITAZAREM trials suggest rituximab may be more effective in reducing relapse rates compared with azathioprine.66,69,70

Long-term therapy may not be required, especially when there is a low risk for relapse. In our Glomerular Disease Collaborative Network (GDCN) cohort, 277 patients (65%) of 427 patients stopped immunosuppressive therapy. Some patients (23%) stayed off therapy for 5 or more years, suggesting long-term remission off therapy is possible. Additionally, 197 patients never relapsed with no difference between those who were on therapy or off.73 In prospective observational studies from the GDCN, the relative risk for relapse was increased in individuals who had PR3-ANCA and respiratory tract disease.42

Patients had more than a threefold risk for relapse compared with individuals having MPO-ANCA and without lung or ear, nose, and throat disease. This model of relapsing disease was investigated in a separate registry in France in which the combination of PR3-ANCA and lung disease was the most important predictive marker.75

Comparison of the major rituximab-based trials (RAVE, RITUXVAS, MAINRITSAN1, MAINRITSAN2, and RITAZAREM) shows a significant underrepresentation of MPO-ANCA patients compared with PR3-ANCA. There were 2 to 3 times as many PR3ANCA patients compared with MPO-ANCA patients in the major rituximab-based trials. Because PR3-ANCA predominates in these trials (232 vs. 111), it is likely that the number of flares seen was higher than what would have been expected with MPO-ANCA patients. Thus, in patients having a much smaller risk for relapse, all therapy may be stopped, provided the patient is closely monitored (e.g., home urinary dipstick testing to monitor for recurrence of hematuria). The risk for relapse is about 10% to 15% even with maintenance therapy.

Transplantation

Kidney transplantation is not contraindicated in patients with ESKD caused by AAV. In a multicenter experience, the vasculitis relapse rate was 0.02 per patient per year76 (see Chapter 113). Although a positive ANCA titer at the time of transplantation is not thought to increase the risk for recurrent disease in the transplant,77 a study of 16 patients suggested a higher likelihood of relapse with PR3-ANCA compared with MPO-ANCA (OR, 2.19; $P = .71$).78 An increase in ANCA titer and an active urine sediment suggest recurrent GN, but the diagnosis requires pathologic confirmation. Recurrent ANCA GN in a kidney transplant responds similarly to recurrent disease in native kidneys and usually is treated with cyclophosphamide and corticosteroids. Rituximab has been used successfully and avoids the risk for cyclophosphamide toxicity.79

Relapse Therapy

POLYARTERITIS NODOSA

One-fourth to one-half of patients with AAV will experience a relapse within several years. Relapses are diagnosed by clinical and pathologic

PAN is a systemic necrotizing arteritis that affects predominantly main visceral arteries and their intraparenchymal branches.2,26,80 The Chapel

Hill nomenclature system limits the diagnosis of PAN to patients who have only arteritis.4 The presence of vasculitis in capillaries and venules excludes a diagnosis of PAN and indicates SVV. Thus, GN excludes a diagnosis of PAN. When PAN is distinguished from MPA, the two categories of vasculitis have different pathologic characteristics, clinical features, and natural histories.81

Pathogenesis

The etiology and pathogenesis of PAN are unknown and probably are diverse.2 When PAN is separated from MPA, the latter is associated with ANCAs. An immune complex trigger for PAN has been proposed but not confirmed. A minority of patients have hepatitis B virus (HBV) infection, suggesting that the HBV infection is producing immune complexes that localize in arterial walls and induce inflammation, ultimately leading to narrowing and weakening of vessel walls, thereby predisposing to aneurysms.2 However, evidence that HBV infection is causing vascular immune complex deposition is stronger in certain forms of GN and SVV than in PAN.

Epidemiology

When defined by the Chapel Hill nomenclature system, PAN has a low prevalence of 1.5 per million.23 Prevalence is higher in regions with higher levels of endemic HBV infection. PAN affects males and females equally and is found in all races. Onset occurs most frequently between ages 40 and 60 years.

Fig. 26.12 Renal Angiogram in Polyarteritis Nodosa. Angiogram shows patchy kidney perfusion defects (arrowheads) and aneurysms (arrows).

Clinical Manifestations

The usual clinical presentation of PAN includes nonspecific constitutional symptoms: fever, malaise, arthralgias, myalgias, weight loss, and manifestations of arteritis.39 81 82 Peripheral neuropathy, typically in the form of mononeuritis multiplex, is common. This is caused by inflammation of small epineural arteries and is clinically indistinguishable from the peripheral neuropathy caused by other forms of vasculitis affecting epineural arteries, such as MPA, GPA, and EGPA.

GI involvement occurs in about half of patients, usually manifesting as abdominal pain and hematochezia. Bowel infarction is uncommon and perforation is rare. Kidney involvement produces infarction and hemorrhage, as indicated by flank pain and hematuria. Rupture of an arterial aneurysm with retroperitoneal or peritoneal hemorrhage is an uncommon but potentially lethal renal complication. Approximately one-third of patients develop hypertension, rarely reaching the malignant range.

Red, tender inflammatory nodules are the most common cutaneous manifestation. Infarction, ulceration, and livedo reticularis may be present.

Arterial aneurysms may be detected by angiography in patients with PAN (Fig. 26.12). This is not a completely specific determination because any necrotizing arteritis that affects arteries large enough to be seen by angiography can produce this finding.

Pathology

Any artery in the kidney can be affected by PAN, although the interlobar and arcuate arteries are affected most often.17 Nodular inflammatory lesions and aneurysms (pseudoaneurysms) can be observed grossly when medium-sized arteries are involved. Inflammation in small arteries can be observed only by microscopy.

The characteristic acute lesion is segmental transmural fibrinoid necrosis of arteries, usually accompanied by infiltrating leukocytes with leukocytoclasia[3] (Fig. 26.13). The earliest lesions have numerous neutrophils, and later lesions have predominantly mononuclear leukocytes. Acute lesions may be complicated by thrombosis or hemorrhage. Older lesions develop fibrosis and end-arterial remodeling.

The aneurysms of necrotizing arteritis are not true aneurysms but

Fig. 26.13 Necrotizing Arteritis in Arcuate Artery of Patient With Polyarteritis Nodosa. The lumen is partially occluded by thrombotic material that is continuous with the fibrinoid material that has replaced the entire wall of the artery. (H&E, ×50.)

rather inflammatory pseudoaneurysms—the walls of the arteries are not dilated but have been eaten away by the necrotizing inflammation, which then erodes into the surrounding perivascular tissue to create an enlarged lumen. This explains the propensity for such lesions to induce thrombosis or rupture.

The necrotizing arteritis of PAN is indistinguishable by light microscopy from arteritis caused by other necrotizing vasculitides affecting arteries.[2,3] For example, necrotizing arteritis in a skeletal muscle biopsy specimen or a peripheral nerve biopsy specimen is histologically identical whether caused by PAN, MPA, GPA, or EGPA. For these vasculitides to be distinguished, additional clinical and serologic information is required.

Differential Diagnosis

Clinical features may assist in distinguishing PAN from other forms of vasculitis, especially other forms of necrotizing vasculitis that can affect arteries, such as MPA[2,3,83] (Table 26.5). A positive ANCA test supports

Clinical Feature

Polyarteritis
Nodosa

Microscopic
Polyangiitis

Microaneurysms by angiography

Yes

No (rare)

arteritis is a complication of KD that is present in some patients. Clinically significant kidney involvement is rare and KD is seldom encountered by nephrologists. If untreated, approximately 20% to 25% of children develop coronary artery aneurysms that may cause myocardial infarction.85 Most patients undergoing autopsy after fatal myocardial infarction (MI) caused by coronary artery arteritis also have vasculitis in renal arteries.84

Rapidly progressive nephritis

No

Yes (very common)

Pulmonary hemorrhage

No

Yes

Pathogenesis

Renovascular hypertension

Yes (10%–33%)

No

Clinical Differences Between
Polyarteritis Nodosa and Microscopic
Polyangiitis
TABLE 26.5

Peripheral neuropathy

Yes (50%–80%)

Yes (10%–20%)

Positive hepatitis B serology

Uncommon

No

Positive ANCA

Rare

Frequent

Relapses

Rare

Frequent

ANCA, Antineutrophil cytoplasmic antibody.
Modified from Scott DGI, Watts RA. Epidemiology and clinical features of systemic vasculitis. Clin Exp Nephrol. 2013;17:607–610.

the diagnosis of one of the AAVs rather than PAN. The presence of GN indicates some form of SVV rather than PAN. Vasculitic pulmonary disease is rare in PAN but common in MPA, GPA, and EGPA.

Peripheral neuropathy or muscle tenderness with arteritis in epineural or skeletal muscle arteries is not a useful differentiating feature because it often occurs in PAN and in AAV. Kawasaki disease (KD) causes necrotizing arteritis but is distinguished from PAN by the presence of the mucocutaneous lymph node syndrome.

Natural History

The natural history of PAN is muddled because early studies grouped MPA with PAN. PAN with multisystem involvement has a poor prognosis without therapy.26 The 10-year survival with appropriate treatment is approximately 80%. Approximately 15% of patients who enter remission do relapse, which is much less frequent than with MPA. Relapse is more likely if treatment is delayed.

Treatment

PAN in patients without HBV infection is treated with corticosteroids and cytotoxic drugs (usually cyclophosphamide) if there is life-threatening major organ involvement.26 81 82 Regimens vary and include treatments similar to those described earlier for MPA and GPA. In patients with no risk factors for poor outcome (e.g., age > 50 years; cardiac, gut, or kidney involvement), corticosteroids alone may be adequate and are less toxic than corticosteroids combined with cytotoxic agents.82 In patients without major organ involvement, azathioprine or methotrexate can be used to reduce steroid exposure.

Aggressive immunosuppressive therapy without initial antiviral therapy is contraindicated in patients with HBV-associated PAN because of potential adverse effects on the outcome of the HBV infection. Patients with hepatitis B viremia should be treated with effective hepatitis B therapy. Often additional immunosuppression is needed, but short-term corticosteroid treatment combined with antiviral agents and possibly PLEX should precede more extensive immunosuppression in such patients.

The occasional occurrence of KD as an endemic or epidemic disease suggests that the cause may be an infectious agent or environmental toxin.2 Both cell-mediated and antibody-mediated mechanisms have been incriminated, as well as dysregulated innate immunity, possibly mediated by innate immune pathogen-associated molecular patterns.86 At present, the etiology and pathogenesis of KD are unknown.

Epidemiology

KD usually occurs in children younger than 5 years (median, 2–3 years).85 First described in Japan, it occurs worldwide but is more common in Asians and Polynesians than in Whites and Blacks. In Japan, the incidence is 50 in 100,000 children younger than 5 years, with 50% of the children younger than 2 years.23 85 KD occasionally occurs in an endemic or epidemic pattern but usually is sporadic (with the COVID-19 pandemic, there have been cases of a Kawasaki-like disease in children after COVID-19 infection). KD is not transmitted person to person and does not occur in clusters within households, schools, or nurseries.86

Clinical Manifestations

MCLN syndrome is the characteristic clinical manifestation of KD.4 85 86 This includes fever (temperature of 38°C to 40°C), mucosal inflammation, swollen red tongue (strawberry tongue), polymorphous erythematous rash, indurative edema of the extremities, erythema of palms and soles, desquamation from the tips of digits, conjunctival injection, and enlarged lymph nodes. Frequency of active arteritic lesions peaks during the first week of the illness and greatly reduces after 1 month. Arteritis often manifests as cardiac disease. Thrombosis of inflamed coronary arteries in patients with KD is the most common cause of childhood MI. Clinically significant kidney disease is surprisingly uncommon given that autopsy reveals arteritis in kidney vessels in up to three-fourths of patients.84

Pathology

KD involves small- and medium-sized arteries. The acute histologic lesion is necrotizing inflammation with less fibrinoid necrosis and more vessel wall edema than usually observed with PAN84 (Fig. 26.14). Aneurysm (pseudoaneurysm) formation and thrombosis may occur. The most frequent site of arteritis is the coronary arteries, followed by the kidney arteries.84 Arteritis most often affects interlobar arteries, occasionally arcuate arteries, and rarely interlobular arteries.

Differential Diagnosis

KAWASAKI DISEASE

KD is sometimes misdiagnosed as childhood PAN. The differentiation of KD from PAN is important because corticosteroid treatment may increase the risk for coronary artery aneurysms in KD. Arteritis in a child younger than 5 years should always raise the possibility of KD. The presence or absence of the MCLN syndrome is the basis for distinguishing between KD and other forms of arteritis.4

Definition

Natural History

KD is an acute febrile illness that usually occurs in young children, often under 1 year, and is characterized by the mucocutaneous lymph node (MCLN) syndrome (see later discussion).2 4 84–86 Necrotizing

KD usually is self-limited, with an uneventful recovery if treated promptly with IV gamma globulins.84 85 Recurrence occurs in less than 5% of patients.85

Fig. 26.14 Kawasaki Disease Arteritis Affecting Renal Interlobar Artery in a Young Child. The artery wall is intact on the far left. The remainder of the wall has extensive edema, infiltration by mononuclear leukocytes, and a band of fuchsinophilic (red) fibrinoid material roughly at the junction between the inflamed intima and muscularis. (Masson trichrome, ×25.)

Treatment

Aspirin and single IV immunoglobulin infusion (2 g/kg) within 10 days of fever onset are the standard therapy for KD.84 85 Moderate to high doses of aspirin are used until resolution of fever followed by lowdose for antiplatelet effect. The role of corticosteroid treatment is controversial but may be beneficial in patients with severe disease that does not respond well to aspirin and intravenous immunoglobulin.

TAKAYASU ARTERITIS AND GIANT CELL ARTERITIS

Takayasu arteritis and giant cell arteritis (GCA) affect the aorta and its major branches more often than other forms of vasculitis.4 87 88 GCA has a predilection for the extracranial branches of the carotid artery but can affect arteries in almost any organ. Takayasu arteritis has a predilection for major arteries supplying the extremities. Both diseases cause chronic vascular inflammation, often with a granulomatous appearance that may include multinucleated giant cells. GCA, but not Takayasu arteritis, is associated with polymyalgia rheumatica (PMR).
The relation of Takayasu arteritis and GCA is not known. The striking demographic differences suggest that they are distinct pathophysiologic entities.

Pathogenesis

The etiology and pathogenesis of GCA and Takayasu arteritis are unknown.2 Because of the histologic changes and the nature of the infiltrating leukocytes, cell-mediated immune mechanisms are incriminated. The inciting antigen or autoantigen has not been identified.

Epidemiology

Takayasu arteritis is seen most frequently in Asia. GCA occurs most often in individuals of northern European ancestry. Takayasu arteritis has a female-to-male ratio of approximately 9:1 and GCA of 4:1.
Takayasu arteritis usually is diagnosed in those between ages 10 and 20 years and is rare after age 50 years. GCA is rare before age 50 years.
Takayasu arteritis has uniform global incidence of 1 to 2 per million.23 Race and ethnicity affect the vascular distribution of Takayasu arteritis, with the aortic arch and its branches affected mainly in Japanese patients, abdominal aorta and its branches affected mainly in Indian patients, lower abdominal aorta affected mainly in African populations, and kidney involvement most common in Asian and African populations.88

Fig. 26.15 Severe Giant Cell Arteritis Affecting a Main Renal Artery. This caused marked renal atrophy and renovascular hypertension. (H&E, ×50.)

GCA is the most common form of vasculitis, with an incidence highest in populations of Scandinavian descent, with an annual incidence of 15 to 35 per 100,000 older than 50 years.23

Clinical Manifestations

In addition to constitutional symptoms, such as fever, arthralgias, and weight loss, the major clinical manifestations of Takayasu arteritis and

GCA are caused by arterial narrowing and resultant ischemia.2 87 Major clinical manifestations of Takayasu arteritis are reduced pulses (95% of patients), vascular bruits, claudication, and renovascular hypertension. Renovascular hypertension results from kidney ischemia caused by renal artery stenosis or aortic coarctation.89 Reduced aortic elasticity and impairment of carotid artery baroreceptors also may play a role in some patients. The European League Against Rheumatism (EULAR) recommends thorough imaging assessment (see later discussion) of the entire major arterial tree when a diagnosis of Takayasu arteritis is suspected.90

Headache is the most common presenting symptom in patients with GCA. Temporal artery tenderness, nodularity, or decreased pulsation is present in half of patients. Other symptoms include blindness, deafness, jaw claudication, tongue dysfunction, extremity claudication, and reduced pulses. More than half of patients with GCA have PMR, characterized by stiffness and aching in the neck and the proximal muscles of the shoulders and hips. Clinically significant kidney disease is less common in GCA than in Takayasu arteritis. Case reports of necrotizing and crescentic GN associated with GCA may represent examples of GPA or MPA with temporal artery involvement.

Computed tomography (CT), magnetic resonance angiography (MRA), fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT), and contrast-enhanced ultrasonography are used to diagnose and assess the activity of vascular inflammation in Takayasu arteritis and GCA.88 CT and MRA identify structural changes (e.g., stenosis, aneurysms). FDG-PET/CT detects active inflammation even in vessels that show no overt structural changes by other imaging techniques.

Pathology

The aortitis and arteritis of Takayasu arteritis and GCA cannot be confidently differentiated by pathologic examination.4 Both are characterized in the active phase by inflammation with a predominance of mononuclear leukocytes, often with scattered multinucleated giant cells (Fig. 26.15). The chronic phase is characterized by progressive fibrosis that may cause severe narrowing of vessels, with resultant ischemia. Major renal arteries are often found to be involved at autopsy in patients with Takayasu arteritis and those with GCA. However, clinically significant kidney disease is relatively common in Takayasu arteritis but rare in GCA. A glomerular lesion characterized by nodular mesangial matrix expansion and mesangiolysis may occasionally be a component of Takayasu arteritis.91

Differential Diagnosis

There is overlap between the clinical manifestations and pathologic features of Takayasu arteritis and GCA. Patient age and presence or absence of PMR are the best factors for distinguishing between these vasculitides.4 GCA has been called temporal arteritis, but not all patients have temporal artery involvement, and patients with other types of vasculitis (PAN, GPA, MPA) can have involvement of the temporal arteries.

Treatment

Corticosteroids are the usual treatment of GCA and Takayasu arteritis.90 EULAR recommends initial daily therapy with prednisolone 1 mg/kg until disease control followed by tapering over several months to over a year.90 92 Prolonged treatment may be dictated by persistent disease activity. Rapid steroid taper is associated with increased risk of relapse.93 Tocilizumab, an interleukin (IL)-6 inhibitor, has been a successful adjunct to corticosteroids in patients at high risk for corticosteroid-related adverse events or with life- or organ-threatening disease.92–94 Methotrexate is an alternative. Cytotoxic agents such as cyclophosphamide may be required in patients with recalcitrant disease. Patients with GCA are at a higher risk of thrombotic vascular events. Antiplatelet or anticoagulant therapy is not recommended unless indicated for another reason.92

Management of kidney disease is typically not an issue with GCA, although rare patients have ischemic kidney manifestations. Renovascular hypertension is the major kidney problem in Takayasu arteritis.88 89 When bilateral renal artery involvement occurs, angiotensin-converting enzyme (ACE) inhibitors may precipitate kidney failure in patients with Takayasu arteritis.95 When medical management fails, the renovascular hypertension in patients with Takayasu arteritis may be controlled by vascular surgery or endovascular angioplasty.88 89 Reconstructive vascular surgery should be performed during a quiescent phase of the disease.90 The management of renovascular hypertension is discussed in Chapter 43

COVID AND MANAGEMENT OF VASCULITIS

Although only case reports exist on development of vasculitis in patients with COVID-19,96–98 the impact is substantial. There are scarce data on treatment in patients with concurrent vasculitis and COVID-19, and controversy on whether immunosuppression is protective or harmful. In some cases immunosuppression was discontinued during active infection,99 and steroids were used for treatment in others.98 It is unclear if one immunosuppression is superior or if rituximab is safe in patients with vasculitis flare and COVID-19. The question about vaccination is unanswered. How does the COVID-19 vaccine affect management, especially around time of vaccination? Some groups suggest avoiding overimmunosuppression,100 but the question remains whether we are adequately treating our patients with vasculitis.

SELF-ASSESSMENT QUESTIONS

1. In a patient who has systemic vasculitis affecting multiple organs, a kidney biopsy showing GN that is a component of the systemic vasculitis is definitive evidence that the systemic vasculitis is a:
A. large-vessel vasculitis.
B. small-vessel vasculitis.
C. medium-vessel vasculitis.
D. variable-vessel vasculitis.
2. If pathologic and serologic studies in a patient with crescentic GN are diagnostic for anti-GBM disease, ANCA testing is:
A. unnecessary because it is unlikely to be positive.
B. unnecessary because it would not change the prognosis if positive.
C. necessary because it is positive in one-fourth to one-third of patients and changes the prognosis.
D. necessary because a positive ANCA result rules out anti-GBM disease.
3. Which of the following is most common in patients with PAN?
A. Glomerulonephritis
B. Pulmonary hemorrhage
C. Polymyalgia rheumatica
D. Hepatitis B infection

4. Which of the following is the most common clinical sign or symptom caused by Takayasu arteritis?
A. Flank pain caused by kidney infarction
B. Acute kidney failure
C. Hematuria
D. Hypertension
5. Is targeted B-cell therapy with rituximab an acceptable component of induction therapy for ANCA-associated vasculitis and glomerulonephritis?
A. Yes, because induction with rituximab has fewer adverse events than induction with cyclophosphamide.
B. Yes, because clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.
C. No, because clinical trials have shown that induction therapy with rituximab is inferior to induction with cyclophosphamide.
D. No, because rituximab is not approved by the FDA for induction therapy.

REFERENCES

1. Jennette JC, Thomas DB. Pauci-immune and antineutrophil cytoplasmic autoantibody glomerulonephritis and vasculitis. In: Jennette JC, Olson JL, Silva FG, D’Agati VD, eds. Heptinstall’s Pathology of the Kidney. 7th ed. Philadelphia: Wolters Klewer; 2015:685–714.
2. Jennette JC, Singh H. Renal invovement in polyarteritis nodosa, Kawasaki disease, giant cell arteritis and Takayasu arteritis. In: Jennette JC, Olson JL, Silva FG, D’Agati VD, eds. Heptinstall’s Pathology of the Kidney. Philadelphia: Wolters Klewer; 2015:715–738.
3. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;337:1512–1523.
4. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1–11.
5. Jennette JC, Nachman PH. ANCA glomerulonephritis and vasculitis. Clin J Am Soc Nephrol. 2017;12:1680–1691.
6. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol. 2014;10:463–473.
7. Damoiseaux J, Csernok E, Rasmussen N, Cohen Tervaert JW, Bossuyt X. Antineutrophil cytoplasmic antibodies: appropriate use and interpretation. Ann Rheum Dis. 2017;76:e24.
8. Mahr A, Katsahian S, Varet H, et al. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis. 2013;72:1003–1010.
9. Schlieben DJ, Korbet SM, Kimura RE, Schwartz MM, Lewis EJ. Pulmonary-renal syndrome in a newborn with placental transmission of ANCAs. Am J Kidney Dis. 2005;45:758–761.
10. Roth AJ, Ooi JD, Hess JJ, et al. Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. J Clin Invest. 2013;123:1773–1783.
11. Free ME, Stember KG, Hess JJ, et al. Restricted myeloperoxidase epitopes drive the adaptive immune response in MPO-ANCA vasculitis. J Autoimmun. 2020;106:102306.
12. Pendergraft III WF, Niles JL. Trojan horses: drug culprits associated with antineutrophil cytoplasmic autoantibody (ANCA) vasculitis. Curr Opin Rheumatol. 2014;26:42–49.
13. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest. 2002;110:955–963.
14. Little MA, Smyth CL, Yadav R, et al. Antineutrophil cytoplasm antibodies directed against myeloperoxidase augment leukocytemicrovascular interactions in vivo. Blood. 2005;106:2050–2058.
15. Xiao H, Schreiber A, Heeringa P, Falk RJ, Jennette JC. Alternative complement pathway in the pathogenesis of disease mediated by antineutrophil cytoplasmic autoantibodies. Am J Pathol. 2007;170:52–64.
16. Xiao H, Dairaghi DJ, Powers JP, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014;25:225–231.
17. Gou SJ, Yuan J, Chen M, Yu F, Zhao MH. Circulating complement activation in patients with anti-neutrophil cytoplasmic antibodyassociated vasculitis. Kidney Int. 2013;83:129–137.
18. Wu EY, McInnis EA, Boyer-Suavet S, et al. Measuring circulating complement activation products in myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2019;71:1894–1903.
19. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of antineutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. Ann Intern Med. 1990;113:656–663.
20. Lyons PA, Rayner TF, Trivedi S, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367:214–223.
21. Merkel PA, Xie G, Monach PA, et al. Identification of functional and expression polymorphisms associated with risk for antineutrophil cytoplasmic autoantibody-associated vasculitis. Arthritis Rheumatol. 2017;69:1054–1066.

22. Hilhorst M, van Paassen P, Tervaert JW. Proteinase 3-ANCA vasculitis versus myeloperoxidase-ANCA vasculitis. J Am Soc Nephrol. 2015;26:2314–2327.

23. Scott DGI, Watts RA. Epidemiology and clinical features of systemic vasculitis. Clin Exp Nephrol. 2013;17:607–610.
24. Cao Y, Schmitz JL, Yang J, et al. DRB1*15 allele is a risk factor for PR3ANCA disease in African Americans. J Am Soc Nephrol. 2011;22:1161–1167.
25. Duna GF, Galperin C, Hoffman GS. Wegener’s granulomatosis. Rheum Dis Clin North Am. 1995;21:949–986.
26. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. clinical aspects and treatment. Rheum Dis Clin North Am. 1995;21:911–947.
27. Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int. 2003;63:1164–1177.
28. Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum. 2012;64:3452–3462.
29. Damoiseaux J, Csernok E, Rasmussen N, Cohen Tervaert JW, Bossuyt X. Antineutrophil cytoplasmic antibodies: reporting and diagnostic strategies. Ann Rheum Dis. 2017;76:e39.
30. Jennette JC, Wilkman AS, Falk RJ. Diagnostic predictive value of ANCA serology. [editorial; comment] Kidney Int. 1998;53:796–798.
31. Savige J, Gillis D, Benson E, et al. International consensus statement on testing and reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). Am J Clin Pathol. 1999;111:507–513.
32. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683–692.
33. Rutgers A, Slot M, van PP, van B V, Heeringa P, Tervaert JW. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. Am J Kidney Dis. 2005;46:253–262.
34. McCall AS, Bhave G, Pedchenko V, et al. Inhibitory anti-peroxidasin antibodies in pulmonary-renal syndromes. J Am Soc Nephrol. 2018;29:2619–2625.
35. Sinico RA, Di TL, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. Am J Kidney Dis. 2006;47:770–779.
36. Han WK, Choi HK, Roth RM, McCluskey RT, Niles JL. Serial ANCA titers: useful tool for prevention of relapses in ANCA-associated vasculitis. Kidney Int. 2003;63:1079–1085.
37. Eisenberger U, Fakhouri F, Vanhille P, et al. ANCA-negative pauciimmune renal vasculitis: histology and outcome. Nephrol Dial Transplant. 2005;20:1392–1399.
38. Hauer HA, Bajema IM, Hagen EC, et al. Long-term renal injury in ANCA-associated vasculitis: an analysis of 31 patients with follow-up biopsies. Nephrol Dial Transplant. 2002;17:587–596.
39. Vizjak A, Rott T, Koselj-Kajtna M, Rozman B, Kaplan-Pavlovcic S, Ferluga D. Histologic and immunohistologic study and clinical presentation of ANCA-associated glomerulonephritis with correlation to ANCA antigen specificity. Am J Kidney Dis. 2003;41:539–549.
40. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol. 2010;21:1628–1636.
41. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010;69:1036–1043.
42. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med. 2005;143:621–631.
43. Jayne D, Rasmussen N. Twenty-five years of European Union collaboration in ANCA-associated vasculitis research. Nephrol Dial

Transplant. 2015;30(suppl 1):i1–i7.
44. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996;7:33–39.
45. Shah S, Hruskova Z, Segelmark M, et al. Treatment of severe renal disease in ANCA positive and negative small vessel vasculitis with rituximab. Am J Nephrol. 2015;41:296–301.

References

46. Geetha D, Kallenberg C, Stone JH, et al. Current therapy of granulomatosis with polyangiitis and microscopic polyangiitis: the role of rituximab. J Nephrol. 2015;28:17–27.
47. Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet. 1991;337:1137–1139.
48. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349:36–44.
49. Alberici F, Smith RM, Jones RB, et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCAassociated vasculitis. Rheumatology (Oxford). 2015;54:1153–1160.
50. Falk RJ, Jennette JC. Rituximab in ANCA-associated disease. N Engl J Med. 2010;363:285–286.
51. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–232.
52. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150:670–680.
53. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003;42:1149–1153.
54. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18:2180–2188.
55. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012;71:955–960.
56. Pepper RJ, McAdoo SP, Moran SM, et al. A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2019;58:260–268.
57. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382:622–631.
58. Jayne DRW, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol. 2017;28:2756–2767.
59. Merkel PA, Jayne D, Yue H, Schall T, Kelleher C, Bekker P. A randomized, double-blind, active-controlled study of avacopan in anti-neutrophilcytoplasmic antibody (ANCA)-associated vasculitis. Ann Rheum Dis. 2020;79:8.
60. Merkel PA, Jayne DR, Wang C, Hillson J, Bekker P. Evaluation of the safety and efficacy of avacopan, a C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: protocol for a randomized, double-blind, active-controlled, phase 3 trial. JMIR Res Protoc. 2020;9:e16664.
61. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–220.
62. Jones RB, Furuta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis. 2015;74:1178–1182.
63. Unizony S, Villarreal M, Miloslavsky EM, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis. 2016;75:1166–1169.
64. McAdoo SP, Medjeral-Thomas N, Gopaluni S, et al. Long-term followup of a combined rituximab and cyclophosphamide regimen in renal

anti-neutrophil cytoplasm antibody-associated vasculitis. Nephrol Dial Transplant. 2019;34:63–73.
65. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. J Am Med Assoc. 2010;304:2381–2388.

66. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–1780.
67. Smith RM, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64:3760–3769.
68. Terrier B, Pagnoux C, Perrodeau E, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis. 2018;77:1150–1156.
69. Gopaluni S, Smith RM, Lewin M, et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials. 2017;18:112.
70. Smith R, Jayne D, Merkel PA. A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease. [Abstract]. Arthritis Rheumatol. 2019;71:806.
71. Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCAassociated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77:1143–1149.
72. Charles P, Perrodeau E, Samson M, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2020;173:179–187.
73. Hogan SL, Nachman PH, Poulton CJ, et al. Understanding long-term remission off therapy in antineutrophil cytoplasmic antibody-associated vasculitis. Kidney Int Rep. 2019;4:551–560.
74. de Groot K, Reinhold-Keller E, Tatsis E, et al. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener’s granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. Arthritis Rheum. 1996;39:2052–2061.
75. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359:2790–2803.
76. Geetha D, Eirin A, True K, et al. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. Transplantation. 2011;91:1370–1375.
77. Nachman PH, Segelmark M, Westman K, et al. Recurrent ANCAassociated small vessel vasculitis after transplantation: a pooled analysis. Kidney Int. 1999;56:1544–1550.
78. Geetha D, Lee SM, Shah S, Rahman HM. Relevance of ANCA positivity at the time of renal transplantation in ANCA associated vasculitis. J Nephrol. 2017;30:147–153.
79. Geetha D, Seo P, Specks U, Fervenza FC. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis postkidney transplant: report of two cases. Am J Transplant. 2007;7:2821–2825.
80. Forbess L, Bannykh S. Polyarteritis nodosa. Rheum Dis Clin N Am. 2015;41:33–46, vii.
81. Gayraud M, Guillevin L, le TP, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum. 2001;44:666–675.
82. de Menthon M, Mahr A. Treating polyarteritis nodosa: current state of the art. Clin Exp Rheumatol. 2011;29:S110–S116.
83. Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to

hepatitis B virus. A prospective study with long-term observation of 41 patients. Medicine (Baltimore). 1995;74:238–253.
84. Naoe S, Takahashi K, Masuda H, Tanaka N. Kawasaki disease. With particular emphasis on arterial lesions. Acta Pathol Jpn. 1991;41:785–797.
85. Patel RM, Shulman ST. Kawasaki disease: a comprehensive review of treatment options. J Clin Pharm Ther. 2015;40:620–625.
86. Hara T, Nakashima Y, Sakai Y, Nishio H, Motomura Y, Yamasaki S. Kawasaki disease: a matter of innate immunity. Clin Exp Immunol. 2016;186:134–143.

References

87. Maksimowicz-McKinnon K, Hoffman GS. Large-vessel vasculitis. Semin Respir Crit Care Med. 2004;25:569–579.
88. Seyahi E. Takayasu arteritis: an update. Curr Opin Rheumatol. 2017;29:51–56.
89. Lagneau P, Michel JB. Renovascular hypertension and Takayasu’s disease. J Urol. 1985;134:876–879.
90. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310–317.
91. Yoshimura M, Kida H, Saito Y, et al. Peculiar glomerular lesions in Takayasu’s arteritis. Clin Nephrol. 1985;24:120–127.

92. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79:19–30.
93. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in giantcell arteritis. N Engl J Med. 2017;377:317–328.
94. Turesson C, Börjesson O, Larsson K, Mohammad AJ, Knight A. Swedish Society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of giant cell arteritis. Scand J Rheumatol. 2019;48:259–265.
95. Rapoport M, Averbukh Z, Chaim S, Klinovski E, Modai D, Gilboa Y. Takayasu aortitis simulating bilateral renal-artery stenoses in patients treated with ACE inhibitors. Clin Nephrol. 1991;36:156.

27

Lupus Nephritis

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DEFINITION

Lupus nephritis (LN), the prototypical immune complex glomerulonephritis (GN), occurs commonly in patients with systemic lupus erythematosus (SLE) and can be very severe. SLE is defined by specific clinical and laboratory features (Table 27.1).1 To be considered as having SLE, a patient must demonstrate antinuclear antibody (ANA) positivity of 1:80 or more using a Hep2 cell or equivalent assay. Other clinical and serologic parameters are assigned points and, in addition to a positive ANA, a patient must have sufficient clinical and laboratory findings to achieve a score of at least 10. Importantly, proteinuria and kidney biopsy findings are heavily weighted. A kidney biopsy showing an immune complex GN consistent with an International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV LN will receive a score of 10, so this plus a positive ANA are together sufficient to establish a diagnosis of SLE and LN.

EPIDEMIOLOGY

The incidence and prevalence of lupus and LN are influenced by age, sex, ethnicity, geographic region, diagnostic criteria used, and method of ascertainment. Clinically important kidney disease occurs in about 50% of patients with SLE, mostly between the ages of 15 and 45 years, with women outnumbering men 8:1 to 15:1.2 Female predominance is less pronounced in children and older individuals. Among patients with lupus, LN affects both sexes equally, is more severe in children and men, and is less so in older adults. The incidence of LN is about 30% in White, 60% in Black and Hispanic, and 40% to 80% in Asian patients with SLE.3 4 The higher frequency of LN in Black patients is independent of socioeconomic status.5 Black and Hispanic patients with SLE develop LN earlier and have worse outcomes than White patients. The prevalence of LN in a Medicaid population was 31 in 100,000.5

A pragmatic review found the 5- and 10-year cumulative incidence of end-stage kidney disease (ESKD) to be 11% and 19%, respectively,2 but this depends on histologic class and the population sampled. The risk for ESKD over 15 years was up to 44% in class IV LN.6 In a Medicaid population with a new diagnosis of LN between 2000 and 2010, the 5-year cumulative incidence of ESKD was about 22%.7

SLE patients with LN die earlier than those without nephritis and have a standardized mortality ratio of 6 to 6.8 versus 2.4 in lupus without kidney involvement.8 9 This increases to 14 for those with chronic kidney disease and 63 for those with ESKD.10 However, if LN remission is achieved through treatment, 10-year survival doubles to 95%.11

ETIOLOGY AND PATHOGENESIS

Genetics and Environment

A genetic predisposition to SLE is supported by disease clustering in families, twin concordance, racial differences in susceptibility, and the high frequency of autoantibodies and other autoimmune disorders in healthy family members.12 In Taiwan the relative risk for lupus in families of those with SLE was 316 for twins, 24 for siblings, 11 for parents, 14 for children of patients, and 4.4 for nonrelated spouses, suggesting that heritability contributed 44% to the risk for SLE, shared environmental exposures contributed 26%, and nonshared environmental exposures 30%.13

Homozygous deficiency of early complement cascade components (C1q, C2, C4) is associated with a high risk of SLE, as are certain FcyRIII receptor polymorphisms. Genome-wide association studies have identified over 100 loci associated with an increased risk for SLE. Genetic risk scores are lowest in Europeans, higher in Asians, and highest in those of African ancestry.14 Genes involved in lupus risk include those affecting B-cell signaling, neutrophil function, interferon regulation, immune-complex clearance, toll-like receptors (TLRs), and the

B-cell survival factor BAFF.12 15 The BAFF variant results in higher levels of BAFF and contributes to the rationale of treating lupus and LN with a monoclonal antibody against BAFF. A disproportionate number of transcription factors have been identified, suggesting an important contribution of gene dysregulation to lupus.16 HLA genes are also strongly associated with lupus risk, at least in Europeans.17 In Whites and Asians, four HLA class II DR allele families confer increased susceptibility or resistance to the development of LN.18 Independent of causation, other polymorphisms in genes such as MYH-9, ACE, TNIP1, and APOL-1 (in Blacks) confer a worse prognosis for LN. Having even one APOL-1 kidney risk allele was associated with progressive chronic kidney disease (CKD) and more chronicity, especially interstitial fibrosis and tubular atrophy, in nonwhite Brazilian patients.19

External environmental factors, such as ultraviolet light exposure and smoking, play a role in the onset and exacerbation of SLE and LN.20 Viral infections may be triggers for lupus, but conclusive evidence for a viral pathogenesis of SLE or LN is lacking. Exposure to certain medications (e.g., procainamide, hydralazine, quinidine, and anti-tumor necrosis factor [TNF] biologics) has been linked to SLE or SLE-like syndromes, but LN occurs infrequently in such individuals.

The internal environment also appears to be relevant in SLE given the strong female predominance, disease exacerbations during or shortly after pregnancy, and the effects of hormone treatment and ablation in animal models of LN. The gut microbiome may also contribute to lupus disease pathogenesis and activity. For example, orthologs of the RNA binding autoantigen Ro60 have been found in gut, skin, and oral commensal bacteria.21 Autoantibodies to Ro60 are seen early in patients who develop SLE. The Ro60 orthologs could trigger autoimmunity in genetically susceptible individuals. Dysbiosis of the gut microbiome occurs in lupus patients. In some patients with active LN, circulating antibodies against overrepresented bacterial species have been found.22 Anti-double stranded DNA (dsDNA) antibodies can recognize an antigen from these bacteria, again supporting a link

TABLE 27.1

ACR/EULAR and SLICC Criteria for the Diagnosis of SLE
SLICC Criteria

ACR/EULAR Criteria
Sensitivity: 96.1%

Sensitivity: 96.7%

Specificity: 93.4%

Specificity: 83.7%

Classification as SLE requires 10 points plus a
positive ANA at any time

Classification as SLE requires four or more of the following (with at least 1
clinical and 1 immunologic criteria)
OR biopsy-proven lupus nephritis with positive ANA or anti-dsDNA

Acute cutaneous (2 points)
SCLE (4 points)

Clinical Criteria

Immunologic Criteria

Acute or subacute cutaneous lupus

Positive ANA

Discoid rash (4 points)

Chronic cutaneous lupus

Positive anti-dsDNA antibody

Nonscarring alopecia (2 points)

Nonscarring alopecia

Positive anti-Sm antibody

Oral ulcers (2 points)

Oral or nasal ulcers

Positive antiphospholipid antibody (includes presence of a
lupus anticoagulant, false-positive RPR, anticardiolipin
antibody, or anti-β2 glycoprotein antibody)

Nonerosive arthritis (involving ≥2 joints,
characterized by tenderness, swelling, or
effusion) (6 points)

Synovitis ≥2 joints (swelling or effusion) or
tenderness in ≥2 joints and ≥30 min of
morning stiffness

Low complement (C3, C4, or CH50)

Serosal effusion (5 points)
Acute pericarditis (6 points)

Serositis

Direct Coombs test (in the absence of hemolytic anemia)

Kidney disease
Proteinuria (4 points)
ISN/RPS class II/V (8 points)
ISN/RPS class III/IV (10 points)

Kidney disease (RBC casts or proteinuria
≥500 mg/day on 24-h urine collection or
spot ratio of urine protein to creatinine
ratio ≥0.5)

Neurologic disorder
Neuropsychiatric seizure (5 points)
Psychosis (3 points)
Delirium (2 points)

Neurologic disorder

Hematologic disorder
Coombs+ hemolytic anemia (4 points)
Leukopenia (3 points)
Thrombocytopenia (4 points)

Hemolytic anemia

Serology
Anti-dsDNA (6 points)
Anti-Sm (6 points)
Antiphospholipid (2 points)
Low C3 or C4 (3 points)
Low C3 and C4 (4 points)

Leukopenia or lymphopenia

Thrombocytopenia
ACR, American College of Rheumatology; ANA, Antinuclear antibody; dsDNA, double-stranded DNA; EULAR, European League Against Rheumatism; ISN, International Society of Nephrology; RBC, red blood cell; RPR, rapid plasma regain; RPS, Renal Pathology Society; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

between gut flora and autoimmunity. Finally, pathobionts may traverse the intestinal wall and trigger autoimmune responses in susceptible individuals.23

Autoimmunity in Systemic Lupus Erythematosus

Patients with SLE typically develop multiple autoantibodies, many directed against nucleic acids and proteins involved in transcription and translation, such as nucleosomes (DNA-histone), chromatin antigens, and small nuclear and cytoplasmic ribonuclear proteins.24 Early in disease, clearance of apoptotic cells is impaired and nuclear autoantigens released from these cells stimulate expression of interferon-α (IFN-α), which facilitates the generation of antigen-presenting cells, promotes the differentiation of autoreactive B cells into plasma cells, and fosters the development of T helper cells. Antigen mimicry (i.e., exposure to viral or bacterial peptides with sequences similar to those of native antigens) also may lead to induction of autoantibody-producing cell lines. Both autoreactive B and T cells clonally expand in lupus, facilitated by failure of apoptotic mechanisms to silence autoreactive cells (i.e., loss of tolerance and an increased expression of B cell trophic factors). The nature of antigen presentation also may be important, with certain nuclear antigens capable of triggering an immunogenic response through interactions with a variety of intracellular TLRs.

The number and type of autoantibodies present in SLE reflects the patient’s ancestry and may be associated with disease severity.[25] Patients of any ancestry, but in particular those of African ancestry, who displayed multiple autoantibodies simultaneously and in association with anti-RNP antibodies, have increased transcriptomic signatures for interferon, plasma cells, T regulatory cells, and myeloid inflammation.

In addition to antibodies against nuclear antigens, patients with LN often have other autoantibodies: Up to 18% of LN patients may have antinuclear cytoplasmic antibodies (ANCA), which occur more often in proliferative than membranous LN and are associated with worse baseline kidney function.26

TABLE 27.2

PATHOGENESIS OF KIDNEY INJURY IN LUPUS NEPHRITIS

Manifestation

The hallmark of LN is the accumulation of immune complexes in glomeruli.27 Patients with LN have autoantibodies against dsDNA, Sm antigen, C1q, nucleosomes, and other antigens. There is direct binding of dsDNA antibodies to the glomerular basement membrane (GBM), and cross-linking of positively charged nucleosome components such as chromatin between autoantibodies and GBM.27 In proliferative LN, immune complexes are found in the subendothelial space, whereas in membranous LN, they localize to the subepithelial space.

Glomerular immune complexes, especially in the subendothelial space, activate proinflammatory mechanisms, including the complement pathway, leukocyte Fc receptors, cytokines that regulate cell proliferation and matrix formation, and procoagulant factors.27–29 Nucleosomes also can activate resident dendritic cells through binding to TLR-2 and -9.30 These activated pathways result in kidney damage, intraglomerular hypertension and coagulation, and leukocyte infiltration with release of proteolytic enzymes. Subepithelial immune complexes are associated with less inflammation but increased production of GBM components and more podocyte injury.

T cells contribute to the progression of LN by facilitating B cell differentiation and expansion. Additionally, T helper cell (Th1) cytokines are overexpressed in kidneys of patients with LN and promote intrarenal inflammation by activation of macrophages, complement, and the Fc receptor pathway. Kidney biopsies of LN patients also contain Th17 cells, which secrete interleukin-17 (IL-17), which is thought to sustain kidney inflammation by driving T cells away from maturing into a regulatory phenotype (CD4+CD25hiFoxP3+) capable of suppressing autoantibody production and attenuating the immune response.31 CD8+ T cells may gradually lose effector function and express inhibitory receptors under persistent antigen exposure and become “exhausted.” Exhaustion may, however, explain, why LN patients whose peripheral T cells displayed an exhausted phenotype had a nonrelapsing disease course.32

In SLE and LN, neutrophils undergo a form of cell death called NETosis, in which a chromatin meshwork (or NET) is released.30 These NETs are a source of autoantigens and are not properly degraded in lupus patients. In addition, lupus patients have an increased number of low-density granulocytes that are more susceptible to NETosis. NET material has been found in LN biopsy samples, and the subset of SLE patients with LN often do not degrade NETs well. The NETs induce production of IFN-α by plasmacytoid dendritic cells, which are also found in LN kidneys.30

Within the tubulointerstitial compartment, T and B cells are often found in close proximity to each other and appear to be interacting, in some cases even forming germinal centers.33 Interstitial B cells aggregating with T cells may show clonal expansion and somatic hypermutation, suggesting intrarenal autoantibody production against kidney-specific antigens, such as vimentin. Such interactions may contribute to interstitial inflammation, a major determinant of long-term kidney survival.33

Single-cell RNA sequencing (scRNA-seq) identified 21 clusters of immune cells in the LN kidney,34 all displaying an interferon signature, much as is seen in the peripheral blood of patients with SLE and LN. Of the three clusters of CD8+ T cells found in the kidney, none had an exhaustion signature, in contrast to that found in the peripheral blood of some patients. This demonstrates the complex and sometimes unexpected relationships among intrarenal immune cells and between tissue and peripheral blood immune cells.

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Frequency of Kidney Manifestations in Patients With Lupus and Kidney Involvement

	Prevalence (%)
Proteinuria	100
Nephrotic syndrome	45–65
Hematuria	
Microscopic	80
Gross	1–2
Red blood cell casts	10
Cellular casts	30
Reduced kidney function	40–80
Rapidly progressive glomerulonephritis	10–20
Acute kidney injury	1–2
Hypertension	15–50
Hyperkalemia	15

CLINICAL MANIFESTATIONS

Immune complex kidney involvement (LN) is usually heralded by proteinuria and active urinary sediment with microhematuria, acanthocytes, and erythrocyte casts (Table 27.2). More severe LN, usually with proliferative histology, may present with hypertension and a decline in the glomerular filtration rate (GFR). Less frequently, kidney disease in lupus presents as a tubulointerstitial disorder such as renal tubular acidosis (see Chapter 13), isolated interstitial nephritis, or as a thrombotic microangiopathy with or without an antiphospholipid antibody syndrome (see Chapters 29 and 30).

Extrarenal Manifestations

Patients with active SLE often present with nonspecific complaints of malaise, low-grade fever, poor appetite, and weight loss. Other common features include patchy alopecia, oral or nasal ulcerations, arthralgias, nondeforming arthritis, and a variety of skin findings, including photosensitivity, Raynaud’s phenomenon, and a “butterfly” (malar) facial rash. Livedo reticularis is seen in up to 15% of cases and may be associated with miscarriage, thrombocytopenia, and antiphospholipid antibodies. Neuropsychiatric involvement presents with headache, nerve palsies, psychoses, or frank coma. Serositis, in the form of pleurisy or pericarditis, affects up to 40% of patients. Pulmonary hypertension can develop silently as a result of multiple pulmonary emboli or intravascular coagulation in association with antiphospholipid antibodies or may be caused by nonthrombotic pulmonary arterial disease. Mitral valve prolapse, and less commonly Libman-Sacks endocarditis, may both be seen in SLE. Splenomegaly and lymphadenopathy are present in about one-fourth of patients, and hematologic abnormalities can affect all three cell lines. SLE-associated anemia can result from impaired erythropoiesis, autoimmune hemolysis, or bleeding. Thrombocytopenia and leukopenia may occur as part of lupus or as complications of therapy. Thrombotic events are common and should prompt a search for antiphospholipid antibodies and other procoagulant abnormalities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although the diagnosis of lupus may be obvious in a young woman with classic manifestations and serologic markers, less typical presentations are common and often result in diagnostic delay. This is, in part, a result of the varied features of the disease and because signs and symptoms evolve over time.

Several autoimmune diseases mimic the extrarenal manifestations of SLE, including fibromyalgia, Sjögren syndrome, thrombotic microangiopathies, primary antiphospholipid syndrome, dermatomyositis, systemic sclerosis, and mixed connective tissue disease. Adding complexity to diagnosis, many of these autoimmune diseases can involve the kidney and, in some cases, are associated with GN. Conversely, several common forms of GN must be distinguished from LN because of similar clinical features, including vasculitides (see Chapters 24 and 26), bacterial endocarditis, and cryoglobulinemia. ANCAs of uncertain significance are detected in 20% of LN patients.

Immunologic Tests in Lupus

ANAs are found in more than 90% of untreated patients with lupus. Although highly sensitive, neither the presence nor pattern (e.g., diffuse, speckled) are specific for SLE. Autoantibodies against dsDNA are more specific but less sensitive, being present in 75% of untreated lupus patients. Whereas high titers of anti-dsDNA antibodies correlate with the presence of SLE and are often used to follow the course of LN, antibodies to single-stranded DNA (ssDNA) are found in many rheumatologic conditions and do not correlate with the course of LN. Sm antibodies are strongly associated with the diagnosis of lupus and LN but are present in only about 25% to 30% of patients. Antibodies to C1q (anti-C1q) have been more closely associated with the activity of LN than anti-dsDNA antibodies and may have a prognostic role in the follow-up.35

Serum levels of total hemolytic complement and complement components C3 and C4 are often depressed in untreated SLE and especially in LN. In general, both C3 and C4 are depressed. Preferential C4 depression in lupus patients may reflect activation of the classic complement pathway. In some cases, low C4 with normal C3 in a patient with lupus may reflect genetic C4 deficiency or the presence of cryoglobulins. Preferential depression of C3 is observed in patients with postinfectious glomerulonephritis (PIGN) and the C3 glomerulopathies (see Chapters 23 and 57) rather than in SLE/LN.

TABLE 27.3

KIDNEY BIOPSY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Although lupus nephritis may be suspected based on clinical symptoms and laboratory markers, a kidney biopsy is required for confirmation, subclassification, prognosis, and management decisions. A biopsy should be done in patients with a persistent urine protein/creatinine ratio greater than 0.5 g/g (equivalent to proteinuria of about 0.5 g/day), with or without an active urine sediment (i.e., glomerular hematuria and/or leukocyturia in the absence of urinary tract infection). Although a fall in GFR because of LN is usually accompanied by proteinuria and hematuria, a biopsy should be done if kidney function declines in an SLE patient in the absence of urinary abnormalities if no other reason (e.g., infection, nephrotoxic medications) for the falling GFR can be found.

The proteinuria cutoff of 0.5 g/g is not an absolute threshold. A kidney biopsy should be considered for individual patients in the context of their overall disease characteristics. For example, proliferative LN can be found in lupus patients with proteinuria less than 0.5 g/g who have glomerular hematuria with or without impaired kidney function. In one cohort, over 80% of such patients had class III or IV LN on kidney biopsy.36

After LN treatment, a second kidney biopsy can be considered for patients who have not responded adequately, have persistently elevated markers of kidney disease activity, or who deteriorate and in whom future treatment is unclear.

PATHOLOGY

Glomerular involvement is the dominant finding in LN. LN is currently classified by the revised ISN/RPS system (Table 27.3)[37] and is based mainly

ISN/RPS Classification of Lupus Nephritis and Associated Clinical Correlations

Class

Definition

Urine Findings

Clinical Findings

I: Minimal mesangial LN

Normal glomeruli by LM but mesangial immune deposits by IF

Usually unremarkable

None relevant to kidney; excellent kidney prognosis[a]

II: Mesangial proliferative LN

Mesangial hypercellularity (4 or more nuclei fully surrounded by matrix in the mesangial area excluding the hilar region) with mesangial immune deposits

Microscopic hematuria; proteinuria, if present, is usually low grade

Preserved kidney function; hypertension infrequent; excellent kidney prognosis[a]

III: Focal LN

Segmental or global, active endocapillary or extracapillary, or inactive glomerulonephritis affecting <50% of glomeruli with mesangial and subendothelial immune deposits

Microscopic hematuria; proteinuria

Hypertension possible; kidney failure and nephrotic syndrome not unusual; variable kidney prognosis

IV: Diffuse LN

Segmental or global active endocapillary or extracapillary, or inactive glomerulonephritis affecting ≥50% of glomeruli with mesangial and subendothelial immune deposits

Microscopic hematuria;
proteinuria

Hypertension; kidney failure and
nephrotic syndrome frequent; variable
kidney prognosis

V: Membranous LN

Glomerular basement membrane thickening with
subepithelial and mesangial immune deposits;
can occur alone or in combination with class III
or IV

High-grade proteinuria;
microscopic hematuria
possible

Preserved kidney function; nephrotic
syndrome common; kidney prognosis
gooda
Anti-PLA2R antibody negative

VI: Advanced sclerosing
LN

≥90% of glomeruli globally sclerosed without
residual disease activity

Microscopic hematuria;
proteinuria not unusual

Kidney failure expected

aAs

long as there is no transformation to a proliferative class.
IF, Immunofluorescence microscopy; ISN/RPS, International Society of
Nephrology/Renal Pathology Society; LM, light microscopy; LN, lupus nephritis.

suggestive of LN. Fibrin staining, corresponding to active lesions, is often noted in the glomerular tuft, especially in crescents. On electron microscopy (EM), the distribution of electron dense, immune complex deposits corresponds to the pattern of immunoglobulins seen by immunofluorescence or immunohistology. Some electron-dense deposits have an organized substructure known as fingerprinting, corresponding to the presence of curvilinear microtubular or fibrillar structures. Tubuloreticular inclusions, which are tubular structures located in the endoplasmic reticulum of kidney endothelial cells, are often found in biopsy specimens of LN patients and are thought to reflect a high interferon milieu.

on glomerular histology (examples are shown in Figs. 27.1 through 27.5). Less common glomerular pathologies omitted from the ISN/RPS system include lupus podocytopathy (see later discussion) and pauci-immune crescentic GN (analogous to ANCA-associated renal vasculitis). Although IgG is generally the dominant glomerular immunoglobulin in LN, IgA, and IgM, along with the complement components C1q and C3, are often co-deposited, giving the “full-house” pattern that is highly suggestive of LN. Strong glomerular C1q staining is also

Tubulointerstitial and Vascular Disease

The original ISN/RPS classification does not assess the kidney tubulo-interstitial or vascular compartments, even though interstitial and vascular damage contribute to poor kidney outcomes.38 The updated ISN/RPS classification includes activity and chronicity scores for glomerular and tubulointerstitial lesions, and vascular lesion grading along the lines of the Banff classification for transplant biopsies.37 About 50% of patients with LN, predominantly those with proliferative glomerular lesions, have immune aggregates along tubular basement membranes. Interstitial inflammatory cell infiltrates, including T cells, B cells, and monocytes, are frequently found, and tubulitis can be seen in active disease (Fig. 27.6). In chronic disease, the interstitium is often expanded by fibrosis and sparser infiltrates. Infrequently, tubulointerstitial nephritis is seen in the absence of glomerular disease and may result in acute kidney injury (AKI) or renal tubular acidosis.

Fig. 27.1 International Society of Nephrology/Renal Pathology Society Class I: Minimal Mesangial Lupus Nephritis. Light microscopy is normal (not shown), but direct immunofluorescence shows C1q deposits in the mesangial area. No capillary walls are involved. (Magnification ×400.)

A

B

Fig. 27.2 International Society of Nephrology/Renal Pathology Society Class II: Mesangial Proliferative Lupus Nephritis. (A) Mesangial expansion with hypercellularity, normal capillary walls, and no endocapillary hypercellularity (PAS stain, ×400). (B) Diffuse mesangial immunoglobulin G deposits shown by direct immunofluorescence (×200).

A

B

C

Fig. 27.3 International Society of Nephrology/Renal Pathology Society Class III: Focal Proliferative Lupus Nephritis. (A) Segmental deposits of immune complexes in the mesangial areas and in some capillary walls (C1q, direct immunofluorescence, ×200). (B) Glomerulus showing segmental endocapillary hypercellularity (silver methenamine stain, ×400). (C) Area of endocapillary hypercellularity with karyorrhexis and a segmental fibrocellular crescent with focal disruption of Bowman’s capsule (PAS stain, ×400).

A

B

C

Fig. 27.4 International Society of Nephrology/Renal Pathology Society Class IV: Diffuse Proliferative Lupus Nephritis. (A) Active diffuse proliferative lupus nephritis showing the presence of endocapillary hypercellularity with lobular accentuation of the glomerular capillaries and hyaline deposits that compromise the majority of the capillary walls (PAS stain, ×40). (B) Prominent global subendothelial deposits, accompanied by immune deposits in the mesangium (direct immunofluorescence for immunoglobulin, ×400). (C) Extensive subendothelial immune deposits thickening almost all the capillary walls, generating a wire loop appearance and hyaline thrombi that occlude capillary lumens (PAS stain, ×400).

A

B

Fig. 27.5 International Society of Nephrology/Renal Pathology Society Class V: Membranous Lupus Nephritis. (A) Global subepithelial deposits with spike formation (silver methenamine stain, ×400). (B) Presence of extensive subepithelial deposits and segmental subendothelial deposits that generate double contours and indicates membranous lupus nephritis with a proliferative component (class V + III/IV) (silver methenamine stain, ×400).

A

B

Fig. 27.6 Tubular Injury in Lupus Nephritis. (A) Interstitial lupus nephritis: mononuclear cells invading and destroying the tubular basement membranes (tubulitis and tubulorrhexis). Interstitial nephritis should not be related to chronic lesions such as tubular atrophy or glomerular scarring to contribute to the activity index. (PAS stain, ×400). (B) Direct immunofluorescence showing immunoglobulin G deposits in the tubular basement membrane (×400). Such tubular basement membrane aggregates are common in lupus nephritis, being found in 60% to 65% of biopsy specimens overall and with increasing frequency from class II (20%) to class IV (75%).

Vascular lesions are common in LN (Fig. 27.7). Five main pathologic types of kidney microvascular injury are seen: (1) vascular immune-complex deposits, (2) arteriosclerosis, (3) thrombotic microangiopathy, (4) noninflammatory necrotizing vasculopathy and, less frequently, (5) true vasculitis.39

Transformation of Histologic Appearance and “Silent” Lupus Nephritis

The ISN/RPS class found for LN is not fixed for an individual’s entire clinical course. Those treated for proliferative (class III/IV) LN may transform to a less serious histology, such as class II, or have resolution

A

B

Fig. 27.7 Vascular Injury in Lupus Nephritis. (A) Lupus vasculopathy: luminal narrowing of arterioles by intramural immune deposits with fibrinoid changes but without inflammation of the vessel wall. (B) Demonstration of C1q deposits along the arterial walls, confirming that the hyaline deposits seen by light microscopy correspond to immune complexes and the diagnosis of lupus vasculopathy (direct immunofluorescence, ×400).

TABLE 27.4

Modified NIH Lupus Nephritis Activity and Chronicity Scoring System a
ACTIVITY INDEX

CHRONICITY INDEX

Semiquantitative
Lesion
Scorea

Cellular/
Fibrocellular
Crescents

Endo-
Neutro-
capillary
Fibrinoid phils/Kary- Hyper-
Necrosis orrhexis
cellularity

Hyaline
Deposits

Total
Glomerulo-
Inter-
sclerosis
stitial
Score
Intersti-
Inflam- (Segmental Fibrous Tubular tial
mation or Global)
Crescent Atrophy Fibrosis

None

0

0

0

0

0

0

0

0

0

0

Mild (<25%)

2

2

1

1

1

1

1

1

1

1

Moderate
(25%–50%)

4

4

2

2

2

2

2

2

2

2

Severe (>50%)

6

6

3

3

3

3

3

3

3

3

[a]Maximum activity index is 24; maximum chronicity index is 12.
NIH, National Institutes of Health.

of inflammatory lesions with scarring and move from an active to a chronic histologic pattern. Conversely, patients initially diagnosed with class II or V LN may transform to proliferative LN, often heralded by increasing proteinuria and activity of the urine sediment.40

Kidney biopsies have been done in patients with SLE but no clinically obvious kidney involvement41; glomerular immune complexes were seen in some cases, most often consistent with class I/II LN but sometimes consistent with class III, IV, or V LN. This has been termed silent LN and may represent a preclinical stage in the evolution of LN.

Clinical, Laboratory, and Histopathologic Correlations and Outcomes

Kidney biopsy remains the gold standard for diagnosis and subsequent management of LN. Table 27.3 summarizes the typical clinicopathologic correlations of LN.

Lupus membranous nephropathy is distinguished from the most frequent type of primary membranous nephropathy by the absence of circulating anti-PLA2r autoantibodies and by the presence of all IgG isotypes in the intrarenal immune deposits, although restriction to the IgG4 isotype has been rarely observed in LN patients.

The importance of the kidney biopsy is underscored by patients with SLE and kidney injury who do not have classic LN. For example, up to 24% of patients may have a renal thrombotic microangiopathy, either alone or associated with immune-complex GN.42 A small (1.3%) but important subset of patients with SLE present with nephrotic syndrome, with or without AKI, but their kidney biopsies either mimic minimal change disease (MCD) or show mild mesangial expansion, proliferation and segmental sclerosis, mimicking focal segmental glomerulosclerosis (FSGS).43 EM shows diffuse podocyte effacement, without immune complexes, or with mesangial deposits but no peripheral capillary deposits of immunoglobulins or complement components. These patients, although not classified by ISN/RPS, have lupus podocytopathy and like MCD or FSGS, most respond to corticosteroids alone.44 However, in a Chinese study, the risk for relapse exceeded 50%, and at repeat kidney biopsy, half of the relapsed patients had transformed to class IV or V LN.44 Although these results may not be generalizable to a non-Asian population, they underscore the importance of histology-driven treatment decision analysis.

Long-Term Prognosis and Kidney Histology

Features of reversible (active) or irreversible (chronic) damage on kidney biopsy are captured by the National Institutes of Health (NIH) activity and chronicity indices now adapted to the proposed revisions of the ISN/RPS classification (Table 27.4; Fig. 27.8).37 Similar to other types of GN, long-term kidney prognosis is poor if the biopsy sample shows extensive glomerulosclerosis or interstitial fibrosis and tubular atrophy. In patients with less extensive scarring, the activity and chronicity indices at diagnostic biopsy may not correlate with the course of

A

B

C

D

E

F

G

Fig. 27.8 Histologic Components of the Activity and Chronicity Indices. (A) Fibrocellular crescent. A crescent is defined by the presence of extracapillary hypercellularity, composed of more than two cell layers that make up 10% or more of the circumference of Bowman’s capsule. Fibrocellular crescents have 25% to 75% cells and fibrin, and the remainder of fibrous matrix, and should be considered in the activity index (silver methenamine stain, ×400). (B) Fibrinoid necrosis. Fibrin associated with glomerular basement membrane disruption; this lesion does not require the presence of karyorrhexis (silver methenamine stain, ×400). (C) Neutrophils/karyorrhexis. Presence of neutrophils in the capillary lumina and karyorrhexis; defined as the presence of apoptotic, pyknotic, and fragmented nuclei (H&E, ×400). (D) Endocapillary hypercellularity. Increased number of infiltrating monocytes causing narrowing of the glomerular capillary lumina (PAS stain, ×400). (E) Hyaline deposits. Wire loop lesions and hyaline thrombi that represent the presence of massive subendothelial deposits that occlude the capillary lumina (Masson’s trichrome stain, ×400). (F) Glomerulosclerosis. Segmental sclerosis with fibrous adhesions to Bowman’s capsule (PAS stain, ×400). For the chronicity index, segmental and global glomerulosclerosis are considered together. (G) Fibrous crescent. Extracapillary proliferation with more than 75% fibrous matrix and less than 25% cells and fibrin (Silver methenamine stain, ×400).

LN.40 In contrast, persistent activity (activity index > 2) despite treatment on repeat kidney biopsy is associated with a worse long-term kidney prognosis, as is high chronicity (chronicity index > 6).40

TREATMENT

The management of patients with SLE (including those with LN but no systemic disease) should include an antimalarial agent such as hydroxychloroquine. Antimalarials are TLR antagonists (specifically TLR-7, -8, and -9) and reduce flare rates (including LN flares), decrease organ damage, and enhance responsiveness to immunosuppression, among other beneficial effects.44 Patients should be monitored for retinal toxicity.

The treatment of patients with active proliferative LN is traditionally divided into induction and maintenance phases, although these distinctions are blurred by the design of novel therapeutic trials (discussed later). The initial or induction phase may be thought of as the first step in controlling kidney inflammation to allow healing of kidney injury. This translates clinically into stabilization or improvement of kidney function, attenuation of proteinuria, and reduction in urine sediment activity. The maintenance phase focuses on consolidating clinical remissions and preventing relapses while reducing exposure to potentially toxic medications.

The ISN/RPS biopsy classification should guide initial therapy (see Table 27.3). In general, the immunosuppressive treatment of extrarenal lupus manifestations is sufficient for class I and II LN. The combination of high-dose glucocorticoids plus an immunosuppressive agent is mainly used for patients with active focal and diffuse proliferative LN (classes III and IV) and membranous lupus (class V).

A complete kidney response is achieved in only 30% to 40% of LN patients by 12 months.45 Most studies define complete kidney response as a reduction in proteinuria to less than 0.5 g/day or a urine protein to creatinine ratio less than 0.5 g/g, absence of glomerular hematuria and red blood cell casts, and normal or stable GFR. However, long-term kidney survival is best predicted by reducing proteinuria to less than 0.7 to 0.8 g/day after 1 year of treatment.46–48 Importantly this cutoff is starting to be incorporated into phase III clinical trials of novel LN therapies.49 The term partial response requires a 50% reduction in proteinuria to subnephrotic levels, and stability or improvement in GFR and is usually achieved before complete response criteria are met.

In addition to immunosuppressive regimens, the kidney protective measures outlined in Chapter 82 should be used as appropriate.

Proliferative Lupus Nephritis: Initial Treatment

Glucocorticoids

The administration of glucocorticoids is fundamental to the treatment of LN. The goal of initial steroid therapy is to quickly control intrarenal inflammation and halt ongoing injury, thereby allowing time for coadministered immunosuppressive agents to attenuate the autoimmune mechanisms that initiated and perpetuate LN. Most regimens start with one to three consecutive intravenous (IV) pulses of methylprednisolone at up to 1000 mg/pulse, followed by oral prednisone or prednisolone, often starting at 1 mg/kg/day with slow tapering. There is considerable variability in cumulative glucocorticoid dosing.

There has been a concerted effort to reduce the cumulative steroid burden for LN patients. The original Euro-Lupus Nephritis Trial (ELNT) initiated oral prednisolone at 0.5 mg/kg/day for 1 month, followed by tapering after three 750 mg pulses of methylprednisolone.50

The RITUXILUP trial used rituximab plus two 500 mg pulses of IV methylprednisolone followed by maintenance with mycophenolate mofetil (MMF) in the absence of oral steroids.51 After a median of 36 weeks, 72% of patients had achieved a complete response. During follow-up, 22% of patients had a LN flare 65 weeks (median) after remission and 64% were managed without oral steroids. A phase II study compared the novel calcineurin inhibitor (CNI) voclosporin to placebo on a background of immunosuppression with MMF and low-dose glucocorticoids.52 Patients were given two IV pulses of 500 mg methylprednisolone, followed by 20 to 25 mg/day prednisone that was tapered to 2.5 mg/day by 4 months. A complete kidney response was achieved by 49% of patients in the voclosporin group and 24% of patients in the placebo group after 48 weeks. Taken together, highdose steroids for all LN patients may not be necessary, oral steroid dosing may be lowered after IV pulses of methylprednisolone, and some therapeutic regimens could be steroid-sparing.

Current LN guidelines recommend initiating steroid treatment with IV methylprednisolone at a total cumulative dose of 250 to 2500 mg (depending on disease severity), followed by oral prednisone at 0.3 to 1 mg/kg/day, and tapered to 7.5 mg/day or less after 3 to 6 months.53,54

Immunosuppressive Agents

Long-term kidney function is better preserved, and LN relapses after 3 to 5 years are reduced if glucocorticoids are combined with cyclophosphamide during initial therapy.55 Both daily oral and IV pulses of cyclophosphamide are effective in LN, although IV cyclophosphamide given as 6-monthly pulses of 0.5 to 1 g/m2 (NIH protocol) has been the standard of care for several years. The ELNT trial compared low-dose IV cyclophosphamide (500 mg/infusion) bimonthly for 3 months to the NIH protocol. Similar efficacy with less toxicity and fewer infections, and similar 5- and 10-year kidney outcomes were demonstrated.50,56 The Euro-Lupus low-dose IV cyclophosphamide regimen achieved similar rates of remission induction in Black, Hispanic, and Southeast Asian patients.57,58 Therefore, LN guidelines now recommend low-dose cyclophosphamide as the first choice if a cyclophosphamide-based regimen is to be used.53 However, because low-dose cyclophosphamide studies have not included patients with serum creatinine levels 2.5 mg/dL or higher or those with extensive crescents or necrosis on kidney biopsy, high-dose IV cyclophosphamide remains an option for such patients.57,58

Oral MMF plus glucocorticoids for 6 months followed by maintenance therapy is as effective as 6-monthly pulses of cyclophosphamide (NIH protocol) plus glucocorticoids followed by maintenance therapy.45 MMF also showed similar treatment response rates to the EuroLupus cyclophosphamide regimen at 24 weeks.58 High-dose (NIH protocol) cyclophosphamide has been favored in patients presenting with marked kidney impairment or severe proliferative LN on biopsy, but there are no convincing differences in outcome between MMF and cyclophosphamide induction for such patients.59 No improvement in overall mortality or severe infection has been seen with MMF; gastrointestinal disturbances are more frequent, but the risk for amenorrhea is lower than with cyclophosphamide.

Optimal MMF dosing and adjustment for different patient subgroups remains unclear. Although concentration-time curve (AUC0-12) of the active MMF metabolite mycophenolic acid (MPA) may provide accurate overall measurements,60 AUC0-12 measurement is expensive and difficult to apply clinically. MPA trough levels correlate poorly with total drug exposure by AUC. A 4-hour AUC (AUC0-4) has been proposed to follow MMF exposure, but targets for efficacy and toxicity still need to be established.60 To date, a dosing range of 2 to 3 g/day for MMF has been recommended for initial treatment of proliferative LN with dose reduction for intolerance.

Long-term kidney outcomes of patients treated with MMF versus cyclophosphamide are not different, although one study reported a nonsignificant increase in LN flares in patients induced with MMF.61 Differences in response between ethnic and geographic subgroups

Initial Treatment of Proliferative Lupus Nephritis
Class III, IV ± class V LN

Intravenous methylprednisolone 250–750 mg/d
for 1–3 days (dose by disease severity)
-followed byoral predniso(lo)ne
0.5–0.8 mg/kg/d
Maximum predniso(lo)ne 60 mg/d
Taper to ≤10 mg/d over 12–16 weeks
PLUS

Intravenous cyclophosphamide
500 mg every 2 weeks for 3 months

MMF
2–3 g/d for 6 months

Additional options:
- Intravenous cyclophosphamide 0.5–1 g/m^2 monthly for 6 months
- Oral cyclophosphamide1–2 mg/kg/d (maximum 150 mg/d) for 2–4 months
- MMF 1–2 g/d plus a calcineurin inhibitor (tacrolimus or voclosporin) for 12 months
- Belimumab 10 mg/kg/month plus MMF for 24 months

Fig. 27.9 Approach to the initial treatment of proliferative lupus nephritis (LN) AZA, Azathioprine; MMF, mycophenolate mofetil.

have been suggested but not confirmed.62 However, a retrospective analysis of a Korean cohort showed similar remission rates for MMF and cyclophosphamide but more relapses and a higher incidence of ESKD in the MMF group.63

Guidelines for immunosuppressive therapy from the nephrology and rheumatology societies have been updated.53 54 Our approach to the initial treatment of proliferative LN is given in Fig. 27.9

Other Immunosuppressive Strategies

Azathioprine (AZA) has been used in combination with glucocorticoids for the induction of remission in proliferative LN. A randomized controlled trial (RCT) comparing AZA with cyclophosphamide found no difference in nonsustained doubling of initial serum creatinine, but more relapses, worse kidney function, and more chronicity on repeat biopsy in the AZA group.64 Although AZA is not recommended as first-line therapy, it remains an option when MMF or cyclophosphamide are unavailable, undesirable, or contraindicated (including during pregnancy).

CNIs in combination with glucocorticoids or as part of a threedrug regimen consisting of prednisone, MMF, and a CNI have been used primarily in Asia for the initial treatment of LN. In the largest Chinese three-drug combination study, tacrolimus plus MMF and glucocorticoids were compared with high-dose cyclophosphamide plus glucocorticoids. The CNI-based regimen resulted in a greater complete kidney remission rate than cyclophosphamide at 6 months for all LN classes.65 A CNI-based approach was also tested in a phase II trial in a highly diverse patient population that compared MMF, prednisone, and placebo with MMF, prednisone, and voclosporin.52 The addition of voclosporin resulted in significantly more complete kidney responses at 6 and 12 months. In a phase III study (AURORA) of 357 patients with class III, IV, or V LN, the additive benefit of voclosporin was confirmed.66 Long-term preservation of kidney function and improvement in kidney histology in CNI-treated LN patients will be addressed to some extent through the extension phase of AURORA. The AURORA trial design did not distinguish between induction and maintenance. Other than a tapering of low-dose glucocorticoids, patients remained on the same medications and doses for 12 months.

Biologic Agents

Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, was tested in the LUNAR trial, a randomized prospective study of patients with active LN. LUNAR failed to detect a difference in complete kidney responses at 1 year when rituximab was added to MMF and glucocorticoids compared with MMF and glucocorticoids alone.67

In subsequent clinical trials, other biologics, such as Abatacept, an inhibitor of T- and B-cell costimulation, an anti-interleukin 6 monoclonal antibody, and an anti-TWEAK monoclonal antibody, also failed to improve the proportion of LN patients achieving a complete kidney response.57 68 69

Despite the trial’s failure, follow-up of LUNAR participants beyond 12 months suggested that the rituximab and placebo groups need more time to show differences.67 Additionally, a post hoc analysis of LUNAR showed that complete kidney responses correlated with complete peripheral B cell depletion that occurred early and was sustained.70

Using this information to inform trial design, the humanized anti-CD20 monoclonal antibody obinutuzumab was tested in NOBILITY, a 2-year, phase II LN RCT. Like rituximab, obinutuzumab depletes peripheral B cells, but compared with rituximab, depletion is more complete and sustained, there is more antibody-dependent cytotoxicity, and there is less reliance on complement-dependent cytotoxicity.71 72 NOBILITY compared obinutuzumab to placebo on a background of MMF and prednisone. Besides being longer than LUNAR, overall glucocorticoid dosing was less, and there was little separation into induction and maintenance phases in NOBILITY,

Treatment of Resistant Proliferative Lupus Nephritis
LN treated initially with an MMF or
cyclophosphamide-based regimen

Patient does not achieve a 25%
decline in proteinuria after 3 months
-orPatient worsens at any time

B cell–targeted therapies
- Rituximab
- Bortezomib
- Anti-CD38

Response

Switch to the alternative
initial regimen

Patient does not achieve a 25%
decline in proteinuria after 3 months
-orPatient worsens at any time

Consider LN as treatment
resistant

No response

Other options
- Intravenous immunoglobulin
- Calcineurin inhibitor
- Immunoablative cyclophosphamide rescued by GCSF or stem cell bone marrow transplant
- Plasma exchange or immunoadsorption

Fig. 27.10 Treatment of resistant proliferative lupus nephritis (LN). GCSF, Granulocyte colony-stimulating factor; MMF, mycophenolate mofetil.

other than the last infusion of obinutuzumab or placebo at month 6. Significantly more patients who received obinutuzumab achieved complete kidney response at week 76 and week 104 compared with placebo.[73,74] Adverse events were comparable between the two groups.

Belimumab, a monoclonal antibody that targets the B-cell growth and survival factor BAFF (also called BLyS), was tested in a large (n = 448) phase III trial (BLISS-LN).[49] BLISS-LN was a 2-year study that allowed investigators to choose background immunosuppression, and the primary endpoint was primary efficacy renal response (PERR), whereas complete kidney response was a secondary endpoint. For PERR, the urine protein to creatinine ratio was 0.7 or less compared with less than 0.5 for complete response, and estimated GFR (eGFR) had to be at least 60 mL/min/1.73 m^2 and no more than 20% below its preflare value, whereas complete response required an eGFR of at least 90 mL/min/1.73 m^2 and no more than 10% below its preflare value. Belimumab was added to MMF plus glucocorticoids followed by MMF or to low-dose cyclophosphamide plus glucocorticoids followed by azathioprine. Glucocorticoids had to be tapered to 10 mg/day or less by week 24 and could only be increased briefly to treat a nonrenal SLE manifestation, and not at all between week 76 and week 104 or the treatment was considered a failure. At 104 weeks, patients who received belimumab had significantly more PERRs and complete kidney responses than those given placebo.49 Belimumab-treated patients had significantly fewer kidney-related events and better preservation of kidney function over the 2 years of the trial. Adding belimumab to background immunosuppression did not increase adverse events compared with placebo.

In summary, although the early experience with biologics for the treatment of LN was discouraging, longer trial duration, a blurring of the line between induction and maintenance therapy, and lower exposure to glucocorticoids allowed for successful trials. B cell–targeted

biologics do not appear to act quickly, consistent with the fact that B cells do not produce autoantibodies but are precursors to autoreactive plasma cells and plasmablasts. Antibodies to type 1 interferon and to complement system components are currently being assessed for the treatment of LN.

Renal Response to Initial Therapy

LN patients who achieve a complete kidney response during treatment generally have 5-year patient and kidney survival of more than a 90% compared with only 69% (patient) and 45% (kidney) for those not achieving complete remission.11 Partial responses are also associated with improved outcomes compared with no response. It is also clear that complete kidney responses take time. About half of LN patients treated with MMF or cyclophosphamide achieve a complete or partial response by 1 year, with an additional 25% by 2 years.75 To avoid prolonged exposure to inflammatory injury, a 25% reduction in proteinuria should be targeted during the first 3 months of therapy and proteinuria should be reduced by 50% by 6 months.53 At 12 months, patients would ideally have a proteinuria level less than 0.7 g/day. Using these metrics, consider switching medications if a patient has not demonstrated a 25% decline in proteinuria at 3 months. If the patient had been started on an MMF-based regimen, a switch to a cyclophosphamide-based regimen is appropriate, or vice versa. After another 3 months, if the patient has not shown a 25% decline in proteinuria, they could be considered as treatment resistant, at least to usual therapies (Fig. 27.10). A critical caveat before calling a patient treatment resistant is to verify adherence to therapy.76

Resistant Proliferative Lupus Nephritis

There is no high-quality RCT evidence to suggest an optimal approach to patients with resistant LN. In uncontrolled trials, cohort studies, and observational studies in resistant LN, rituximab was added to, or given after, intense conventional immunosuppression and converted 40% to 50% of nonresponders to complete responders.77 78 Rituximab also has been combined with belimumab for refractory LN.79 Plasma cells have been targeted in a small number of resistant LN patients with bortezomib or anti-CD38 antibodies with some success.80 81

Other possible beneficial approaches tested in small series of patients with resistant LN include plasma exchange, IV immunoglobulin, and CNIs.82 83 84 Infusion of allogeneic mesenchymal stem cells derived from umbilical cord or bone marrow has been tested in refractory LN.85 At 12 months, about 23% of patients had a complete renal response, but 40% of patients were considered to have treatment failures. Finally, for patients with life-threatening resistant disease, small pilot studies have tested total lymphoid irradiation and immunoablation by high-dose cyclophosphamide and antithymocyte globulin, with or without autologous stem cell reconstitution. These approaches have led to sustained treatment-free remissions, but toxicity and treatmentrelated mortality are considerable.86

Proliferative Lupus Nephritis: Subsequent Therapy

The high adverse event rate from intense cytotoxic treatment can be mitigated with no loss of efficacy if cyclophosphamide is discontinued after 3 to 6 months and drugs such as azathioprine or MMF are substituted in for long-term disease control.87 The concept of induction followed by maintenance therapy has been challenged (see earlier), and LN is thought of as a chronic disease for which preservation of kidney function is the most important outcome.

MMF is the drug of choice for long-term immunosuppression after initial therapy with cyclophosphamide or MMF, based on a trial that demonstrated MMF was superior to azathioprine at preventing renal flares, preserving kidney function over 3 years, and delaying progression to ESKD.61 If MMF is not tolerated, or in specific circumstances such as pregnancy, azathioprine or a CNI may be used for long-term immunosuppression.

The optimal duration of immunosuppression in patients with LN is unknown. Patients generally remain on immunosuppression for several years, and the longer the duration of therapy, the less chance of flare.88 The concern with withdrawing therapy too early is that LN will flare (relapse) and that every flare will increase the risk of progressive kidney disease. On the other hand, continuing immunosuppression increases the risk for adverse events.

Protocol kidney biopsies may help decide whether immunosuppressive therapy can be safely withdrawn. In patients with proliferative LN, a protocol biopsy done after 36 months of immunosuppression and at least 12 months of complete clinical renal remission showed that 30% of patients still had ongoing immunologic activity. Immunosuppression was withdrawn from all patients in clinical remission and LN relapsed almost exclusively in patients with a residual histologic activity index of at least 2.89 Using a similar approach,90 if a 42-month protocol biopsy showed a histologic activity index of 0, immunosuppression was discontinued, but if the activity index was 1 or greater, immunosuppression was continued. After 24 months, biopsies were performed again in the patients who remained on immunosuppression, and if the activity index was 0, the immunosuppressives were discontinued. Using this approach, the observed flare rate was fivefold less than that expected after discontinuation of immunosuppression based only on clinical data. Thus, performing a kidney biopsy can help inform the decision to withdraw immunosuppression. It is conceivable that lower cumulative immunosuppression may be sufficient for some patients, perhaps those with no histologic activity on kidney biopsy after 1 or 2 years of treatment.

The long-term management of immunosuppression for patients with persistent proteinuria who have achieved only partial remission is even less certain. Persistent proteinuria may be because of ongoing inflammatory disease activity or chronic damage and nephron loss. It has been found that a proportion of patients with persistent proteinuria no longer has histologic activity on kidney biopsy.[91] Such patients may not need ongoing immunosuppression.

Membranous Lupus Nephropathy

Membranous nephropathy is often diagnosed together with proliferative forms of LN. In these patients, treatment is directed at the proliferative component. Alternatively, the combination of low doses of glucocorticoids, MMF, and a CNI has shown considerable success in an Asian cohort of mixed membranous and proliferative LN.[92] Immunosuppressive therapy should be used for patients with nephrotic syndrome and/or impaired kidney function. The only RCT in patients with pure class V LN was small and compared cyclophosphamide or cyclosporine with glucocorticoids alone.[93] The patients studied had preserved kidney function and a mean proteinuria of almost 6 g/day. Complete and partial remissions were more frequent in the cyclophosphamide and cyclosporine-treated patients. Cyclosporine induced remission more rapidly than the other drugs, but LN relapses were fewer in the cyclophosphamide group. Two trials of MMF versus cyclophosphamide as initial therapy of LN included 84 patients with pure membranous nephropathy, among others.[94] Remissions, relapses, and courses were similar in the class V patients treated with MMF and cyclophosphamide. Pure class V LN with subnephrotic proteinuria can be treated with renoprotective and antiproteinuric therapies and immunosuppression dictated by extrarenal lupus symptoms.

Our approach to treatment of class V LN is outlined in Fig. 27.11.

Long-Term Monitoring of Lupus Nephritis Patients

The relapse (flare) rate for LN ranges from 35% to 60%, depending on the population studied, the criteria for relapse, and the maintenance therapy used.[90] In LN patients in remission, quarterly monitoring (including blood pressure, kidney function, proteinuria, urinary sediment, and serum C3 and C4) is recommended, with anti-dsDNA measured at least biannually. Changes in serology alone do not warrant therapeutic action, although some investigators report lower flare rates when modest preemptive treatment is given to such patients.[95] At the very least, patients should be watched even more closely for flare. If LN does flare, a repeat biopsy should be considered if a change in histologic class is suspected. Patients with proliferative LN tend to remain proliferative at flare, but patients with class II and V not infrequently develop a proliferative component.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME, ATHEROSCLEROSIS, AND PREGNANCY IN LUPUS NEPHRITIS

Intrarenal thrombosis caused by the antiphospholipid antibody syndrome is found in 30% of patients with SLE and may occur in the presence or absence of LN (see Chapter 29). The mainstay of treatment for antiphospholipid nephropathy is anticoagulation plus an antimalarial, although immunosuppressive agents have also been used. Vitamin K antagonists such as warfarin (VKAs) are the anticoagulants of choice for arterial thromboses; the choice between VKAs and direct oral anticoagulants for patients with venous thrombosis remains controversial.[96]

Patients with lupus have markedly elevated risk for atherosclerotic cardiovascular disease and a greater atherosclerotic plaque burden compared with age-matched controls.[97,98] Reduction of atherosclerotic

Treatment of Membranous Lupus Nephritis
Pure class V LN

Subnephrotic proteinuria
-andNormal kidney function
-andAsymptomatic

Nephrotic proteinuria
-orAbnormal kidney function
-orSymptomatic

Renin-angiotensin-aldosterone system blockade
-plusimmunosuppression as needed for extrarenal lupus

Response

Proteinuria remains >1 g/d

Cyclophosphamide, low or high dose
-orCalcineurin inhibitor, lowest effective dose
-orRituximab

Renin-angiotensin-aldosterone system blockade
-andMMF 2–3 g/d for 6 months
+/− glucocorticoids

No response

Partial/complete response

Long-term MMF 1–2 g/d

Fig. 27.11 Treatment of membranous lupus nephritis (LN). MMF, Mycophenolate mofetil.

risk should focus on blood pressure control (goal of <130/80 mm Hg), use of statins and hydroxychloroquine,99 and reduction of inflammatory disease activity.

The effects of SLE and LN on pregnancy and fetal outcomes and the effects of pregnancy on LN activity are discussed in Chapter 45

END-STAGE KIDNEY DISEASE AND KIDNEY REPLACEMENT THERAPY

Although survival of LN patients on dialysis was noted to be similar to patients with other causes of ESKD,100 a study from Australia suggested worse survival.101 LN patients who received a kidney transplant had significantly better survival than those who did not,102 suggesting that kidney transplantation is the kidney replacement modality of choice for LN patients with ESKD. Extrarenal lupus is often quiescent by the time patients reach ESKD, but those with active extrarenal disease may still require immunosuppression. It has been suggested that patients with LN defer transplantation for 3 to 6 months to allow SLE to become inactive; however, an increased risk for allograft failure was found when LN patients waited more than 3 months before transplantation.103 Recurrent LN after kidney transplantation may occur but is generally not the cause of allograft loss.104

SELF-ASSESSMENT QUESTIONS

1. A 21-year-old African-American woman presents for initial therapy of LN. She was diagnosed with SLE 1 year ago, when she was found to have alopecia, malar rash, and arthralgias with ANAs and dsDNA antibodies. At that time, urine sediment was unremarkable, serum creatinine was 0.6 mg/dL, and she had no proteinuria. She was treated with low-dose glucocorticoids and hydroxychloroquine, with resolution of her symptoms. Over the past month, she noticed foamy urine and mild ankle swelling. Evaluation showed blood on her urine dipstick, 24-hour urine with 4 g protein, serum creatinine of 1 mg/dL, and a rising dsDNA titer with both C3 and

C4 now newly decreased. A kidney biopsy revealed class IV LN, without crescents or glomerular capillary necrosis. The patient wants children in the future. Considering options for initial therapy for this patient's LN, which of the following statements is incorrect?
A. She could be treated with MMF and glucocorticoids.
B. She could be treated with a calcineurin inhibitor in combination with MMF and glucocorticoids.
C. She could be treated with low-dose cyclophosphamide and receive ovarian protection.
D. She could be treated with belimumab alone.

2. A 24-year-old Hispanic woman has been treated for the last 6 months with MMF 3 g/day and a tapering dose of glucocorticoids for active focal proliferative class III LN. Her initial proteinuria decreased from 3.4 g/day to 1.2 g/day, urine sediment became inactive, serum creatinine decreased from 1.6 to 0.9 mg/dL over the 6 months of therapy, anti-dsDNA titer declined, and serum complement values returned to normal. She has tolerated her treatment well and reports no side effects. What should be done with her immunosuppression?

A. Continue the current dose of MMF, follow patient for a complete renal remission, and when achieved, reduce MMF to 2 g/day and continue for at least 36 months of total immunosuppressive therapy, with ongoing monitoring for any evidence of LN relapse.

B. Change to intravenous cyclophosphamide at 500 mg every 2 weeks for 6 doses and then administer azathioprine at 2 mg/kg daily.

C. Add a calcineurin inhibitor to her current regimen.

D. Add rituximab to her current regimen.

3. A 32-year-old White woman with a past history of LN wants to become pregnant and is concerned about flares during the pregnancy. Which of the medications listed should NOT be used during pregnancy?

A. Glucocorticoids

B. Calcineurin inhibitor

C. Hydroxychloroquine

D. Azathioprine

E. Mycophenolate mofetil

4. A 28-year-old White man had been diagnosed 4 years ago with class IV LN by kidney biopsy. He was treated with MMF and glucocorticoids, and his kidney function improved to an eGFR of 89 mL/min/1.73 m2. Proteinuria fell from 2.7 g/day to 950 mg/day. His antidsDNA antibody titer fell by 75% and his C3 complement increased to the normal range, but C4 remained low. He has been on MMF 2 g/day for 3 years. He has been on 5 mg of prednisone every other day for 2 years. He has had no extrarenal signs or symptoms of lupus for over 3 years. He wants to know if he needs to stay on immunosuppression or can safely come off. What should be done?

A. Continue his MMF and prednisone until the anti-dsDNA antibody is no longer detectable and then stop immunosuppression.

B. Order a kidney biopsy to determine whether there is any residual histologic activity.

C. Continue his MMF and prednisone until his C4 level is in the normal range and then stop immunosuppression.

D. Continue his MMF and prednisone until his proteinuria is less than 250 mg/day.

REFERENCES

1. Aringer M, Costenbader K, Daikh D, et al. 2019 European League against rheumatism/American College of rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400–1412.
2. Mahajan A, Amelio J, Gairy K, et al. Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: a pragmatic review mapping disease severity and progression. Lupus. 2020;29:1011–1020.
3. Bastian HM, Roseman JM, McGwin Jr G, et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. Lupus. 2002;11:152–160.
4. Hanly JG, O’Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology. 2016;55:252–262.
5. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum. 2013;65:753–763.
6. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015, a systematic review and Bayesian meta-analysis. Arthritis Rheum. 2016;68:1432–1441.
7. Feldman CH, Broder A, Guan H, Yazdany J, Costenbader KH. Sex differences in health care utilization, end-stage renal disease, and mortality among medicaid beneficiaries with incident lupus nephritis. Arthritis Rheumatol. 2018;70:417–426.
8. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27:3248–3254.
9. Lerang K, Gilboe IM, Steinar Thelle D, Gran JT. Mortality and years of potential life loss in systemic lupus erythematosus: a population-based cohort study. Lupus. 2014;23:1546–1552.
10. Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. Arthritis Rheum. 2013;65:2154–2160.
11. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ, Collaborative Study G. Value of a complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008;3:46–53.
12. Munroe ME, James JA. Genetics of lupus nephritis: clinical implications. Semin Nephrol. 2015;35:396–409.
13. Kuo CF, Grainge MJ, Valdes AM, et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern Med. 2015;175:1518–1526.
14. Morris DL, Sheng Y, Zhang Y, et al. Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. Nat Genet. 2016;48:940–946.
15. Friebus-Kardash J, Trendelenburg M, Eisenberger U, et al. Susceptibility of BAFF-var allele carriers to severe SLE with occurrence of lupus nephritis. BMC Nephrol. 2019;20:430.
16. Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet. 2015;47:1457–1464.
17. Alarcon-Riquelme ME, Ziegler JT, Molineros J, et al. Genome-wide association study in an amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. Arthritis Rheumatol. 2016;68:932–943.
18. Niu Z, Zhang P, Tong Y. Value of HLA-DR genotype in systemic lupus erythematosus and lupus nephritis: a meta-analysis. Int J Rheum Dis. 2015;18:17–28.
19. Vajgel G, Lima SC, Santana DJS, et al. Effect of a single apolipoprotein L1 gene nephropathy variant on the risk of advanced lupus nephritis in Brazilians. J Rheumatol. 2020;47:1209–1217.
20. Sparks JA, Costenbader KH. Genetics, environment, and geneenvironment interactions in the development of systemic rheumatic diseases. Rheum Dis Clin North Am. 2014;40:637–657.

21. Greiling TM, Dehner C, Chen X, et al. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. Sci Transl Med. 2018;10.

22. Azzouz D, Omarbekova A, Heguy A, et al. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. Ann Rheum Dis. 2019;78:947–956.
23. Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science. 2018;359:1156–1161.
24. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358:929–939.
25. Catalina MD, Bachali P, Yeo AE, et al. Patient ancestry significantly contributes to molecular heterogeneity of systemic lupus erythematosus. JCI Insight. 2020;5.
26. Turner-Stokes T, Wilson HR, Morreale M, et al. Positive antineutrophil cytoplasmic antibody serology in patients with lupus nephritis is associated with distinct histopathologic features on renal biopsy. Kidney Int. 2017;92:1223–1231.
27. Pedersen HL, Horvei KD, Thiyagarajan D, Seredkina N, Rekvig OP. Murine and human lupus nephritis: pathogenic mechanisms and theoretical strategies for therapy. Semin Nephrol. 2015;35:427–438.
28. Birmingham DJ, Hebert LA. The complement system in lupus nephritis. Semin Nephrol. 2015;35:444–454.
29. Goilav B, Putterman C. The role of anti-DNA antibodies in the development of lupus nephritis: a complementary, or alternative, viewpoint? Semin Nephrol. 2015;35:439–443.
30. Lorenz G, Anders HJ. Neutrophils, dendritic cells, toll-like receptors, and interferon-alpha in lupus nephritis. Semin Nephrol. 2015;35:410–426.
31. Iikuni N, Lourenco EV, Hahn BH, La Cava A. Cutting edge: regulatory T cells directly suppress B cells in systemic lupus erythematosus. J Immunol. 2009;183:1518–1522.
32. McKinney EF, Lee JC, Jayne DR, Lyons PA, Smith KG. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. Nature. 2015;523:612–616.
33. Clark MR, Trotter K, Chang A. The pathogenesis and therapeutic implications of tubulointerstitial inflammation in human lupus nephritis. Semin Nephrol. 2015;35:455–464.
34. Arazi A, Rao DA, Berthier CC, et al. The immune cell landscape in kidneys of patients with lupus nephritis. Nat Immunol. 2019;20: 902–914.
35. Moroni G, Radice A, Giammarresi G, et al. Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis. 2009;68:234–237.
36. De Rosa M, Rocha AS, De Rosa G, Dubinsky D, Almaani SJ, Rovin BH. Low-grade proteinuria does not exclude significant kidney injury in lupus nephritis. Kidney Int Rep. 2020;5:1066–1068.
37. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018;93:789–796.
38. Hsieh C, Chang A, Brandt D, Guttikonda R, Utset TO, Clark MR. Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. Arthritis Care Res. 2011;63:865–874.
39. Wu LH, Yu F, Tan Y, et al. Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. Kidney Int. 2013;83:715–723.
40. Parikh SV, Alvarado A, Malvar A, Rovin BH. The kidney biopsy in lupus nephritis: past, present, and future. Semin Nephrol. 2015;35:465–477.
41. Gonzalez-Crespo MR, Lopez-Fernandez JI, Usera G, Poveda MJ, GomezReino JJ. Outcome of silent lupus nephritis. Semin Arthritis Rheum. 1996;26:468–476.
42. Song D, Wu LH, Wang FM, et al. The spectrum of renal thrombotic

microangiopathy in lupus nephritis. Arthritis Res Ther. 2013;15:R12.
43. Kraft SW, Schwartz MM, Korbet SM, Lewis EJ. Glomerular podocytopathy in patients with systemic lupus erythematosus. JASN J Am Soc Nephrol. 2005;16:175–179.
44. Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, et al. Characterization of patients with lupus nephritis included in a large cohort from the Spanish society of rheumatology registry of patients with systemic lupus erythematosus (RELESSER). Medicine. 2016;95:e2891.

45. Parikh SV, Rovin BH. Current and emerging therapies for lupus nephritis. JASN. 2016;27:2929–2939.
46. Tamirou F, Lauwerys BR, Dall’Era M, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med. 2015;2:e000123.
47. Dall’Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the EuroLupus Nephritis cohort. Arthritis Rheumatol. 2015;67:1305–1313.
48. Ugolini-Lopes MR, Seguro LPC, Castro MXF, et al. Early proteinuria response: a valid real-life situation predictor of long-term lupus renal outcome in an ethnically diverse group with severe biopsy-proven nephritis? Lupus Sci Med. 2017;4:e000213.
49. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383:1117–1128.
50. Houssiau FA, Vasconcelos C, D’Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46:2121–2131.
51. Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013;72:1280–1286.
52. Robin BH, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int. 2011;100:753–779.
53. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79:713–723.
54. Rovin BH. KDIGO GN GUIDELINE; 2021.
55. Austin 3rd HA, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986;314:614–619.
56. Houssiau FA, Vasconcelos C, D’Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis. 2010;69:61–64.
57. Group AT. Treatment of lupus nephritis with abatacept: the abatacept and cyclophosphamide combination efficacy and safety study. Arthritis Rheumatol. 2014;66:3096–3104.
58. Rathi M, Goyal A, Jaryal A, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. Kidney Int. 2016;89:235–242.
59. Rovin BH, Parikh SV, Hebert LA, et al. Lupus nephritis: induction therapy in severe lupus nephritis-should MMF be considered the drug of choice? Clin J Am Soc Nephrol. 2013;8:147–153.
60. Pourafshar N, Karimi A, Wen X, et al. The utility of trough mycophenolic acid levels for the management of lupus nephritis. Nephrol Dial Transplant. 2019;34:83–89.
61. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886–1895.
62. Isenberg D, Appel GB, Contreras G, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology. 2010;49:128–140.
63. Koo HS, Kim YC, Lee SW, et al. The effects of cyclophosphamide and mycophenolate on end-stage renal disease and death of lupus nephritis. Lupus. 2011;20:1442–1449.
64. Grootscholten C, Ligtenberg G, Hagen EC, et al. Azathioprine/

methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int. 2006;70:732–742.
65. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015;162:18–26.
66. Rovin BH, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021;397:2070–2080.

67. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64:1215–1226.
68. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014;66:379–389.
69. Rovin BH, van Vollenhoven RF, Aranow C, et al. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of treatment with sirukumab (CNTO 136) in patients with active lupus nephritis. Arthritis Rheumatol. 2016;68:2174–2183.
70. Gomez Mendez LM, Cascino MD, Garg J, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. Clin J Am Soc Nephrol. 2018;13:1502–1509.
71. Reddy V, Klein C, Isenberg DA, et al. Obinutuzumab induces superior Bcell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology. 2017;56:1227–1237.
72. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther. 2013;12:2031–2042.
73. Robin BH, ALvarez A, et al. A phase 2 randomized, controlled study of obinutuzumab with mycophenolate and corticosteroids in proliferative lupus nephritis. Am Soc Nephrol. 2019. abstract FR-OR136. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3267128.
74. Furie R, et al. Two-year results from a randomized controlled study of obinutazumab for proliferative lupus nephritis. Am Coll Rheumatol. 2020. abstract 0988. https://acrabstracts.org/abstract/two-yearresults-from-a-randomized-controlled-study-of-obinutuzumab-forproliferative-lupus-nephritis/.
75. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825–835.
76. Feldman CH, Collins J, Zhang Z, et al. Azathioprine and mycophenolate mofetil adherence patterns and predictors among Medicaid beneficiaries with systemic lupus erythematosus. Arthritis Care Res. 2019;71:1419–1424.
77. Weidenbusch M, Rommele C, Schrottle A, Anders HJ. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant. 2013;28:106–111.
78. Alshaiki F, Obaid E, Almuallim A, Taha R, El-Haddad H, Almoallim H. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol. 2018;5:118–126.
79. Kraaij T, Arends EJ, van Dam LS, et al. Long-term effects of combined B-cell immunomodulation with rituximab and belimumab in severe, refractory systemic lupus erythematosus: 2-year results. Nephrol Dial Transplant. 2020.
80. Segarra A, Arredondo KV, Jaramillo J, et al. Efficacy and safety of bortezomib in refractory lupus nephritis: a single-center experience. Lupus. 2020;29:118–125.
81. Scheibe F, Ostendorf L, Reincke SM, et al. Daratumumab treatment for therapy-refractory anti-CASPR2 encephalitis. J Neurol. 2020;267:317–323.
82. Kronbichler A, Brezina B, Quintana LF, Jayne DR. Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: a systematic review. Autoimmun Rev. 2016;15:38–49.
83. Wenderfer SE, Thacker T. Intravenous immunoglobulin in the management of lupus nephritis. Autoimmune Dis. 2012;2012:589359.
84. Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of

cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. Lupus. 2010;19:162–169.
85. Gu F, Wang D, Zhang H, et al. Allogeneic mesenchymal stem cell transplantation for lupus nephritis patients refractory to conventional therapy. Clin Rheumatol. 2014;33:1611–1619.
86. Huang X, Chen W, Ren G, et al. Autologous hematopoietic stem cell transplantation for refractory lupus nephritis. Clin J Am Soc Nephrol. 2019;14:719–727.
87. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971–980.

88. Moroni G, Gatto M, Raffiotta F, et al. Can we withdraw immunosuppressants in patients with lupus nephritis in remission? An expert debate. Autoimmun Rev. 2018;17:11–18.
89. De Rosa M, Azzato F, Toblli JE, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. Kidney Int. 2018;94:788–794.
90. Malvar A, Alberton V, Lococo B, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. Kidney Int. 2020;97:156–162.
91. Alvarado AS, Malvar A, Lococo B, et al. The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. Lupus. 2014;23:840–847.
92. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. JASN. 2008;19:2001–2010.
93. Austin 3rd HA, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. JASN. 2009;20:901–911.
94. Radhakrishnan J, Moutzouris DA, Ginzler EM, Solomons N, Siempos II , Appel GB. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. Kidney Int. 2010;77:152–160.
95. Yap DYH, Kwan LPY, Ma MKM, Mok MMY, Chan GCW, Chan TM. Preemptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis: a cohort study. Nephrol Dial Transplant. 2019;34:467–473.

96. Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials. Autoimmun Rev. 2021;20:102711.
97. Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum. 2003;48:3159–3167.
98. Garg S, Raval AN, Hansen KE, et al. Renal arteriosclerosis strongly associated atherosclerotic cardiovascular disease risk in lupus nephritis. Arthritis Care Res. 2021.
99. Cairoli E, Rebella M, Danese N, Garra V, Borba EF. Hydroxychloroquine reduces low-density lipoprotein cholesterol levels in systemic lupus erythematosus: a longitudinal evaluation of the lipid-lowering effect. Lupus. 2012;21:1178–1182.
100. Sabucedo AJ, Contreras G. ESKD, transplantation, and dialysis in lupus nephritis. Semin Nephrol. 2015;35:500–508.
101. Zhang L, Lee G, Liu X, et al. Long-term outcomes of end-stage kidney disease for patients with lupus nephritis. Kidney Int. 2016;89:1337–1345.
102. Jorge A, Wallace ZS, Lu N, Zhang Y, Choi HK. Renal transplantation and survival among patients with lupus nephritis: a cohort study. Ann Intern Med. 2019;170:240–247.
103. Plantinga LC, Patzer RE, Drenkard C, et al. Association of time to kidney transplantation with graft failure among U.S. patients with end-stage renal disease due to lupus nephritis. Arthritis Care Res. 2015;67:571–581.
104. Contreras G, Mattiazzi A, Guerra G, et al. Recurrence of lupus nephritis after kidney transplantation. JASN. 2010;21:1200–1207.

28

Monoclonal Immunoglobulin–Related Glomerular Diseases and Renal Amyloidosis

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MONOCLONAL GAMMOPATHY OF RENAL/CLINICAL SIGNIFICANCE

The glomerulus is a favorite site for the deposition of aggregated, misfolded, or abnormal proteins. Among these, monoclonal immunoglobulins (Igs) are increasingly recognized as a major cause of glomerular disorders (see also Chapter 22). Monoclonal Ig is produced by an abnormal B-cell clone, which most commonly does not cause cancerous symptoms but is quiescent or indolent, corresponding to a monoclonal gammopathy of undetermined significance (MGUS) or to an indolent lymphocytic or plasmacytic disorder. The association of such a “dangerous small B-cell clone” with related kidney manifestations is now recognized as monoclonal gammopathy of renal significance (MGRS).1 Recently, the concept has been extended to monoclonal gammopathy of clinical significance (MGCS) to encompass the involvement of other organs.2

Importantly, in patients with MGR(C)S-related organ lesions, current treatment is based on targeting the underlying B-cell clone, although it is not malignant per se.

Overt hematologic malignancies, such as symptomatic myeloma, B-cell lymphoma, or Waldenström macroglobulinemia (WM), may be complicated by the same kidney diseases as in MGR(C)S. More frequently, kidney disorders occurring during these malignant lymphoid and/or plasmacytic proliferations are related to tumor mass, including light chain (LC) cast nephropathy, kidney infiltration by malignant cells, and intracapillary thrombi of monoclonal IgM.3,4 In these cases, treatment is directed at the hematologic malignancy.

Kidney disorders related to MGRS are classified into three categories according to the composition and appearance of deposits by immunofluorescence (IF) and electron microscopy (EM), respectively (Table 28.1).5 The first category includes diseases with deposition of monoclonal Ig organized ultrastructurally into fibrils (immunoglobulinic amyloidosis) or microtubules (cryoglobulinemic glomerulonephritis [GN] and immunotactoid GN). The second category includes disorders characterized by nonorganized electron-dense granular monoclonal Ig deposits (i.e., monoclonal Ig deposition disease) and proliferative GN with monoclonal Ig deposits. In the third category, encompassing C3 glomerulopathy and thrombotic microangiopathy, no Ig deposits are present and glomerular lesions are thought to derive from local or systemic complement activation by the monoclonal Ig. This chapter focuses on glomerular diseases with organized and nonorganized monoclonal Ig deposits, except for cryoglobulinemic GN (Chapter 22), fibrillary GN (Chapter 29), monoclonal Ig-associated C3 glomerulopathy (Chapter 23), and renal thrombotic microangiopathy (Chapter 30).

Pathophysiology

The large spectrum of MGR(C)S-related diseases reflects the diversity of pathogenic mechanisms and affected tissues or organs. Kidney lesions most commonly result from deposition of all or part of the monoclonal immunoglobulins as aggregates, amorphous, crystalline, microtubular, or fibrillar forms. Other identified mechanisms include autoantibody activity directed against a tissue antigen or resulting in the deposition of immune complexes and complement activation.2,5,6 Of note, monoclonal Ig-mediated activation of the alternative pathway of the complement system has been documented recently in monoclonal Ig-associated C3 glomerulopathy (see Chapter 23).7

Only a minority of monoclonal immunoglobulins produced in clonal B-cell disorders are nephrotoxic. Pathogenicity appears mostly due to sequence peculiarities in the variable (V) domain that govern monoclonal Ig toxicity, including their propensity to aggregate and deposit.[6] In light chain amyloidosis (AL), there is a strong prevalence for λ LC isotype, and two germline Vλ genes are implicated in half of λ-LC-associated AL amyloidoses.[8] In light chain deposition disease (LCDD), κLC isotypes are predominant, with overrepresentation of the Vκ4-1 gene. The LC V domain features frequent glycosylation, hydrophobic residues, and high isoelectric point (pI) that could account for propensity to deposit along the anionic proteoglycans of the basement membranes.[6,9]

Diagnostic Considerations

In any patient with proteinuria, serum and urine protein electrophoresis must be performed. In addition, serum and urine immunofixation and serum free light chain (FLC) assay should be considered, particularly in the 40- to 80-year age range.[1,2,5]

In Patients With Known Monoclonal Gammopathy and Kidney Manifestations

The first step is to rule out symptomatic multiple myeloma (MM), WM, chronic lymphocytic leukemia (CLL), or other B-cell lymphoma, which would per se require specific hematologic treatment.

In patients with monoclonal gammopathy and no evidence of symptomatic hematologic disease, the diagnosis of MGRS-related kidney disease should be considered.

Regarding kidney disease, immunologic investigations should include serum complement studies and tests for cryoglobulins. In the absence of contraindications, a kidney biopsy should be performed in most patients. Exceptions are AL amyloidosis already proven on an extrarenal biopsy (see later), and any condition including age and comorbidities that would question the benefits of chemotherapy. If a concurrent cause of kidney disease such as diabetes is present, kidney biopsy should be considered only if presentation or clinical course is

Proteinuria, NS
CKD
Microhematuria
Hypertension
Possible nephritic
syndrome, AKI

Proteinuria, NS
CKD
Microhematuria
Hypertension

Congo red–positive
mesangial and CW
deposits
Vascular and
tubulointerstitial
deposits common
Mesangial proliferative
GN
Atypical MN
MPGN pattern
Interstitial tumoral
infiltrate common
(CLL)
MPGN pattern
Endocapillary GN
Glomerular thrombi
common
Intrarenal vasculitis
occasional

Nonorganized Monoclonal Ig Deposits
Monoclonal Ig
Proteinuria, NS
Nodular
deposition disease
CKD
glomerulosclerosis
Microhematuria
(constant in HCDD)
Hypertension
Less often mesangial
proliferative GN,
crescents rare (<10%)
and focal
Thickened TBM and
vascular walls

Immunotactoid
glomerulopathy/
glomerulonephritis
with organized
microtubular
immunoglobulin
deposits
Type I
cryoglobulinemic
GN

Organized Monoclonal Ig Deposits
Amyloid: AL, AH,
Proteinuria, NS
AHL

CKD
Hypertension
and hematuria
uncommon

Glomerular
Disease

Light Microscopic
Renal Symptoms Findings

Linear deposits along TBM,
GBM, and arteriolar
myocytes
LCDD: LC deposits only
(mostly κ)
HCDD: HC deposits only (γ
or α), with CH1 deletion
LHCDD: LC + HC deposits

Granular/smudgy deposits
in mesangium and
CW (predominantly
subepithelial).
Monotypic IgG deposits (IgG1
most common) (κ > λ)
C3, C4, C1q deposits
Deposits in mesangium,
CW (predominantly
subendothelial), vascular
walls.
Glomerular thrombi
IgG, IgM, or IgA (κ > λ)
C3, C4, C1q deposits

AL: LC deposits (mostly λ)
AH: HC deposits (γ1, or γ4,
or α), with CH1 deletion
AHL: LC and HC deposits

Immunohistology

Amorphous, finely
granular deposits in
TBM, GBM, mesangium,
and arteriolar walls

Frequent (often
oligosymptomatic):
heart, liver,
peripheral nerve

Frequent: skin ++,
peripheral nerve,
joints

Rare (peripheral
nerve, skin)

10–60 nm microtubules
with hollow core,
arranged in parallel;
similar microtubules in
leukemic lymphocytes

(if present)
10–90 nm microtubules
with hollow core
Extra + intracellular
crystals (crystalcryoglobulinemia)

Frequent: heart, liver,
peripheral nerves

Extrarenal
Involvement

7–14 nm fibrils randomly
arranged

Ultrastructural
Findings

EP/IFIX: 70%–100%
FLC: ~100%

EP/IFIX: 80%
FLC: unknown

EP/IFIX: 40%–70%
FLC: 20%

EP/IFIX: 70%–90%
FLC: 80%–90%

Identification of
a Monoclonal
Immunoglobulin

MGR(C)S
Symptomatic MM
WM
Hypocomp. common
in γ1 and γ3 HCDD

MGR(C)S
MM
B-cell lymphoma
WM
Hypocomp. common

CLL (common)
B-cell lymphoma
MGRS
MM
Hypocomp. ~30%

MGR(C)S
Symptomatic MM
uncommon
WM

Hematologic and
Immunologic
Characteristics

Classification of Glomerular Disorders With Monoclonal Immunoglobulin Deposits and Comparison With Fibrillary Glomerulonephritis

TABLE 28.1

Proteinuria, NS
CKD
Microhematuria
Hypertension

Proliferative GN
with monoclonal Ig
deposits

Immunohistology
None

None

12–24 nm fibrils randomly arranged

Extrarenal Involvement

Nonorganized granular deposits in mesangium, subendothelial, and/or subepithelial zone

Ultrastructural Findings

EP/IFIX <10% (fortuitous association in most cases)

EP/IFIX: 30%
FLC: unknown

Identification of a Monoclonal Immunoglobulin

HCV, autoimmune diseases, nonhematologic malignancy
Hematologic disease very rare

Usually none
MGRS
MM, B-cell lymphoma
WM rare
Hypocomp. ~30%

Hematologic and Immunologic Characteristics

fibrillary GN cases with Congo red weakly positive glomerular deposits have been described. 46
cases of IgG-negative fibrillary GN have been described. 47
AH, Amyloid with immunoglobulin heavy chains; AL, amyloid with immunoglobulin light chains; AKI, acute kidney injury; CLL, chronic lymphocytic leukemia; CKD, chronic kidney disease; CW,
glomerular capillary walls; DNAJB9, DnaJ homolog subfamily B member 9; EP/IFIX,

electrophoresis/immunofixation; FLC, serum free light chains; GN, glomerulonephritis; HC, immunoglobulin
heavy chains; HCDD, heavy chain deposition disease; Hypocomp., hypocomplementemia; Ig, immunoglobulin; LC, immunoglobulin light chains; LCDD, light chain deposition disease; LHCDD,
light and heavy chain deposition disease; ITGP, immunotactoid glomerulopathy; MGR(C)S, monoclonal gammopathy of renal (clinical) significance; MM, multiple myeloma; MN, membranous
nephropathy; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; TBM, tubular basement membrane; WM, Waldenström macroglobulinemia.

bRare

aRare

Granular mesangial and
CW deposits
IgG deposits (mostly IgG3),
(κ> λ), rarely IgM, IgA, or
LC alone
C3 + C1q deposits
Fibrillary GN (See Chapter 29): Not Related to Monoclonal Ig Deposits
Fibrillary GN
Proteinuria, NS
Mesangial proliferative
IgG deposits (almost
CKD
GN
always polyclonal, mostly
Microhematuria
MPGN pattern
IgG4)b
Hypertension
Crescents in 10–20%
C3 ± C4, C1q
Acute nephritic
Positive DNAJB9
syndrome rare
staining in 100%
Congo red negativea

MPGN pattern
Endocapillary GN
Membranous GN
Mesangial proliferative
GN

Light Microscopic
Renal Symptoms Findings

Glomerular
Disease

atypical. Importantly, when a kidney biopsy is performed, a sample should be processed for EM. Light microscopy (LM) should include Congo red staining. Immunofluorescence studies are crucial to determine the composition of deposits, to assess their monotypic nature and their concordance with the circulating monoclonal Ig. They should be performed using antibodies specific for κ and λ LCs, and, when deposits are composed of an entire IgG, heavy chain subclass typing is recommended. Except for most cases of AL amyloidosis, EM is required to assess the diagnosis of MGRS-related lesions to demonstrate the distribution and ultrastructural pattern of organization of deposits. When the diagnosis remains uncertain, additional techniques including paraffin IF after pronase digestion, proteomic analysis, and immuno-EM are required, preferentially after expert advice from a reference center.5 Careful attention should be paid to extrarenal manifestations. Tests for liver function and cardiac biomarkers (NT-proBNP and troponin) are mandatory.

Hematologic workup is the cornerstone of the management of MGR(C)S. It must include bone marrow examination with flow cytometric characterization of lymphocytic and plasmacytic populations and serum FLC (sFLC) measurement. Interpretation of FLC assays may be difficult in patients with impaired kidney function. Physiologically, FLCs undergo renal elimination, and the level of polyclonal κ and λ FLCs increases as glomerular filtration rate decreases. With the Freelite test, the “normal” FLC ratio is 0.26 to 1.65 in patients with preserved kidney function but is 0.34 to 3.10 in patients with severe kidney failure (chronic kidney disease [CKD] stage 5 or greater). Of note, several different assays for measuring FLC are now available but results from different assays cannot be directly compared so the same FLC assay must be used to monitor a particular patient throughout follow-up.

The nature of the clone is usually in accordance with the isotype of the monoclonal Ig: plasmacytic when the monoclonal Ig is IgG, IgA, or LC only; and lymphoplasmacytic or lymphocytic when it is IgM.1,2,5,10 Exceptions exist, such as plasma cell clones harboring translocation t(11;14) and producing monoclonal IgM. Considering the high prevalence of monoclonal immunoglobulins after age 50 years (>3%), it is crucial to exclude a chance association between the kidney disease and the monoclonal gammopathy and obtain support for a causal link between the two. For example, demonstrating tissue deposition or precipitation of all or part of the circulating monoclonal Ig is a strong argument for clone toxicity. In the absence of such evidence, an indication for chemotherapy is more uncertain and should be validated by multidisciplinary evaluation.1,2,5,10

In Patients Without Known Monoclonal Gammopathy but Monotypic Deposits/Inclusions or C3 Deposits/Thrombotic Microangiopathy on Kidney Biopsy

In this situation, the main concern is detecting and characterizing the pathogenic clone. The monotypic nature of renal deposits should be carefully assessed. Detailed immunologic hematologic investigations are required to identify a small monoclonal Ig, including serum and urine immunofixation, measurement of sFLC, and sensitive techniques (flow cytometry) to detect a small blood or bone marrow B-cell population.5,10

Principles of Treatment

General Considerations

In patients with MGRS-related glomerulopathies, targeting the underlying B-cell clone is the only therapeutic option and requires collaboration between nephrologists and hematologists. Treatment is based on chemotherapy, either conventional or with high-dose melphalan (HDM) supported by autologous stem cell transplantation (ASCT), and anti–B-cell monoclonal antibodies (Mabs).2,10

No strategy is available to limit monoclonal Ig toxicity by reducing its secretion, inhibiting its deposition, or other interventions. In AL amyloidosis, approaches aimed at eliminating amyloid deposits have been developed, using antibodies directed against conformational fibril epitopes, or agents targeting amyloid P component. However, none has been approved yet for use.8,11,12

The choice of chemotherapy should consider kidney metabolism of drugs and their potential renal and extrarenal toxicity. Bortezomib can be used without dose adjustment, even in patients with end-stage kidney disease (ESKD). Thus, bortezomib-based regimens are often recommended because of their favorable benefit/risk profile.13 HDM/ASCT is feasible with acceptable toxicity in carefully selected patients with kidney failure due to AL amyloid or monoclonal Ig deposition disease (MIDD).8-10,14 The administration of rituximab raises no concerns in patients with reduced glomerular filtration rate (GFR). Current experience regarding the use of antiplasma cell Mabs, such as anti-CD38 Mabs in AL amyloidosis, is encouraging.8,15

Indication for treatment and its modalities rely upon a benefitto-risk approach considering natural history of kidney disease, extrarenal involvement, and comorbidities. It is reasonable to consider polychemotherapy and even HDM/ASCT in a patient with MGR(C)S and potential life-threatening clone-related lesions. In contrast, these strategies are not appropriate in a frail patient with MGRS and kidneylimited disease who already progressed to ESKD and is not eligible for kidney transplantation. In patients on maintenance dialysis, chemotherapy should be considered if extrarenal manifestations are present or if the patient is a candidate for kidney transplantation, given the high recurrence rate of MGRS-related kidney diseases in the allograft (see later).10

Treatment should be adapted to the nature of the clone. If the clone is plasmacytic, treatment is based on antimyeloma agents, particularly bortezomib-based regimens. Anti-CD38 Mabs are increasingly used in all MGR(C)S types. Treatment with an anti-CD20 Mab, such as rituximab, is usually not appropriate in patients with a plasmacytic clone, whose cells are commonly CD20 negative. If the clone is lymphoplasmacytic or corresponds to CLL or B-cell lymphoma, treatment should be adapted accordingly, usually based on anti-CD20 Mabs. The place of new agents, such as Bruton kinase inhibitors, remains to be assessed.2,5,8,10

Evaluation of Response to Treatment

Achievement of the best hematologic response is the goal of treatment and the primary criterion for determining its optimal duration.2,5,8,10,16 In the most frequent types of MGC(R)S, AL amyloidosis, and MIDD, the quality of hematologic response is the main prognostic factor for both kidney and patient survival.8,9,13-18

Accordingly, assessment of hematologic response to treatment is crucial. It depends on repeat evaluations of the pathogenic monoclonal Ig component, usually based on FLC variations. International response criteria have been validated in AL amyloidosis (see later).8,16 The validity of these criteria in MIDD is currently under evaluation. When the causal monoclonal Ig is not detectable or difficult to measure, evaluating the hematologic response is challenging. Repeated bone marrow examination, including molecular studies, may be considered.10

For kidney (and extrarenal) outcomes, hematologic response is necessary but not sufficient. The probability of improving organ function is also governed by the severity and chronicity of tissue damage. When a complete or near complete hematologic response has been achieved, chemotherapy should be stopped even if kidney symptoms persist, because organ response is usually delayed.

For example, in AL amyloidosis, remission of nephrotic syndrome may require up to 1 year after hematologic remission.14 At least partial regression of monoclonal Ig deposits and associated lesions after deep hematologic response has been documented histologically in animal models and in few patients with MIDD or AL amyloidosis.6 19

Symptomatic Measures and Kidney Replacement Therapies

Supportive measures in MGRS-related glomerulopathies are generally similar to that recommended in glomerular diseases (see Chapter 82). In AL amyloidosis, blockers of the renin-angiotensin system and anticoagulants should be used cautiously due to the risk of severe hypotension and bleeding, respectively. Monitoring of side effects of chemotherapy includes prophylactic antibiotics.8 10

Indications and modalities of chronic dialysis are similar to that in patients with other causes of ESKD. Patients with AL amyloidosis are more frequently exposed to complications due to multisystemic organ involvement.8 10 20

Kidney transplantation may be proposed to selected patients with MGC(R)S without severe extrarenal disease. Transplantation should be performed preferentially in those who have achieved sustained deep hematologic remission (for at least 6 months) prior to the procedure.9 21-23 Recurrence occurs after variable delay depending on the type of kidney disease, leading to rapid graft loss in proliferative GN with monoclonal Ig deposits (PGNMID),23 or after several years in AL amyloidosis.21 22 The recurrence rate is mostly determined by the quality of hematologic response prior to transplantation. In AL amyloidosis and MIDD, achievement of very good partial hematologic response or more is associated with acceptable long-term allograft and patient outcomes.9 21 22 Compared with the broader population of kidney transplant recipients, recipients with AL amyloidosis or MIDD are exposed to an increased risk of neoplastic and infectious complications.9 21 In contrast, as in all patients with MGRS, the risk of progression to overt symptomatic myeloma is low.9 21-23

GLOMERULOPATHIES WITH ORGANIZED MONOCLONAL IMMUNOGLOBULIN DEPOSITS

On EM examination, glomerular monoclonal Ig deposits may be organized into fibrils, crystals, or microtubules.

Fibrillar Deposits

Fibrillar deposits nearly always correspond to LC (AL) amyloidosis, which is the main type of renal AL amyloidosis (see later). Nonamyloid fibrillary GN is nearly always characterized by deposition of polyclonal IgG (see Chapter 29).5 24 25

Crystalline Deposits

Type I cryoglobulins (usually IgG) sometimes display a crystalline pattern defining crystalglobulinemia.5 LC crystalline inclusions within glomerular cells have been rarely described, mostly in patients with Fanconi syndrome or crystal-storing histiocytosis5 (see Chapter 50).

Microtubular Deposits

Microtubular deposits are observed in type I and type II cryoglobulinemic GN (see Chapter 22).5 They also characterize immunotactoid glomerulopathy, also referred to as GN with organized microtubular monoclonal Ig deposits (GOMMID).24-27

IMMUNOTACTOID GLOMERULOPATHY (GOMMID)

Immunotactoid glomerulopathy (ITGP/GOMMID) is extremely rare, representing less than 0.05% of all kidney biopsies.25 26 Diagnosis is usually made between age 50 and 60 years. Kidney manifestations include proteinuria often of nephrotic range, microscopic hematuria, and mild to severe CKD.24-27 Extrarenal deposits in the skin or peripheral nerves have been very rarely reported.24

Histologically, ITGP/GOMMID usually shows atypical membranous glomerulopathy with segmental mesangial proliferation, or a membranoproliferative GN (MPGN) pattern. Interstitial infiltration with clonal lymphocytes is common in patients with an underlying CLL. On IF, glomerular deposits stain for IgG (most commonly IgG1) and C3 and exhibit LC restriction in most cases. Electron microscopy is mandatory for diagnostic confirmation, showing glomerular deposition of microtubules of 10 to 90 nm in external diameter, with a distinct hollow core at magnification of less than 50,000, and arranged at least focally in parallel arrays (Fig. 28.1).24-27

As in all glomerulopathies with monotypic Ig deposits, hematologic investigations searching for an underlying monoclonal B-cell clone are required. Two-thirds of patients have detectable serum and/or urine monoclonal gammopathy matching kidney deposits. ITGP/GOMMID complicates CLL or small lymphocytic lymphoma in about half of cases, and MGRS in the remaining cases.24-27

Intracytoplasmic microtubules, identical to those found in glomeruli, are commonly observed in clonal lymphocytes from these CLL patients (Fig. 28.1).24,27

Data regarding treatment and outcomes in ITGP/GOMMID are limited. Kidney response to clone-targeted chemotherapy, using alkylating agents, rituximab-based, or bortezomib-based regimens, appears to be frequent and often sustained. When it occurs, renal relapse often precedes hematologic recurrence.26,27

GLOMERULOPATHIES WITH NONORGANIZED MONOCLONAL IMMUNOGLOBULIN DEPOSITS

Glomerulopathies with nonorganized monoclonal immunoglobulins include two distinct entities: Randall-type MIDD and PGNMID.

Randall-Type Monoclonal Immunoglobulin Deposition Disease

Monoclonal Ig deposition disease encompasses three subtypes, depending on the composition of deposits. LCDD, in which the deposits contain monoclonal LC only (κ in 80% of cases) is by far the most common subtype. Heavy chain deposition disease (HCDD), with deposits derived from monoclonal heavy chains only (most frequently γ and always lacking the first constant [CH1] domain) is rare. Light and heavy chain deposition disease (LHCDD), in which the deposits are composed of monoclonal light and heavy chains (most commonly γ and κ) is even rarer.9,28-31

Epidemiology

Monoclonal Ig deposition disease occurs with a slight male predominance and a wide range of age distribution, but predominantly in the sixth decade. Its diagnosis is made in around 0.3% to 0.5% of native kidney biopsies, representing a 10-fold lower prevalence compared with AL amyloidosis.28,29

Clinical Manifestations

Monoclonal Ig deposition disease is due to MGRS in around twothirds of cases but noticeably complicates symptomatic myeloma in more than 30% of cases. Abnormal LFC level and κ/λ ratio is a nearly constant finding in all types of MIDD.9 Monoclonal Ig deposition disease rarely occurs during WM, CLL, or non-Hodgkin lymphoma.9,29

A

B

C

D

Fig. 28.1 Immunotactoid Glomerulopathy/Glomerulonephritis With Organized Microtubular Monoclonal Immunoglobulin (Ig) Deposits in a Patient With Underlying Chronic Lymphocytic Leukemia. (A) Endocapillary proliferative glomerulonephritis with segmental double contour appearance of capillary walls. Interstitial infiltration with malignant B cells (PAS ×400). (B). Immunofluorescence microscopy. Glomerular granular deposits stained with anti-IgG2 and anti-κ (not shown) antibodies (×400). (C). Interstitial malignant B cells showing same positivity with anti-IgG2 antibody (×400). (D) Ultrastructurally, glomerular deposits are organized into microtubules of 10 nm in external diameter, with a distinct hollow core (electron microscopy ×100,000). Inset: similar microtubules within the endoplasmic reticulum of clonal B-lymphocytes (electron microscopy ×100,000).

Kidney involvement is an almost constant feature of MIDD. Heavy proteinuria is present in about 90% of cases, with hematuria and hypertension in around half of the patients. Nephrotic syndrome is more frequent in HCDD. High prevalence, early appearance, and rapid progression of CKD are other characteristics of kidney disease in MIDD.[9,28-31] Around 10% of LCDD cases have prominent kidney arteriolar involvement and present with slowly progressive CKD and low-grade proteinuria (<0.5 g/day).[9]

Extrarenal monoclonal Ig deposition is frequent, particularly in LCDD. Liver, cardiac, and peripheral nerve manifestations have been reported in up to 30% of patients. Liver deposits may be confined to the sinusoids and basement membranes of biliary ducts, without associated parenchymal lesions. They are sometimes massive, with dilation and ruptures of sinusoids, resembling peliosis. Hepatomegaly with mild isolated cholestasis is the main presentation. Rarely, life-threatening hepatic insufficiency and portal hypertension may occur. Cardiac involvement results in hypertrophic cardiomyopathy, resembling AL amyloidosis cardiopathy, with potential development of diastolic dysfunction, arrhythmias, conduction blocks, and heart failure. Neuropathy due to deposits along peripheral nerve fibers or in the choroid plexus has been described. Deposits may affect a variety of other organs and tissues, including spleen, pancreas, salivary glands, thyroid, gastrointestinal tract, lungs, and skin.[9]

Kidney Pathology

By LM, the most characteristic lesion is nodular mesangial sclerosis, resembling diabetic nodular glomerulosclerosis (see Chapters 29 and 31), found in two-thirds of patients with LCDD and in almost all patients with HCDD. Mesangial nodules are composed of periodic acid–Schiff–positive material, with bitonal appearance, often accompanied by mild mesangial hypercellularity. Occasionally prominent endocapillary cellularity and mesangial interposition are present, mimicking MPGN. Crescents are uncommon, except in α-HCDD.[9,30]

Milder forms of LCDD may feature increased mesangial matrix or cellularity, with modest thickening of glomerular basement membranes (GBMs), often with abnormal brightness and rigidity. In early stages, glomerular deposits may be detected only by IF or EM.9,28-30

The most characteristic and almost constant feature of MIDD is the presence of tubular lesions, predominantly in distal tubules, and characterized by the deposition of a refractile eosinophilic, ribbonlike material along tubular basement membranes (TBM). Deposits are commonly found in arterioles and peritubular capillaries. Variable degrees of tubular atrophy and interstitial fibrosis are present.9,28-30

Immunofluorescence study is the cornerstone of diagnosis, which relies on the demonstration of diffuse linear TBM staining of monotypic LC only (LCDD), heavy chain only (HCDD), or both (LHCDD).

A

B

C

Fig. 28.2 Light Chain Deposition Disease. (A) Nodular glomerulosclerosis with mesangial matrix accumulation (Masson trichrome stain, ×312). (B) Staining of mesangial nodules and tubular basement membranes with anti-κ antibody (immunofluorescence, ×312). (C) Electron micrograph showing a layer of dense granular deposits (arrow) along the inner aspect of the glomerular basement membrane (×2500). (Courtesy Dr. Béatrice Mougenot, Paris.)

Similar deposits are common along GBMs, within the mesangium, and around vascular myocytes (Fig. 28.2).[9,28-30] In γ-HCDD, diagnostic confirmation requires not only the absence of staining for κ and λ LCs, but also confirmation of monotypic γ–heavy chain deposits using antibodies specific for IgG subclasses. In addition, the use of antibodies specific for the constant domains invariably demonstrates deletion of the first (CH1) domain in HCDD. In most cases of γ1 and γ3 HCDD, codeposition of complement components C4 and C1q is present, associated with activation of the complement classical pathway in the serum.[9,30]

By EM, the most characteristic feature is the presence of linear, finely granular punctate (“powdery”) electron-dense deposits along the inner aspect of GBMs and the outer aspect of TBMs.[9,28-30]

A pattern of LCDD may be observed in patients with symptomatic myeloma and LC cast nephropathy. In this situation, glomerular lesions are typically absent, and linear deposits along glomerular and tubular basement membranes are identified by IF, defining the socalled LCDD by IF only.[28] LCDD with concurrent glomerular AL amyloidosis has been also described.[9]

Management and Outcomes

The outcome of patients with MIDD has improved with earlier diagnosis and development of efficient chemotherapy. In LCDD, before the era of novel antiplasma cell agents, kidney and overall median survivals were 2 and 4 years, respectively.[28] Currently 80% of patients are dialysis-free at 2 years from diagnosis. Median overall survival is estimated at more than 10 years in patients achieving hematologic response, who account for more than 70% of cases. Predictors of kidney response and survival include baseline GFR greater than 30 mL/min/1.73 m^2 and achievement of very good partial response (difference between involved and noninvolved sFLC <40 mg/L). In addition to hematologic and renal responses, factors influencing patient survival are age, presence of symptomatic myeloma, and extrarenal LC deposition.[9,31]

Proliferative GN With Monoclonal Immunoglobulin Deposits

Epidemiology

PGNMID is a rare disorder with biopsy incidence around 1%. The mean age at presentation is 55 years, but PGNMID more commonly affects young patients than the other MGRS-related glomerulopathies.[32-35]

Clinical Manifestations

Proliferative GN with monoclonal Ig deposits is a renal-limited disorder, without any known description of extrarenal monoclonal Ig deposits. Kidney manifestations are nonspecific, with constant proteinuria and full-blown nephrotic syndrome in nearly half of patients.

Hematuria, sometimes macroscopic, is found in 80% of cases. Twothirds of patients have reduced GFR, but less than 10% require dialysis at the time of diagnosis. Rapidly progressive GN is uncommon. Low C3 and/or C4 serum levels are observed in around 20% of patients, and tests for cryoglobulins are negative.32-35

Diagnosis

Histologically, PGNMID mimics immune complex GN, with the association of proliferative glomerular lesions and deposits of immunoglobulins and complement.32-35 Predominant LM patterns are MPGN, endocapillary proliferative GN, or mesangial proliferative GN. In contrast to immune complex–type GN, glomerular deposits on IF appear monotypic, with staining for single LC isotype and a single γ–heavy chain subclass, admixed with C3 and C1q. There is a striking overrepresentation of the IgG3 κ isotype, particularly in young patients. The deposits are restricted to glomeruli (without extraglomerular or extrarenal involvement). PGNMID rarely features deposits made of other isotypes than IgG, including IgM, IgA, or LCs only.5 32 35 Electron microscopy shows granular, nonorganized deposits, typically in a subendothelial and mesangial distribution, with or without subepithelial deposits (Fig. 28.3).32-35

In contrast with most types of MGRS-related nephropathies, an underlying clone is infrequent, particularly in patients with IgG3 deposits.32-35 A monoclonal Ig is found in around 30% using immunofixation and sFLC measurement. The diagnostic rate of bone marrow studies is also low, even using sensitive techniques such as flow cytometry.33 35 Accordingly, whereas some cases of PGNMID are actually MGRS-related, others, particularly those featuring IgG3 deposits, might involve oligoclonal production of nephrotoxic Ig, secondary to skewed B-cell repertoire induced by viral or other putative antigenic stimulation.

Management and Outcomes

The specific management of PGNMID remains unclear, currently based on data from small cohorts. The frequent absence of a detectable clonal disorder affects both the choice of treatment and evaluation of its efficacy, which in many cases relies on kidney response only.

Renin-angiotensin system blockade alone can be a reasonable strategy

A

B

C

D

Fig. 28.3 Proliferative Glomerulonephritis (GN) with Monoclonal Immunoglobulin (Ig) Deposits. (A) Mesangial proliferative GN (trichrome staining ×400). (B–C) Immunofluorescence microscopy showing glomerular granular deposits stained with anti-IgG3 (B) and anti-κ LC (light chain) (C) antibodies (×400). (D) By electron microscopy, discontinuous electron dense deposits appear nonorganized and have predominant subendothelial distribution (×10,000).

in patients without nephrotic syndrome and stable mild CKD, particularly if they are frail.[10,32] Because PGNMID is a renal-limited disease, chemotherapy is not indicated in patients who have reached ESKD and are not candidates for kidney transplantation. In other situations, chemotherapy may be recommended, adapted to the underlying clone when identified, or empirically chosen and most often rituximab or bortezomib based.[32,35]

RENAL AMYLOIDOSIS

The term amyloidosis refers to a heterogeneous group of diseases due to extracellular deposition of a protein material in an abnormal fibrillar conformation. Amyloidosis is classified according to the nature of the precursor protein that composes the fibrils. To date, more than 30 different types have been described in humans. Amyloidosis is most often an acquired disorder resulting from overproduction of a normal precursor protein. It may also be an inherited condition deriving from an abnormal genetically modified precursor. Most types of amyloidosis are systemic disorders, often with predominant kidney involvement[8,36] (Table 28.2).

Common Properties to All Types of Amyloidosis

Whatever the protein precursor, amyloid deposits are composed of randomly arranged, rigid, nonbranching aggregated fibrils of indefinite length. Each amyloid fibril is composed of 4 to 6 twisted protofilaments, each displaying the typical “cross-β” structure, where antiparallel β-sheets are perpendicular to the filament axis. This configuration accounts for the affinity for Congo red staining that colors all amyloid deposits in a sensitive and specific manner, with a characteristic yellow-green birefringence under polarized light. All types of amyloid fibrils are associated with common nonfibrillar components. Most important is the amyloid P component, a glycoprotein that represents up to 15% of deposits and accounts for their incapacity to be solubilized in an organic milieu. It derives from serum amyloid P protein (SAP), a member of the pentraxin family (as C-reactive protein), synthesized by the liver. Serum amyloid P protein is resistant to proteolytic digestion, and its coating to amyloid fibrils results in their reduced tissue catabolism.[8,11] Another constant component of amyloidosis are glycosaminoglycans (GAGs), which are linear polysaccharides made of repeating units of hyaluronic acid. Linked to a protein core, they form proteoglycans, mostly of the heparan sulfate type. Serum amyloid P protein easily binds to GAGs, which appear to induce and stabilize the β-pleated amyloid structure.[8,36]

Amyloid formation results from abnormal folding of the precursor protein, which modifies its structure leading to the formation of intermolecular β-sheets. Amyloidogenesis involves a nucleation-dependent polymerization process. Formation of an ordered nucleus is the initial and thermodynamically limiting step, followed by addition of monomers and elongation of the fibrils. This process depends on (1) the natural propensity of the precursor to adopt an abnormal configuration (e.g., chronic accumulation of native transthyretin with aging, leading to wild-type transthyretin amyloidosis); (2) overproduction or

Mutations in TTR gene

Acquired

Hereditary

ATTR

Hereditary

Hereditary

Hereditary

Hereditary

Hereditary

Hereditary

AGel

AApoA1

AApoA2

AApoC2

AApoC3

ALm

Mutations in apolipoprotein
A1 gene
Mutations in apolipoprotein
A2 gene
Mutations in apolipoprotein
C2 gene
Mutations in apolipoprotein
C3 gene
Mutation in κ LC constant
domain gene
+++
+++

Constant κ LC
domain

+++

+++

++

+

–

–

–

+

–

–

+
±

–
–

+

–

++

+++

± (late)

+++

Heart

+++
+++ (glomerular)

–

–

+

–

+++

+++

Kidneys

ApoC3 variant

ApoC2 variant

ApoA2 variant

ApoA1 variant

Gelsolin variant

Wild-type Lect2
Fibrinogen Aα
chain variant
Lysozyme variant

Aβ2M variant

Wild-type Aβ2M

TTR variant

Wild-type TTR

Monoclonal Ig LC
Monoclonal Ig
heavy chain
SAA

Precursor
Protein

+

+

–

–

++

–

++

++
±

+

–

–

–

+ (late)

++

Liver

–

–

–

–

++ cranial
(–)
± (–)

–

–
–

+(+)

–

+++(+++)

–

–

+(+)

PN (AN)

GI, thyroid, pancreas

GI, salivary glands, bronchial

–

–

Testis, larynx, skin, eye

Eye, skin

GI, spleen, skin, salivary glands

Arthropathy
Carpal tunnel
GI, salivary glands, spleen, adrenal glands
–
Spleen

Eye

Carpal tunnel syndrome

GI, adrenal glands, thyroid

Soft tissue, GI

Other

ORGAN INVOLVEMENT

Supportive

Supportive

Supportive

Supportive

Supportive, organ transplant

Supportive

Supportive

Supportive
Supportive, organ transplant

Supportive treatment of heart failure
Tafamidis
Supportive treatment of heart failure
Tafamidis, RNA interference
Liver transplantation (in selected patients)

Efficient hemodialysis, renal
transplant
Supportive

Suppression of inflammation
Anti-TNF and anti-IL1 agents
Colchicine

Chemotherapy ± anti-CD38
Mab HDM/ASCT

Treatment

AH, Heavy chain amyloidosis; AL, light chain amyloidosis; FMF, familial Mediterranean fever; GI, gastrointestinal; HDM/ASCT, high-dose melphalan/autologous stem cell transplantation; Ig, immunoglobulin; IL-1, interleukin-1; LC, light chain; MGR(C)S, monoclonal gammopathy of renal (clinical) significance; SAA, serum amyloid A; TNF, tumor necrosis factor.
Modified from Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387:2641–2654.

Hereditary

ALys

Unknown
Mutations in fibrinogen α
chain gene
Mutations in lysozyme
gene
Mutations in gelsolin gene

Mutation in Aβ2M gene

Hereditary

Acquired
Hereditary

Long-term dialysis

Acquired

ALECT2
Afib

Aβ2M

Chronic inflammatory
disorders (infections,
chronic arthritis, FMF,
other periodic fever
syndromes)
Aging

Acquired

AA

Plasma cell clone (usually
MGR(C)S)

Acquired

AL, AH

Underlying
Disorder

Acquired or
Hereditary

Main Characteristics of Systemic Amyloidoses

Type

TABLE 28.2

A

B

C

D

Fig. 28.4 Light Chain Amyloidosis. (A) Glomerular mesangial and capillary wall Congo red–positive deposits (Congo red staining, ×400). (B) Glomerular amyloid deposits showing dichroism and birefringence under polarized light (Congo red staining, ×400). (C) Immunofluorescence microscopy: positive staining with anti-λ antibody (×400). (D) Electron microscopy: randomly arranged unbranched amyloid fibrils of 7 to 10 nm in external diameter (×100,000).

accumulation of the precursor (e.g., serum amyloid A protein [SAA] or β-2 microglobulin, resulting in acquired amyloid A [AA] amyloidosis or β-2 microglobulin amyloidosis, respectively); (3) genetic mutation generating or increasing amyloidogenicity of a precursor protein in hereditary amyloidosis; and (4) modification of the precursor through proteolytic cleavage or other mechanisms. In AL amyloidosis the LC variable domain (VL) is the main component of the fibrils, its polymerization being favored by proteolysis of the constant domain. In AA amyloidosis, macrophages seem to enhance fibril formation through C-terminal proteolysis of the precursor SAA.8 36

Diagnosis of Amyloidosis

General Considerations

Amyloidosis should be considered in any patient with suggestive presentations, including heart failure with preserved ejection fraction, albuminuria, or peripheral neuropathy, particularly if a monoclonal gammopathy is present. However, this diagnosis requires histologic confirmation. Whenever possible, noninvasive biopsies of abdominal fat and minor salivary glands should be performed initially. If necessary (i.e., when tissue biopsies fail to demonstrate amyloid deposition or are insufficient for amyloid typing), biopsy of a clinically affected organ (usually the kidney) should be considered. The diagnosis of amyloid is based on light microscopic examination, showing amorphous extracellular Congo red–positive deposits (Fig. 28.4). Congo red staining may be falsely negative if tissue sections are less than 5 μm in thickness. When a kidney biopsy is performed in patients with kidney involvement, it allows identification of Ig LC amyloid deposits in more than 80% of cases.5 8 36

Rapid identification of the nature of the amyloid precursor is crucial, as it dictates therapeutic management. It relies primarily on immunohistochemistry on paraffin-embedded tissue sections, or preferably on IF microscopy on frozen sections, using a panel of reactive antibodies that should include at least conjugates specific for κ and λ LC, Ig heavy chains, SAA, and transthyretin. Immunofluorescence is associated with higher rate of successful typing than immunohistochemistry (Fig. 28.4C). However, even IF has limitations due to local proteolysis, inaccessibility of the epitopes, or lack of commercial antibodies. Considerable progress has been achieved with the development of novel techniques, such as immuno-EM and laser capture microdissection combined with tandem mass spectrometry. Due to their high sensitivity and specificity, they allow correct typing in nearly 100% of cases. Although available only in a few specialized centers, they should be systematically considered when routine antibody-based techniques are inconclusive.37 38

Kidney Pathology

On LM, extracellular eosinophilic deposits appear faintly red after Congo red staining (Fig. 28.4A) and show characteristic apple-green birefringence under polarized light (Fig. 28.4B). The earliest lesions are located in the mesangium (Fig. 28.4A), on the external aspect of GBMs, and in blood vessels. Mesangial deposits may be sparse or more diffuse, sometimes featuring a lobular distribution. When glomeruli become massively sclerotic (or at the opposite, in the very early stages), the deposits may be difficult to demonstrate by Congo red staining. In this situation, EM may be useful to confirm the presence of amyloid deposits that typically display the ultrastructural appearance of randomly arranged fibrils 7 to 10 nm in external diameter (Fig. 28.4D).5

Main Types of Systemic Amyloidosis With Kidney Involvement

Acquired systemic AL, AA, and leukocyte cell-derived chemotaxin 2-associated amyloidosis (ALECT2) are the most frequent causes of amyloid kidney disease. Rarely, amyloidosis-associated kidney disease is inherited, induced by a mutation of the precursor protein (Table 28.1).

Clinical Presentation

Whatever its type, amyloidosis-associated kidney disease most commonly manifests with chronic glomerular symptoms, including heavy proteinuria (usually around 5 g/day at presentation) predominantly composed of albumin. Proteinuria is sometimes massive (>20 g/day), and about half of patients have full-blown nephrotic syndrome, often accompanied by diffuse edema. Fluid retention is of variable severity, sometimes resulting in anasarca. Nephrotic syndrome due to amyloidosis increases the risk of thromboembolic complications including renal vein thrombosis, particularly in AA amyloidosis. The prevalence of hematuria and hypertension varies according to the type of amyloidosis, being uncommon in AL whereas observed in around 30% in patients with AA. Kidney failure appears more frequent and usually more severe in AA compared with AL, reported in 50% to 75% and less than 50% in newly diagnosed patients, respectively.39 Classically, enlarged kidneys on imaging studies are suggestive of amyloidosis, but kidneys of normal or even reduced size should not exclude the diagnosis, particularly in patients with kidney failure.15 35 36

Rarely, amyloid deposits predominantly or exclusively involve the tubulointerstitial compartment, manifesting with low-grade tubular proteinuria, slowly progressive chronic kidney failure, and impaired urine concentration with polyuria. This misleading presentation has been mostly reported in AA and in AL amyloidosis, and more specifically in hereditary apoA1 amyloidosis related to the Leu75Pro variant.40 Amyloid deposits may predominantly affect intrarenal vessels, inducing severe hypertension, as in apoC3 hereditary amyloidosis (Table 28.2).

Immunoglobulinic Amyloidosis (Light Chain and Heavy Chain)

In the vast majority of cases, the main component of amyloid fibrils derives from the VL of a monoclonal LC. Heavy chain (AH) amyloidosis, made of a peptide derived from an Ig heavy chain, is rare. The incidence of AL amyloidosis is 9 to 12 cases per million inhabitants per year. AL is always due to a LC-secreting clonal population of cells belonging to the B-cell lineage. The abnormal population rarely causes an overt lymphoid disorder, such as symptomatic MM or WM. In over 80% of cases, it corresponds to a MG(R)CS, as defined earlier.8 36 The plasma cell clone that usually characterizes these MGCS-related ALs is featured by similar cytogenetic abnormalities as in symptomatic MM, except for a striking overrepresentation of the translocation t(11–14) (more than 50% compared with 15%, respectively). This translocation is associated with relative resistance to apoptosis and may predict high efficacy of BCL2 inhibitors and less sensitivity to bortezomib and immunomodulatory drugs.8

Physicochemical and structural characteristics determining the amyloidogenic potential of monoclonal LC remain poorly understood. The λ LC isotype is up to fourfold more frequent than the κ isotype, whereas in other monoclonal gammopathies, κ accounts for two-thirds of cases. The tropism of organ involvement is influenced

Main Clinical and Laboratory Features at Presentation in 816 Patients With Proven Light Chain (AL) Amyloidosis

TABLE 28.3

Median age (years)
Male sex
Organ involvement
Median number of involved organs
Kidney
Heart
Peripheral nerves
Liver
eGFR value (mL/min/1.73 m2)
30–59
15–29
<15 or dialysis
Median proteinuria (g/day)
NYHA class III or IV
Cardiac staging
I
II
III
Involved LC type
κ
λ
Positive serum/urine immunofixation
Monoclonal gammopathy
IgG
IgA
IgM
LC only
Serum FLCs
Abnormal κ/λ ratio
Median involved FLC concentration (mg/L)
Median dFLC (mg/L)
Median bone marrow plasma cell infiltration

63
59.9%
2
68.1%
64.8%
18.7%
16.0%
25.1%
8.5%
6.9%
2.9
26.8%
30.9%
43.7%
25.4%
24.6%
75.4%
94.2%
38.8%
10.0%
3.0%
47.6%

84.8%
178
157
10%

eGFR, Estimated glomerular filtration rate; NYHA, New York Heart Association; FLC, free light chain; dFLC, difference between involved and noninvolved FLC; Ig, immunoglobulin; LC, light chain.
Modified from Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30:4541–4549.

both by the germline gene used for the light-chain VL and by somatic mutations occurring in the secreting clone. Thus, the usage of genes belonging to the rare Vλ6 family is constantly associated with kidney involvement, whereas κ LCs of the Vκ1 family are more likely to induce dominant hepatic involvement. In addition, organ-specific environmental factors are also involved. Independently of deposition as fibrils, circulating free amyloid LCs may also participate in organ damage, as documented in the heart and suspected in the kidney.6 8

Clinical Manifestations

The median age at diagnosis is 64 years, with a slight male predominance (Table 28.3). About 10% of the patients are younger than 50 years. The clinical presentation of AL amyloidosis depends on the pattern and severity of organ involvement. Amyloid deposits may affect virtually any organ or tissue. Except for the combination of macroglossia (Fig. 28.5) and periorbital purpura (Fig. 28.6), which is rare but pathognomonic of AL amyloidosis, clinical features are not specific, with weakness being the most frequent initial symptom. Thus the through adsorption on amyloid fibrils. Accordingly, coagulation and hemostasis screening tests are particularly important before biopsy of the kidney or any other deep organ.8 36

Management and Outcomes

Fig. 28.5 Macroglossia in patient with light chain amyloidosis.

Fig. 28.6 Periorbital purpura in patient with light chain amyloidosis.

clinical diagnosis may be challenging, and when facing a patient with glomerular symptoms, it is crucial to carefully search for extrarenal manifestations.

Kidney disease is present in up to 70% of patients. Cardiac involvement is as frequent, and it is the major cause of mortality through arrhythmia, conduction blocks, and congestive heart failure. It is typically featured by restrictive hypertrophic cardiomyopathy, which should be systematically detected with measurement of sensitive cardiac biomarkers (troponin and brain natriuretic peptide [BNP] or NT-proBNP) and Doppler echocardiography showing increased septum ventricular wall thickness and decreased left ventricular longitudinal strain. Magnetic resonance imaging is useful in difficult cases. AL amyloidosis may infiltrate articular structures, such as carpal tunnel. Peripheral nerve involvement may result in a sensory polyneuropathy, often associated with dysautonomia including orthostatic hypotension, impotence, and bladder dysfunction. Involvement of the liver, spleen, and gastrointestinal tract is common and usually pauci-symptomatic. The most common skin manifestation is purpura, secondary to amyloid infiltration of capillaries. This implies a hemorrhagic risk, sometimes increased by an acquired deficiency of Factor X, thought to occur

The diagnostic workup of AL amyloidosis is similar to that of other MG(R)CS (see earlier). As already mentioned, the presence of a monoclonal gammopathy is not sufficient for the diagnosis, which should be secured by histologic identification of the Ig nature of amyloid deposits. AL amyloidosis is a systemic disease, and once the diagnosis has been confirmed, biopsies of other potentially involved sites are unnecessary and should be avoided because of the bleeding risk.

Elevation of NT-proBNP and cardiac troponin strongly correlate with prognosis and are therefore used for risk assessment according to the Mayo staging system. This prognostic score identifies 3 stages: stage 1, normal serum levels of troponin T and NT-proBNP; stage 2, increase in a single marker level; and stage 3, increase in both markers with thresholds at 332 ng/L for NTproBNP and 0.035 µg/L for troponin, respectively.8 16 36 Of note, NT-proBNP serum levels are influenced by eGFR. This limitation can be partly overcome by using BNP in patients with severe kidney failure.

Patients presenting with very high concentrations of NT-proBNP (>8500 ng/L) with systolic hypotension less than 100 mm Hg (Mayo Clinic stage IIIb) have a median survival of only 4 months. Cardiac transplantation may be considered in selected patients. Kidney involvement has a lesser impact on survival.8 Proteinuria greater than 5 g/24 h with eGFR of 50 mL/min/1.73 m2 or less at diagnosis have been associated with a high risk for progression to ESKD (up to 85% at 3 years).16

Regarding clone-targeted chemotherapy, pioneering studies established a modest efficacy of the oral melphalan and prednisone (MP) regimen. An important progress was achieved by using high-dose dexamethasone instead of prednisone (MDex combination), which significantly increased both frequency and rapidity of hematologic response. From the early 1990s, HDM/ASCT has been performed in selected patients with AL. Even in reference centers and after careful patient selection, HDM/ASCT is associated with significant morbidity and an early mortality rate of around 5%.8 36 A randomized controlled trial performed in a multicenter setting did not provide evidence for a survival benefit of HDM/ASCT compared with MDex.41 However, some centers still offer HDM/ASCT to highly selected young Mayo stage 1 individuals, who represent a minority of AL patients. Other investigators consider that the results of HDM/ASCT are biased by the selection process.

A decisive step has been the introduction of novel antimyeloma agents, particularly the proteasome inhibitor bortezomib.

To date, bortezomib-melphalan-dexamethasone (BMDex) or cyclophosphamide-bortezomib-dexamethasone (CyBorD) regimens are the backbone of initial treatment.13 The use of antiplasma cell monoclonal antibodies, such as anti-CD38 Mabs, is likely to further increase hematologic response rate, which remains the key prognostic factor.15 Results of a recent phase III trial indicate that addition of subcutaneous daratumumab to CyBorD results in hematologic response rate of more than 90%, compared with 77% with CyBorD alone. In addition, deep responses were significantly more frequent in the daratumumab arm, and this translated into increased organ improvement.42

Hematologic response should be regularly evaluated to assess treatment efficacy and to rapidly detect disease relapse. It is based on repeat sFLC measurements, using the difference between serum level of involved and noninvolved light chains (dFLC). Current response criteria are defined as complete response (negative serum and urine immunofixation with normalized FLC ratio), very good partial response (reduction of dFLC <40 mg/L), and partial response (50% reduction of dFLC). Regarding organ response, the modification of serum NT-ProBNP and troponin levels is an important prognostic factor in patients with cardiac amyloidosis. Because improvement in kidney parameters is usually delayed by several months following hematologic remission, treatment modifications should be based on FLC response.8 16-19 Although several agents developed to increase clearance of amyloid deposits have failed to demonstrate a clinical benefit,11 this approach is still under evaluation, particularly using novel antifibril antibodies.8 12

AA Amyloidosis

General Considerations

AA amyloid fibrils derive from SAA, which is produced by the liver during inflammatory reaction, where its serum concentration may increase by a factor of 1000. Among the different SAA isotypes, whose function is unknown, only SAA1 and SAA2 are amyloidogenic.

AA amyloidosis is consecutive to chronic inflammation, either of infectious origin or due to chronic inflammatory diseases, most commonly acquired and represented by rheumatoid disorders.

AA amyloidosis sometimes complicates a genetic disorder due to mutation in a factor involved in the control of inflammatory reaction. These disorders, referred to as hereditary periodic fever syndromes, are increasingly recognized as the underlying condition in AA amyloidosis.

Patients at risk for of AA amyloidosis are those with long duration of chronic inflammatory disease (median 17 years), high serum SAA levels, homozygosity for the SAA1 genotype, familial Mediterranean fever (FMF) trait (heterozygosity for variant pyrin), or other family history of AA amyloidosis (e.g., periodic fever syndromes).39 43

AA Amyloidosis Due to Acquired Inflammation

AA amyloidosis is rare in high-income countries, where it mostly complicates chronic inflammatory arthritis, particularly rheumatoid arthritis and systemic juvenile idiopathic arthritis, less commonly poorly controlled inflammatory bowel disease, or chronic infections such as in bronchiectasis and osteomyelitis. Rarely, AA amyloidosis complicates neoplasia, Castleman disease, and WM. AA is still frequent in lower-income countries and is commonly observed during granulomatous infections such as tuberculosis and pyogenic infections, particularly chronic osteomyelitis.

The usual clinical presentation of these forms of AA amyloidosis is proteinuria, often in the nephrotic range, with or without reduced glomerular filtration rate, in the context of a chronic infectious process or poorly controlled inflammatory arthritis.

Compared with AL amyloidosis, kidney disease in AA amyloidosis is more frequent and severe and is the main prognostic factor for survival. In contrast, symptomatic cardiac involvement is observed in less than 10% of cases. Gastrointestinal tract infiltration, hepatomegaly, and spleen enlargement are common, often asymptomatic, but hyposplenism may occur resulting in infectious complications. Marked cholestasis is rare, but associated with poor outcomes. Endocrine manifestations, including adrenal and thyroid dysfunction may occur. Peripheral neuropathy is rarely reported (Table 28.4).

Amyloid load and clinical outcomes relate to circulating concentrations of SAA. The risk for death among patients with an SAA concentration of 4 mg/L or less is almost 18 times lower than in those with an SAA concentration of 155 mg/L or greater. Even a very modest elevation in the SAA concentration of 4 to 9 mg/L is associated with a fourfold increased risk for death. These data emphasize the importance of vigorous treatment of the underlying inflammatory disease.

Characteristics at Presentation of 374 Patients With Systemic Secondary (AA) Amyloidosis

TABLE 28.4

Age, years (range)	50 (9–87)
Male sex	210 (56%)
Race or Ethnic Group	
White	307 (82%)
South Asian	27 (7%)
Other	40 (11%)
Duration of Inflammatory Disease at Diagnosis (Years)	
Median	17
Range	0–68
Kidney Dysfunction	
Proteinuria >500 mg/day or serum creatinine >133 µmol/L	363 (97%)
End-stage kidney disease	41 (11%)
Proteinuria, g/day median (range)	3.9 (0–26.0)
Liver Involvement	
Hepatomegaly, n (%)	35 (9%)
Deposits on SAP scintigraphy	85 (23%)
Splenic Involvement	
Deposits on SAP scintigraphy	370 (99%)
Cardiac Involvement	
Cardiac failure (n)	1
Cardiac infiltration (n)	2

From Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356:2361–2371.

Antibiotic treatment or surgical resection of an infectious site efficiently prevents and may even cure infection-related AA amyloidosis by suppressing its cause. The increasing use of effective diseasemodifying treatments for chronic inflammatory arthritis, such as anti–tumor necrosis factor and anti–interleukin-1 agents, accounts for the decline of AA in developed countries.39

AA Amyloidosis in Autoinflammatory Syndromes

Familial Mediterranean fever, also referred to as periodic fever, is the most frequent auto-inflammatory syndrome complicated by AA amyloidosis. Familial Mediterranean fever is an autosomal recessive disorder occurring most often in Sephardic Jews and Armenians. It is caused by mutations of the Mediterranean fever (MEFV) gene encoding a protein called pyrin (also known as marenostrin). Clinically, there are two independent phenotypes. In the first, brief episodic, febrile attacks of peritonitis, pleuritis, or synovitis occur in childhood or adolescence and precede the kidney manifestations. In the second phenotype, kidney symptoms appear first and may long be the only manifestation of the disease. The attacks are accompanied by dramatic elevations of acute phase reactants, including SAA. Amyloid deposits are responsible for severe kidney lesions with prominent glomerular involvement, leading to ESKD at a young age. When given early, colchicine can prevent the development of proteinuria. It is less effective in preventing eGFR decline in patients with nephrotic syndrome or kidney impairment. The minimum daily dose of colchicine for prevention of amyloidosis is 1 mg, but doses of 1.5 to 2 mg are required in patients with symptomatic amyloid nephropathy. In patients unresponsive or intolerant to colchicine, or noncompliant, interleukin-1 receptor antagonists should be considered.43

Other autoinflammatory syndromes associated with specific genetic mutations have been identified. All may be complicated by

AA amyloidosis. The main are TNF-α receptor–associated periodic fever syndrome (TRAPS), Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and hyperIgD syndrome. Most can be efficiently controlled by anti–interleukin-1 or anti–tumor necrosis factor-α agents.39 43

Other Types of Amyloidosis With Kidney Involvement

Leukocyte Cell–Derived Chemotaxin 2–Associated Amyloidosis

Recently identified, ALECT2 is currently the third most common type of kidney amyloidosis in the United States. It preferentially affects certain ethnic groups, particularly Hispanic Americans. LECT2 is a chemotactic factor to neutrophils mainly produced by the liver. ALECT2 manifests around 60 years of age, without family history. Kidney disease is predominant, including proteinuria and CKD that progresses to ESKD in 40% of cases. Nephrotic syndrome is rare. Kidney deposits predominate in the cortical interstitium, with variable glomerular and vascular distribution. Deposits may involve the liver and adrenal glands. The pathophysiology remains unknown. There is no mutation in LECT2 but affected individuals show homozygous polymorphism for the G allele, suggesting the disease may be favored by environmental factors on a predisposing genetic background.44

Hereditary Kidney Amyloidoses

The kidney is the major site of organ involvement in most types of hereditary amyloidosis, including fibrinogen A-α, apolipoprotein A-I, apoliprotein A-II, apolipoprotein C2, apolipoprotein C3, gelsolin, and lysozyme amyloidosis. The exception is hereditary transthyretin amyloidosis (ATTR), the most frequent type of genetically transmitted amyloidosis, in which cardiac disease and peripheral neuropathy with dysautonomia are prominent, whereas proteinuria and kidney failure develop in 30% to 50% of patients only. All hereditary amyloidoses are autosomal dominant conditions, but due to variable penetrance, a relevant family history may be absent. Thus, kidney hereditary amyloidosis should be suspected whenever IF studies of the kidney biopsy fail to type amyloid deposits. In this situation, the diagnosis is established by proteomic and/or immuno-EM completed by genetic studies to confirm an amyloidogenic mutation of the precursor protein. Careful clinical investigation of extrarenal manifestations is required to guide diagnosis and to evaluate organ involvement.36

Fibrinogen A-β Amyloidosis

Fibrinogen A-α Amyloidosis (AFib) is the most frequent hereditary kidney amyloidosis, deriving from a single mutation in the fibrinogen A-α-chain gene. It clinically manifests with chronic glomerular disease, usually around age 58 years. A family history is often lacking, resulting in delayed diagnosis. Age at diagnosis and severity of presentation vary according to the type of mutation. Symptomatic extrarenal manifestations are uncommon, although liver and spleen involvement may occur. In the kidney, amyloid deposits have a characteristic distribution, because they massively infiltrate the glomerulus but almost always spare the interstitial and vascular compartments. Kidney disease progresses to ESKD after a median time of 4.6 years. Kidney transplantation is usually associated with acceptable graft survival, despite disease recurrence. In the most severe forms (juvenile onset, hepatic failure) combined liver and kidney transplantation should be considered because it prevents amyloid recurrence by removing the source of the amyloidogenic fibrinogen variant, taking into account the increased risk of perioperative complications.45

SELF-ASSESSMENT QUESTIONS

1. Which of the following applies to heart involvement in AL (light chain) amyloidosis?
A. A contraindication to cardiac transplantation
B. Less common than in AA amyloidosis
C. Primarily responsible for valve dysfunction
D. A contraindication to hemodialysis
E. A major prognostic factor for patient survival

2. Regarding renal disease in monoclonal immunoglobulin deposition disease (MIDD), which of the following is true?
A. A contraindication to kidney transplantation
B. Characterized by crescent formation
C. Frequently responsible for nondiabetic glomerulosclerosis
D. Characterized by microtubular deposits
E. Caused by deposition of cryoglobulin

3. Which of the following is the key investigation for the diagnosis of immunotactoid glomerulopathy?
A. Immunofixation of serum proteins
B. Immunofixation of urinary proteins
C. Bone marrow aspiration
D. Immunofluorescence examination of kidney biopsy sample
E. Electron microscopy

4. Which of the following is the most common clinical sign or symptom caused by MIDD?
A. Renal failure
B. Hematuria
C. Hypertension
D. Jaundice
E. Heart failure

REFERENCES

1. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012;120:4292–4295.
2. Fermand JP, Bridoux F, Dispenzieri A, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018;132:1478–1485.
3. Royal V, Leung N, Troyanov S, et al. Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study. Blood. 2020;135:1833–1846.
4. Chauvet S, Bridoux F, Ecotière L, et al. Kidney diseases associated with monoclonal immunoglobulin M-secreting B-cell lymphoproliferative disorders: a case series of 35 patients. Am J Kidney Dis. 2015;66:756–767.
5. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International kidney and monoclonal gammopathy research group. Nat Rev Nephrol. 2019;15:45–59.
6. Sirac C, Herrera GA, Sanders PW, et al. Animal models of monoclonal immunoglobulin-related renal diseases. Nat Rev Nephrol. 2018;14:246–264.
7. Chauvet S, Roumenina LT, Aucouturier P, et al. Both monoclonal and polyclonal immunoglobulin contingents mediate complement activation in monoclonal gammopathy associated-C3 glomerulopathy. Front Immunol. 2018;9:2260.
8. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018;4:38.
9. Joly F, Cohen C, Javaugue V, et al. Randall-type monoclonal immunoglobulin deposition disease: novel insights from a nationwide cohort study. Blood. 2019;133:576–587.
10. Fermand JP, Bridoux F, Kyle RA, et al. How I treat monoclonal gammopathy of renal significance (MGRS). Blood. 2013;122:3583–3590.
11. Richards DB, Cookson LM, Berges AC, et al. Therapeutic clearance of amyloid by antibodies to serum amyloid P component. N Engl J Med. 2015;373:1106–1114.
12. Edwards CV, Bhutani D, Mapara M, et al. One year follow up analysis of the phase 1a/b study of chimeric fibril-reactive monoclonal antibody 111F4 in patients with AL amyloidosis. Amyloid. 2019;26(sup1):115–116.
13. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, melphalan, and dexamethasone for light-chain Amyloidosis. J Clin Oncol. 2020;38:3252–3260.
14. Leung N, Dispenzieri A, Lacy MQ, et al. Severity of baseline proteinuria predicts renal response in immunoglobulin light chain-associated amyloidosis after autologous stem cell transplantation. Clin J Am Soc Nephrol. 2007;2:440–444.
15. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood. 2020;135:1531–1540.
16. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30:4541–4549.
17. Pinney JH, Lachmann HJ, Bansi L, et al. Outcome in renal Al amyloidosis after chemotherapy. J Clin Oncol. 2011;29:674–681.
18. Rezk T, Lachmann HJ, Fontana M, et al. Prolonged renal survival in light chain amyloidosis: speed and magnitude of light chain reduction is the crucial factor. Kidney Int. 2017;92:1476–1483.
19. Safadi S, Saad A, Quint PS, et al. Disappearance of immunoglobulins from persistent renal amyloid deposits following stem cell transplantation for heavy-and light-chain amyloidosis. Nephrol Dial Transplant. 2015;30:1151–1155.
20. Decourt A, Gondouin B, Delaroziere JC, et al. Trends in survival and renal recovery in patients with multiple myeloma or light-chain amyloidosis on chronic dialysis. Clin J Am Soc Nephrol. 2016;11:431–441.
21. Angel-Korman A, Stern L, Sarosiek S, et al. Long-term outcome of kidney transplantation in AL amyloidosis. Kidney Int. 2019;95:405–411.
22. Heybeli C., Bentall A., Wen J., et al. A study from the Mayo Clinic

evaluated long-term outcomes of kidney transplantation in patients with immunoglobulin light chain amyloidosis. Kidney Int. 2020:S0085–S2538.

23. Said SM, Cosio FG, Valeri AM, et al. Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits is associated with high rate of early recurrence in the allograft. Kidney Int. 2018;94:159–169.
24. Bridoux F, Hugue V, Coldefy O, et al. Fibrillary glomerulonephritis and immunotactoid (microtubular) glomerulopathy are associated with distinct immunologic features. Kidney Int. 2002;62:1764–1775.
25. Rosenstock JL, Markowitz GS, Valeri AM, Sacchi G, Appel GB, D’Agati VD. Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. Kidney Int. 2003;63:1450–1461.
26. Nasr SH, Kudose SS, Said SM, et al. Immunotactoid glomerulopathy is a rare entity with monoclonal and polyclonal variants. Kidney Int. 2021;99:410–420.
27. Javaugue V, Dufour-Nourigat L, Desport E, et al. Results of a nationwide cohort study suggest favorable long-term outcomes of clonetargeted chemotherapy in immunotactoid glomerulopathy. Kidney Int. 2021;99:421–430.
28. Lin J, Markowitz GS, Valeri AM, et al. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. J Am Soc Nephrol. 2001;12:1482–1492.
29. Nasr SH, Valeri AM, Cornell LD, et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol. 2012;7:231–239.
30. Bridoux F, Javaugue V, Bender S, et al. Unravelling the immunopathological mechanisms of heavy chain deposition disease with implications for clinical management. Kidney Int. 2017;91:423–434.
31. Kourelis TV, Nasr SH, Dispenzieri A, et al. Outcomes of patients with renal monoclonal immunoglobulin deposition disease. Am J Hematol. 2016;91:1123–1128.
32. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009;20:2055–2064.
33. Bhutani G, Nasr SH, Said SM, et al. Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. Mayo Clin Proc. 2015;90:587–596.
34. Nasr SH, Larsen CP, Sirac C, et al. Light chain only variant of proliferative glomerulonephritis with monoclonal immunoglobulin deposits is associated with a high detection rate of the pathogenic plasma cell clone. Kidney Int. 2020;97:589–601.
35. Gumber R, Cohen JB, Palmer MB, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Kidney Int. 2018;94:199–205.
36. Gillmore JD, Hawkins PN. Pathophysiology and treatment of systemic amyloidosis. Nat Rev Nephrol. 2013;9:574–586.
37. Fernández de Larrea C, Verga L, Morbini P, et al. A practical approach to the diagnosis of systemic amyloidoses. Blood. 2015;125:2239–2244.
38. Gonzalez Suarez ML, Zhang P, et al. The sensitivity and specificity of the routine kidney biopsy immunofluorescence panel are inferior to diagnosing renal immunoglobulin-derived amyloidosis by mass spectrometry. Kidney Int. 2019;96:1005–1009.
39. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007;356:2361–2371.
40. Gregorini G, Izzi C, Obici L, et al. Renal apolipoprotein A-I amyloidosis: a rare and usually ignored cause of hereditary tubulointerstitial nephritis. J Am Soc Nephrol. 2005;16:3680–3686.
41. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007;357:1083–1093.
42. Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyborD) in

patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 Andromeda study. Abstract LB2604. EHA25 Virtual , June 14, 2020.
43. Lachmann HJ. Periodic fever syndromes. Best Pract Res Clin Rheumatol. 2017;31:596–609.
44. Nasr SH, Dogan A, Larsen CP. Leukocyte cell-derived chemotaxin 2-associated amyloidosis: a recently recognized disease with distinct clinicopathologic characteristics. Clin J Am Soc Nephrol. 2015;10:2084–2093.

45. Gillmore JD, Lachmann HJ, Rowczenio D, et al. Diagnosis, pathogenesis, treatment, and prognosis of hereditary fibrinogen A alpha-chain amyloidosis. J Am Soc Nephrol. 2009;20:444–451.
46. Alexander MP, Dasari S, Vrana JA, et al. Congophilic fibrillary glomerulonephritis: a case series. Am J Kidney Dis. 2018;72. 325–336.

47. Said SM, Rocha AB, Royal V, et al. Immunoglobulin-negative DNAJB9associated fibrillary glomerulonephritis: a report of 9 cases. Am J Kidney Dis. 2021;77:454–458.

29

Rare Glomerular Disorders

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This chapter describes several uncommon or rare glomerular disorders and the clinical syndromes that tend to affect adults and infrequently have glomerular disease as a major clinical manifestation. These disorders must be recognized and differentiated from other more common glomerular diseases to determine whether a familial disorder is present, estimate the prognosis, plan therapy, or determine the risk for recurrence in a transplanted kidney. The chapter also describes primary and secondary antiphospholipid antibody syndromes in detail.

MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS WITHOUT IMMUNOGLOBULIN A DEPOSITS

Mesangial proliferative glomerulonephritis (MesPGN) encompasses a heterogeneous collection of disorders with a largely unknown etiology. The common feature is a light microscopy (LM) histologic glomerular pattern of injury characterized by diffuse mesangial proliferation[1–4] (Fig. 29.1). MesPGN has a diffuse and global increase in mesangial cells, often with an increase in mesangial matrix. Other cells (e.g., neutrophils and monocytes) may contribute to the hypercellularity. Thus, MesPGN is a glomerular pattern of injury, not a specific disease entity. On the other hand, mesangial cellular proliferation can also occur as focal and segmental lesions, often accompanied by segmental glomerular necrosis and very localized crescents. This phenotype may accompany the evolution of pure MesPGN but often signifies the presence of systemic disease, including systemic lupus erythematosus (SLE), immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura), IgA nephropathy, infection-related glomerulonephritis (i.e., postinfectious glomerulonephritis [GN] or human immunodeficiency virus [HIV]),[5] microscopic polyangiitis, granulomatous polyangiitis, Goodpasture disease (anti–glomerular basement membrane [GBM] disease), rheumatoid vasculitis, mixed connective tissue disease, and monoclonal immunoglobulin-associated glomerular diseases (see disease-specific chapters). On occasion, focal and segmental proliferative GN is discovered without any associated identifiable multisystem disease process or IgA deposits (i.e., idiopathic focal and segmental proliferative GN). Such patients have a clinical presentation, course, and response to treatment similar to those described for pure MesPGN but are not discussed further in this section.

In “pure” MesPGN, the peripheral capillary walls are thin and delicate, without obvious deposits, reduplication, focal disruptions, or necrosis. The visceral and parietal epithelial cells, although occasionally enlarged, have not undergone proliferation, and there are no crescents or segments of sclerosis. Large mesangial deposits staining with periodic acid–Schiff (PAS) or fuchsin are absent; such deposits suggest IgA nephropathy (see Chapter 24), lupus nephritis (LN; see Chapter 27), C3 glomerulonephritis (see Chapter 23), or, less often, HIV-associated glomerular diseases (see Chapter 58), which commonly manifest as a mesangial proliferative lesion. Postinfectious GN may also cause MesPGN (see Chapter 57). The tubulointerstitium and vasculature are usually normal, unless reduced kidney function or hypertension is present or the patient is of advanced age.

On immunofluorescence (IF) microscopy, a wide variety of immunoglobulin and complement deposition is observed (Table 29.1). Most often, diffuse and global granular immunoglobulin M (IgM) and C3 deposits are scattered throughout the mesangium (so-called IgM nephropathy; see later discussion), but isolated C3, C1q, or even IgG deposits may be seen.[6–8] If IgA is the predominant immunoglobulin, the diagnosis is IgA nephropathy. Occasionally, no immunoglobulin deposits are found. Prominent C3 deposits without immunoglobulin deposition should suggest C3 glomerulopathy.6 Extensive C1q deposits, with or without immunoglobulin deposits, should suggest C1q nephropathy (see later discussion).9 On electron microscopy (EM), the number of mesangial cells is increased, with an occasional leukocyte. Mesangial matrix material is frequently, but not invariably, diffusely increased. Mesangial electron-dense deposits often can be seen but there are no subendothelial, intramembranous, or subepithelial deposits. In the absence of glomeruli for IF, very large mesangial or paramesangial electron-dense deposits suggest IgA nephropathy. Deposits in locations other than the mesangium suggest a postinfectious etiology or an underlying disease, such as LN or C3 glomerulopathy. Deposits of multiple immunoglobulin classes and EM identification of numerous tubuloreticular inclusions suggest underlying LN.

The clinical presentation of MesPGN is varied, but persistent or recurring microscopic or macroscopic hematuria with mild proteinuria is most common. It commonly affects young adults,1,2 with a slight male predominance. Nephrotic syndrome is a less frequent initial presentation but more often occurs with diffuse mesangial IgM deposits (IgM nephropathy; see later discussion),3 C1q deposits (C1q nephropathy9), or C3 glomerulonephritis.6 Pure MesPGN is uncommon (<5%) in patients with idiopathic nephrotic syndrome. In some countries, such as India and China, MesPGN is found in 10% to 15% of kidney biopsy samples, but the frequency is much less in wealthy countries with a lower burden of infectious diseases. MesPGN also has been observed in acute parvovirus B19 disease and in association with Castleman disease.

Kidney function and blood pressure are usually normal, at least initially. Serologic studies are generally unrewarding but should be performed in most patients to exclude known causes. Serum C3 and C4 and hemolytic complement activity (CH50) are typically normal. A low C3 and normal C4 level suggest C3 glomerulopathy or poststreptococcal GN. Antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibody (ANCA), anti-GBM autoantibody, and cryoimmunoglobulins are negative. MesPGN can indicate resolving postinfectious (poststreptococcal or nonpoststreptococcal) GN, often with isolated C3 deposits with scanty, subendothelial, intramembranous, or

Immunofluorescence Microscopy Patterns in Mesangial Proliferative Glomerulonephritis

TABLE 29.1

Fig. 29.1 Pure Mesangial Proliferative Glomerulonephritis. There is segmental increase in mesangial cellularity (arrows) with single contoured capillary walls and no sclerosis or epithelial cell hypertrophy.

subepithelial (hump-like) deposits on EM. Urinary protein biomarkers may help determine prognosis.7

The prognosis of non-IgA MesPGN depends on the IF findings (see later discussion of IgM and C1q nephropathy) but is often benign. The 30-year kidney survival has been estimated to be 50%.2 Severe and persistent nephrotic syndrome indicates a poor prognosis, particularly in males.2 Patients with nephrotic syndrome may evolve to typical focal and segmental glomerulosclerosis (FSGS) over time.

The treatment of pure MesPGN, unaccompanied by other underlying diseases or lesions, such as SLE, minimal change disease (MCD) lesion, or IgA nephropathy, is not well defined.1 2 The prognosis for patients with isolated hematuria or hematuria combined with mild proteinuria (<500 mg/day) is generally benign, and only supportive measures are needed (see Chapter 82) unless a distinct change in the course is observed. Repeat kidney biopsy may be indicated in such circumstances. For patients with nephrotic syndrome (with or without impaired kidney function), a more aggressive approach is recommended in addition to supportive therapy, especially in the presence of diffuse IgM deposits (IgM nephropathy), as discussed later. Even in the absence of randomized controlled trials (RCTs), an initial course of corticosteroid therapy is justified in most patients with nephroticrange proteinuria, such as prednisone 60 mg/day or 120 mg every other day for 2 to 3 months, followed by lower doses on an alternateday regimen for 2 to 3 additional months. About 30% to 50% of these patients experience a decrease in proteinuria to subnephrotic levels, and complete remissions may occur. Relapses of proteinuria are common when steroids are tapered or discontinued. Such relapsing, partially corticosteroid-responsive patients may benefit from the addition of cyclophosphamide, calcineurin inhibitor agents (cyclosporine, tacrolimus, voclosporin), mycophenolate, or rituximab, although information on the efficacy and safety of these agents in pure MesPGN is limited.

Persistent treatment-unresponsive nephrotic syndrome almost invariably progresses to end-stage kidney disease (ESKD), accompanied by a conversion to FSGS over several years. Although transplantation is not contraindicated, patients who rapidly progress to ESKD with superimposed FSGS have a high risk for recurrence of proteinuria and FSGS in the transplanted kidney (see Chapters 19 and 113).

Pattern	Associated Disorders
Predominantly mesangial IgA deposits (± IgM, C3)	IgA nephropathy
Predominantly mesangial IgG deposits (± IgM, C1q, C3)	

Often associated with lupus nephritis

Predominantly mesangial IgM
deposits (± C3)

IgM nephropathy

Mesangial C1q deposits (±
IgG, IgM, C3)

C1q nephropathy
If IgG present, need to exclude lupus
nephritis

Isolated mesangial C3
deposits

Often associated with resolving
poststreptococcal GN or C3 GN

Negative for immunoglobulin
or complement deposits

Idiopathic MesPGN

Ig, Immunoglobulin; GN, glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis.

Immunoglobulin M Nephropathy

IgM nephropathy is characterized by diffuse and generalized glomerular deposits of IgM often accompanied by C3[3,8] with mesangial electron-dense deposits. On LM, pure MesPGN is usually observed, sometimes with superimposed FSGS[8] or crescentic disease. A proposed consensus definition of IgM nephropathy includes (1) dominant mesangial staining for IgM by IF, (2) mesangial electron-dense deposits by EM, and (3) absence of any identifiable systemic disease.[9]

Patients with only IgM deposits by IF but MCD by LM and EM do not have IgM nephropathy, according to this definition. IgM deposits in steroid-sensitive MCD or FSGS do not have any clinical significance.[10]

Patients may present with recurring macrohematuria and proteinuria, the latter in the nephrotic range in up to 40% to 50% of patients.[8] Middle-aged adults are most commonly affected, with a slight male predominance.[8]

Glomerulosclerosis (but not the extent of mesangial proliferation), persisting nephrotic syndrome, and a poor response to corticosteroids or immunosuppressive therapy connote a poor prognosis. As many as 80% of patients with IgM nephropathy and nephrotic syndrome will eventually progress to typical FSGS lesions and, if unresponsive to corticosteroids, will slowly develop progressive chronic kidney disease (CKD). Thus, IgM nephropathy may be an early form of primary FSGS. Patients with IgM deposition accompanying MesPGN but without nephrotic syndrome tend to have a benign course. IgM nephropathy can coexist with IgA nephropathy, diabetic nephropathy, and Fabry disease.[11–13]

Treatment of IgM nephropathy with nephrotic syndrome is uncertain, although steroid therapy may be associated with a complete or partial remission in as many as 50% of patients. Anecdotal reports of success with rituximab also have appeared. The etiology and pathogenesis are unknown, but IgM deposition itself is believed to be an important pathogenic factor acting to augment complement-mediated injury.

C1q Nephropathy

C1q nephropathy is characterized by IF showing diffuse dominant or codominant mesangial C1q deposition, often accompanied by IgG, IgM, or both,4 9 and, much less frequently, by C3 deposits. These immunopathologic features resemble those seen in LN; however, these

BOX 29.1

Rheumatic Diseases Associated With Glomerular Lesions

BOX 29.2

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Glomerular Lesions That May Be Direct Complications of the Disease

- MN
- MesPGN (± IgA or IgM deposits)
- Diffuse proliferative GN
- Necrotizing and crescentic GN (rheumatoid vasculitis)
- Amyloidosis (AA type)

Systemic lupus erythematosus (see Chapter 27)
Rheumatoid arthritis
Mixed connective tissue disease
Rheumatic fever
Ankylosing spondylitis
Reiter syndrome
Dermatomyositis/polymyositis
Scleroderma
Relapsing polychondritis
Psoriasis/psoriatic arthritis
Systemic or renal-limited polyangiitis (see Chapter 26)

patients lack the clinical features of SLE and usually do not develop SLE even after prolonged follow-up. Anti-C1q vasculitis (also known as hypo-complementemic urticarial vasculitis or McDuffie syndrome) can resemble C1q nephropathy, although urticarial lesions and systemic symptoms are more common in anti-C1q vasculitis with low levels of serum C1q and elevated anti-C1q autoantibodies.

LM findings of C1q nephropathy are heterogeneous, including MesPGN (the mesangial proliferative variant), MCD, and FSGS.[9,14] Electron-dense deposits are seen in mesangial regions often initially near the arteriolar pole and less frequently in subepithelial and subendothelial areas. Nephrotic-range proteinuria occurs, often with hematuria. Males predominate and African Americans are often affected.

Serum C3 components, ANA, and anti–double-stranded DNA (antidsDNA) antibodies are normal or negative. The response to treatment is poor, and progression to ESKD may occur, particularly when nephrotic syndrome is present, when FSGS lesions predominate, and when the biopsy displays significant tubular atrophy and interstitial fibrosis.[9,15] Anecdotal reports of success with immunosuppressive agents, including rituximab, have appeared. Patients with C1q deposits and MCD appear to respond well to conventional steroid therapy.

Mesangial Proliferative Glomerulonephritis Associated With Minimal Change Disease

MesPGN may be a part of the spectrum of MCD-FSGS lesions (see Chapters 18–20). Distinct mesangial hypercellularity superimposed on MCD (diffuse foot process effacement seen on EM) suggests a greater likelihood for the presence of hematuria, corticosteroid unresponsiveness, and an eventual evolution to FSGS.

GLOMERULONEPHRITIS WITH RHEUMATIC, COLLAGEN-VASCULAR, OR CONNECTIVE TISSUE DISEASE

Several collagen vascular diseases other than SLE may be complicated by GN[16] (Box 29.1), including rheumatoid arthritis (RA), mixed connective tissue disease, polymyositis and dermatomyositis, acute rheumatic fever, scleroderma, relapsing polychondritis, and psoriatic arthritis. IgA nephropathy also may be seen in association with the seronegative spondyloarthropathies. Toxic or hypersensitivity reactions to nonsteroidal antiinflammatory drugs (NSAIDs) can contribute to glomerular disease.[17]

Rheumatoid Arthritis

A wide variety of glomerular, tubulointerstitial, and renovascular lesions may complicate RA (Box 29.2).[16] Clinical abnormalities, including hematuria, leukocyturia, proteinuria, and reduced kidney function are common in patients with severe or longstanding RA. Membranous nephropathy (MN; see Chapter 21) is the most common glomerular lesion. Possibly because of the underlying disease, the presence of human leukocyte antigen (HLA)-DR3 increases the risk for MN in a patient with RA, which is not associated with anti–phospholipase A2 receptor (anti-PLA2R) autoantibodies. RA-associated MN has a course similar to that of idiopathic disease, although spontaneous remissions are less likely to occur. Secondary (AA) amyloidosis (see Chapter 28) is found in up to 30% of patients with RA, of which 56% have proteinuria. Half of these have nephrotic syndrome, which commonly progresses to kidney failure.[18]

Arthritis

Kidney Disease in Rheumatoid

Glomerular Lesions Associated With Agents Used to Treat Rheumatoid Arthritis

- Gold: MN, MCD, acute tubular necrosis
- Penicillamine: MN, crescentic GN, MCD
- NSAIDs: acute TIN with MCD, acute tubular necrosis, MCD without TIN
- Cyclosporine: chronic vasculopathy and TIN, focal and segmental glomerulosclerosis
- Azathioprine/6-mercaptopurine: TIN
- Pamidronate: collapsing glomerulopathy
- TNF-α inhibitors: lupus-like lesions, crescentic GN

GN, Glomerulonephritis; MCD, minimal change disease; MesPGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; NSAIDs, nonsteroidal antiinflammatory drugs; TIN, tubulointerstitial nephritis; TNF, tumor necrosis factor.

NSAIDs may produce tubulointerstitial nephritis alone, or with MCD or MN (more commonly the former; see Chapters 18 and 64).

A severe, necrotizing polyangiitis may complicate the course of longstanding RA (rheumatoid vasculitis). These patients may have profoundly reduced C3 levels, striking elevation of rheumatoid factors, and marked polyclonal hypergammaglobulinemia. Kidney involvement in rheumatoid vasculitis is now relatively uncommon. Tumor necrosis factor (TNF)-α inhibitors used to treat RA can evoke a picture resembling LN (see Chapter 27).

Mixed Connective Tissue Disease

Mixed connective tissue disease is characterized by overlapping features of SLE, scleroderma, and polymyositis. Typically, the serum of such patients contains high-titer autoantibodies to extractable nuclear antigens (ribonucleoprotein-extractable nuclear antigen, U1 ribonucleoprotein antigen) and may have low titers of anti-dsDNA antibody. Kidney disease, originally thought to be quite rare, is found in 10% to 50% of patients, most frequently MN and MesPGN. Steroid treatment is generally effective, but some patients exhibit progressive CKD. Patients with severe GN may respond to treatment regimens similar to those used for LN (see Chapter 27).

Polymyositis and Dermatomyositis

The related collagen vascular diseases polymyositis and dermatomyositis are characterized by inflammatory lesions in muscle with variable skin lesions and often include Raynaud phenomenon. Patients may have proteinuria and hematuria secondary to MesPGN with IgM deposits. Acute kidney injury (AKI) may rarely supervene when severe muscle injury and myoglobinuria are present. Treatment with steroids may ameliorate the kidney manifestations and improve the muscle and skin manifestations.

Acute Rheumatic Fever

Acute rheumatic fever secondary to a pharyngeal infection with a rheumatogenic strain of group A β-hemolytic streptococci is seldom accompanied by kidney disease (see Chapter 57). Cutaneous streptococcal infections are never associated with acute rheumatic fever sequelae. Poststreptococcal GN and acute rheumatic fever almost never coexist because of distinct differences between nephritogenic and rheumatogenic strains of streptococci. Nevertheless, MesPGN is rarely associated with acute rheumatic fever. MesPGN usually manifests with hematuria and scant proteinuria and often resolves with appropriate treatment of acute rheumatic fever.

Ankylosing Spondylitis and Reiter Syndrome (Seronegative Spondyloarthropathies)

The seronegative spondyloarthropathies and oligoarticular arthropathies may be associated with mesangial IgA deposition or MesPGN. Clinical manifestations are usually mild and nonprogressive. AA amyloidosis may complicate longstanding ankylosing spondylitis.

Scleroderma (Systemic Sclerosis)

Scleroderma is a heterogeneous disorder of unknown etiology characterized by uncontrolled expansion of connective tissue in the skin and other visceral organs,[19] as well as vascular thickening and narrowing. Clinical manifestations vary from increased connective tissue in localized patches of skin (morphea) to diffuse and generalized disease (systemic sclerosis). The latter leads to skin thickening of the face and hands, telangiectasia, Raynaud phenomenon, tendon friction rubs, and sclerodactyly. Nail beds display a characteristic pattern of blood vessel abnormalities. Visceral involvement causes interstitial pulmonary fibrosis, loss of esophageal and other gastrointestinal motility, restrictive cardiomyopathy, and kidney disease. Limited forms of the disease (CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) occur but are seldom associated with kidney disease. The disorder is more frequent in females, with an onset usually in young adults. Approximately 90% of patients will have a speckled pattern of fluorescent ANA, and 30% will have detectable antibody to topoisomerase I (Scl-70). Anticentromere antibody is strongly associated with the CREST syndrome. Anti–RNA polymerase III, antitopoisomerase, and anticentromere antibodies are associated with more systemic and kidney involvement and a poor prognosis. Rarely, the visceral abnormalities occur without cutaneous lesions (systemic sclerosis sine scleroderma).

Kidney involvement in scleroderma ranges from low-grade proteinuria and slight impairment of glomerular filtration rate to a more marked reduction in renal blood flow leading to a greatly elevated filtration fraction secondary to mild MesPGN to severe AKI.[20,21] The last is referred to as scleroderma renal crisis (SRC), affecting 5% to 10% of patients with scleroderma and consisting of severe (hyperreninemic) hypertension, encephalopathy, systolic and diastolic congestive heart failure, and AKI. Posterior reversible encephalopathy has been reported. Rare cases of SRC may occur without cutaneous features and even with relatively normal blood pressure. These patients are often positive for anti-RNA polymerase III antibody, and complement activation can be observed.22 There is often accompanying

Fig. 29.2 Scleroderma. An interlobular artery shows pronounced mucoid edematous subendothelial thickening with myofibroblasts on Masson trichrome stain (arrows), with endothelial cell swelling and luminal narrowing. The process is limited to the intima with preservation of the internal elastic lamina. Note the ischemic glomerulus (arrowhead) with severely wrinkled and retracted capillary walls.

microangiopathic hemolytic anemia with schistocytes and elevated serum lactate dehydrogenase. AKI results from primary involvement of the arcuate and interlobular arteries (Fig. 29.2). It may be superimposed on lesions of hypertensive emergencies (e.g., fibrinoid necrosis of the afferent arterioles) and ischemic glomerular changes (e.g., wrinkling of the capillary wall and thickening of the basal lamina).

The prognosis of patients with SRC has improved remarkably with the use of angiotensin-converting enzyme (ACE) inhibitors.20 21 In one study, ACE inhibitor treatment was associated with better patient survival at 1 year (75% vs. 15%) and with significant preservation or recovery of kidney function.22 Captopril is the preferred therapeutic agent; there is wide experience with it in SRC and its short half-life facilitates rapid dosing uptitration.22 Various biologic agents, including transforming growth factor (TGF)-β inhibitors, anti-CD20 (rituximab), interleukin 6 (IL-6) monoclonal antibodies, eculizumab, and tyrosine kinase inhibitors are undergoing evaluation as therapies for scleroderma or SRC.23

In an observational analysis of patients with scleroderma in 19 European kidney registries, the annual incidence of ESKD was 0.11 to 0.26 per 1 million population and the adjusted prevalence was 0.73 to 0.95. Recovery of kidney function occurred in 7.6% (compared with 0.6% for diabetes and 2.1% for nondiabetic kidney diseases). Recovery time may be prolonged. ACE inhibitor treatment should continue during dialysis therapy. Posttransplant 5-year patient survival is 88.2% and allograft survival is 72.4%, but disease in other visceral organs may limit life expectancy.24

Relapsing Polychondritis

Relapsing polychondritis is a chronic, often repetitive, episodic or continuous disorder characterized by destructive inflammation of cartilage (ear, nose, trachea, costal cartilage). Reports have associated it rarely with crescentic GN, MesPGN, MN, or tubulointerstitial IgG4 related disease.25 In one international study of relapsing polychondritis, kidney injury was uncommon and the authors suggested that kidney involvement should raise the possibility of an alternative primary disorder.26

Cartilage lesions may cause deformities (saddle nose, floppy ears, tracheal collapse or stenosis, cardiac valvular disease). When kidney disease occurs, it may be severe and progressive, particularly with crescentic disease. Although corticosteroids may be adequate to treat the nonrenal manifestations, patients with refractory relapsing polychondritis may require additional agents such as azathioprine, methotrexate, cyclophosphamide, infliximab, tocilizumab, abatacept, or occasionally rituximab. For progressive kidney disease, cytotoxic agents (e.g., cyclophosphamide) may be indicated, particularly for crescentic GN.

Psoriasis/Psoriatic Arthritis

Psoriasis is an autoimmune inflammatory disease with a strong familial component, with excessive and rapid growth of the skin epidermal layer. Up to 30% of affected patients also develop psoriatic arthritis. Psoriasis (especially if severe or associated with arthritis) is associated with IgA nephropathy, MN, MesPGN, and, very rarely, with membranoproliferative glomerulonephritis (MPGN) pattern of injury on histology.27–29 Treatment for psoriasis with glomerular disease may include steroids, methotrexate, calcineurin inhibitors, and TNF-α antagonists, the latter having some success in patients with psoriasisassociated IgA nephropathy.

Fig. 29.3 Podocyte Infolding Disease. Electron microscopy shows a thickened glomerular capillary basement membrane (GBM) containing microspheres and microtubular structures. These likely represent entrapped podocyte cytoplasm and, in areas, podocyte cytoplasm is extending into the GBM (arrows).

Non-Lupus “Full House” Glomerulonephritis

Patients can present with findings indicative of an immune-complex mediated glomerulonephritis resembling LN, with deposition of C1q, C3, IgG, IgA, IgM by IF (“full-house”), and a typical MPGN or MN pattern of injury, without the typical clinical and serologic features required for diagnosis of SLE.30 The pathogenesis of this uncommon disorder is unknown, but it may follow certain infections such as COVID-19, parvovirus, HIV, or syphilis.31 32 A subset of such patients may evolve to typical SLE over many years. The prognosis seems to be poor,30 and treatment is not well understood, but management similar to that used for LN is often recommended.

Podocyte Infolding Glomerulopathy

This clinicopathologic entity was first recognized in Japan in 2006.33 It is commonly associated with autoimmune phenomena and connective tissue disease, such as LN or Sjögren syndrome.34–36 Proteinuria, including nephrotic syndrome, is universal. The lesion is characterized on EM by microspheres and microtubular structures (likely representing remnants of infolded podocyte cytoplasm) incorporated into thickened GBMs (Fig. 29.3) and can resemble MN or FSGS by LM. There may be concomitant immunoglobulin deposition and subepithelial electron dense deposits in some, but not all, cases.34 The natural history and treatment are largely unknown, but partial remissions of proteinuria can occur.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The antiphospholipid antibody syndrome (aPLA syndrome) is characterized by venous and arterial thrombosis and circulating autoantibodies to phospholipid-protein complexes, including those of the coagulation cascade.37 38 The syndrome was first recognized by Hughes in 198337 and has protean manifestations ranging from migraine headaches to multiple thrombosis and multiorgan failure (catastrophic aPLA syndrome [CAPS]).37 38 The frequency of thrombotic episodes is about 7.5 per 100 patient years for 5 years after the first thrombotic event and often can be the presenting feature.39 Neurologic symptoms and signs are common, including transient cerebral ischemic attacks (TIAs), strokes, migraine headaches, seizures, myelitis, and balance and sensory disturbances (often resembling multiple sclerosis).37 38

Fig. 29.4 Livedo Reticularis in Patient with Antiphospholipid Antibody Syndrome. Note reticulated skin changes (inset, higher magnification) on the patient’s back, in addition to hematomas related to her warfarin therapy. (Courtesy J. Floege, Aachen, Germany.)

Cardiovascular problems, such as pulmonary hypertension, premature atheromatous disease, renal artery stenosis, and myocardial infarction, are common.37 38 Livedo reticularis is an important diagnostic clue (Fig. 29.4). Adrenal infarction or hepatic venous thrombosis may lead to acute adrenal insufficiency or Budd-Chiari syndrome, respectively. Visual loss, visual field defects, anosmia, aseptic bone necrosis, fracture, spinal claudication, and autonomic dystrophy are less frequent complications. Pulmonary hemorrhage or fibrosing alveolitis can be a presenting feature.40 Repeated pregnancy loss is common.

The kidneys are frequently involved with a thrombotic microangiopathy (TMA; see Chapter 30).41 CAPS is a rare but often fatal form of aPLA syndrome frequently associated with SLE or infections. It involves many organ systems, including the brain, kidneys, heart, and lungs.42

aPLA syndrome may occur without known systemic disease or may accompany SLE (see Chapter 27) or infection with SARS-CoV-2 (see Chapter 59). In the latter, antibodies are directed at different

A

B

Fig. 29.5 Antiphospholipid Syndrome. (A) Thrombosis of the peri- and intraglomerular arteriole and segmental glomerular capillaries (arrows) with associated mesangiolysis characterized by mesangial matrix dissolution (arrowhead). The adjacent glomerular capillaries show ischemic wrinkling and retraction. (B) Arteriole with luminal fibrin-platelet thrombus and endothelial cell loss. Note the muscular wall is intact and without inflammation.

β2-glycoprotein 1 epitopes than in SLE or the primary syndrome, and titers correlated poorly with clinically significant thrombotic events.43

The presence of aPLA syndrome in SLE confers a much worse prognosis and greater risk for neuropsychiatric and cardiovascular complications. aPLA syndrome (primary or SLE related) should always be suspected with a history of migraine headache, TIA or stroke, multiple pregnancy loss, arterial or venous thrombosis, or a family history of autoimmune disease. Diagnosis of aPLA syndrome requires at least one clinical criterion plus one laboratory criterion.44 Clinical criteria are (1) thrombosis (arterial or venous) or (2) spontaneous abortions or stillbirths. Laboratory criteria (two or more occasions at least 6–12 weeks apart)44 are (1) lupus anticoagulant, (2) anticardiolipin antibody, or (3) anti–β2 glycoprotein 1 antibody. The pathogenic antibodies in aPLA syndrome appear to be primarily directed against the domain I of β2-glycoprotein 1.45 Antibodies to prothrombin, thrombin, or phosphatidylserine may predict severe thrombophilia and/or pregnancy loss.

The pathogenesis of aPLA is probably multifactorial.46 The thrombotic state seems to involve generation of reactive oxygen species leading to alterations in β2-glycoprotein 1 function, impaired function of endothelial nitric oxide synthase, activation of prothrombotic receptors by autoantibodies, increased expression/activation of tissue factor, increased modified forms of prothrombotic factor XI, disruption of annexin A5 shield, and antibody-mediated activation of C3 and/or C5.46 There is prominent involvement of the mammalian target of rapamycin complex (mTOR) in aPLA syndrome.47 Transplanted patients with aPLA syndrome who receive the mTOR inhibitor sirolimus for prevention of allograft rejection have a lower risk for recurrence of vascular lesions. Complement and toll-like receptor (TLR) activation have also been reported.

Laboratory testing usually reveals an autoantibody to phospholipids (anticardiolipin, anti–β2-glycoprotein 1, or prothrombin), but “antibody-negative” aPLA syndrome has been described.42 45 Falsepositive test results for syphilis and a lupus anticoagulant are common.

A prolonged prothrombin or partial thromboplastin time that does not correct when plasma is diluted 1:1 with normal plasma is found in such circumstances. Antiphospholipid antibodies may cross-react with platelet factor 4–heparin complex and thus may generate a false positive antibody test in heparin-induced thrombocytopenia. Mild thrombocytopenia is common (platelet counts about 100,000/mm3 but usually not less than 80,000/mm3). Thrombocytopenia may be an in vitro phenomenon related to the effect of the aPLA antibody on platelet membrane biology. Lymphocytopenia is common in patients with SLE and aPLA syndrome. A mild hemolytic anemia (Coombs negative or positive) may coexist, giving rise to confusion with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and Evans syndrome. A frank microangiopathic hemolytic anemia is relatively uncommon. Patients with aPLA syndrome and reduced ADAMTS13 activity may be at higher risk for thrombotic events.48 Anti-C1q autoantibodies are found frequently in primary aPLA syndrome and might contribute to abnormal complement activation, particularly in severe refractory cases.

Kidney manifestations of aPLA syndrome are broad and may include renal artery/vein thrombosis, hypertension, small vessel microangiopathy, including glomerular capillaries, and allograft thrombosis (Fig. 29.5). In primary aPLA syndrome, overt kidney manifestations are generally mild and are frequently absent. Nephrotic syndrome is relatively rare. In aPLA syndrome associated with SLE, the kidney manifestations are determined largely by the underlying glomerular disease severity, but the coexistence of aPLA syndrome contributes to a worse prognosis and extrarenal manifestations (neurologic, cardiovascular, osseous, ophthalmologic, pulmonary, hepatic, visceral, and obstetric; see Chapter 27). A strong association of aPLA with alveolar hemorrhage exists in SLE.40

The therapy for primary aPLA syndrome and that accompanying SLE is controversial. Immunosuppressive agents, such as steroids or cytotoxic agents, even when they are used to control SLE, have yielded disappointing results. Symptomatic patients are best treated with anticoagulation. Aspirin (or clopidogrel) can be used in mild cases. Combinations of aspirin and low-dose warfarin might be effective, but the risk for bleeding is increased. Vitamin K antagonism is the mainstay of treatment in severe cases, with the international normalized ratio (INR) adjusted to a level depending on symptoms; INR between 2.0 and 3.5 may be required. Low-molecular-weight heparin (subcutaneous or intravenous [IV]) is the treatment of choice for pregnancy complicated by aPLA syndrome and is also useful in alleviating migraine headache. Aspirin therapy in pregnancy with an aPLA-like syndrome does not appear to be effective. Long-term use of hydroxychloroquine can be beneficial in patients with primary aPLA syndrome without evidence of SLE.49 A meta-analysis showed similar venous thrombosis rates in patients treated with direct-acting oral anticoagulants (DOAC) and warfarin but a higher rate of arterial thrombosis with DOAC treatment.50

Sirolimus has been suggested for treatment of aPLA syndrome,47 but it may increase the risk for thrombosis in susceptible individuals. High-dose IV IgG (IVIG) can have dramatic beneficial effects, especially in acutely evolving disease associated with SLE. Combinations of plasma exchange and IVIG seem to be beneficial in high-risk pregnancy with aPLA syndrome,51 and plasma exchange alone can be helpful in CAPS.52 Given reported TLR activation, plaquenil, which inhibits TLR-7, has been tried and reportedly reduced aPLA in patients with SLE. None of these novel strategies have been tested in controlled trials.

The benefits of immunomodulating agents such as rituximab have not been adequately evaluated in aPLA syndrome, but preliminary reports are encouraging when used alone or with plasma exchange. In severe, life-threatening disease, combinations of rituximab and plasma exchange should be seriously considered. Intensive plasma exchange (plus immunosuppression) has been used in other circumstances, such as in aPLA syndrome associated with SLE, with variable degrees of success. Monoclonal antibodies to C5 (eculizumab) or to CD20 (rituximab) also have been used to treat CAPS with some success.53,54

Other novel therapeutic approaches to the aPLA syndrome, such as coenzyme Q10, statins, N-acetylcysteine, phosphodiesterase inhibitors, and factor XI inhibitors have not been thoroughly tested for safety and efficacy.

OTHER UNCOMMON GLOMERULAR DISORDERS

Fibrillary Glomerulonephritis (DNAJB9 Deposition Disease)

Fibrillary glomerulonephritis (FGN) is encountered in about 0.5% to 1% of native kidney biopsies, most commonly in older adults, usually in the sixth decade of life, with females affected more than males.55 Proteinuria (including nephrotic syndrome), hypertension, hematuria, and reduced GFR are typically found at presentation. Autoimmune phenomenon, including RA, Sjögren syndrome, lupus-like disorders, and serologic abnormalities (+ANA, ANCA) are seen in 10% to 30% of cases, but hypocomplementemia is rare. Hematologic or nonhematologic malignancies occur in about 8% of cases and may be coincidental. Concomitant hepatitis C virus (HCV) infection is present in about 15% of cases and a small minority (<10%) may have a paraprotein disorder55 (see Chapters 22 and 28). Familial forms have been described.

On LM, an MPGN or MesPGN pattern is often seen with superimposed crescents in about 25% of cases.55,56 IF shows irregular or granular IgG deposition, which occasionally may be coarsely linear, resembling anti-GBM disease, or rarely absent by IF.57 The defining characteristic is glomerular fibrillary deposits seen by EM, usually predominantly in the subendothelial and mesangial areas

(Fig. 29.6). These fibrils are nonbranching, haphazardly arranged, 15nM in average diameter (range, 9–25nM), and typically Congo Red negative, although 5% may be Congo Red positive.55,56,58 The deposits contain codeposited IgG, usually polytypic, complement, and DNAJB9 (Dnaj homolog subfamily member 9).55,56 The finding of DNAJB9 deposition is pathognomonic and now required for a correct diagnosis of FGN, leading to a revised nosology for the disease as DNAJB9 deposition disease.55,56,59 Elevated serum levels of the DNAJB9 protein may be found; although the specificity of this finding is high (>95%), the low sensitivity (about 67%) precludes employment as a noninvasive screening or diagnostic test.60 Thus, the diagnosis of FGN rests on finding DNAJB9-containing glomerular deposits, and this may preclude the need for an EM search for fibrils. A comparison of monoclonal and nonmonoclonal forms of glomerular disease with fibrillary deposits is presented in Chapter 28 (see Table 28.1).

FGN tends to be progressive, and full remissions are rare. Progression to kidney failure within 2 to 5 years occurs in over 50% of cases, especially in males or those with superimposed crescentic disease and reduced GFR at presentation. Very rarely, anti-GBM disease may coexist with FGN, but such cases have not been proven to be DNAJB9 positive.61 Therapy is uncertain, but rituximab is associated with stabilization of GFR,55,62 even though proteinuria is unaffected. If HCV infection is present, antiviral therapy likely is indicated (see Chapter 57). FGN uncommonly recurs in kidney transplants, usually with late onset and an indolent course.63

Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy (LPG) is a kidney lipidosis associated with apolipoprotein gene mutations in an autosomal dominant pattern with incomplete penetrance.64,65 LPG may be caused by an abnormality in lipoprotein metabolism and/or a lipoprotein secondary structure conformational change related to molecular thermodynamic instability. Most patients harbor mutations of apolipoprotein E (ApoE), usually a heterozygous E2/E3 or E2/E4 phenotype, but homozygosity for ApoE2 or ApoE3 also has been observed. ApoE3 mutations usually are associated with type III hyperlipoproteinemia.66 APOE-Sendai and APOE-Kyoto are the most frequent variants and frequently are in or around the lowdensity lipoprotein (LDL) receptor binding region. The disease may be associated with psoriasis and hypertensive emergencies accompanied by TMA. Otherwise, there are no distinctive clinical features. Clinically, there usually is heavy proteinuria with nephrotic syndrome and microhematuria may be present.

Histologically LPG is characterized by intracapillary accumulation of apolipoproteins A, B, and E in the glomeruli (mostly ApoE), leading to greatly expanded lumens filled with PAS-negative, bubbly to foamy lipoprotein pseudothrombi, which may be vaguely lamellated and stain positively with oil red O (Fig. 29.7). Foam cells are not a typical feature, and when present more often indicate crystal-storing histiocytosis, macrophage activation syndrome, ApoE2 glomerulopathy, or lecithin–cholesterol acyltransferase deficiency (see later discussion).67 IF stains for ApoE are strongly positive, but immunoglobulins and complement are absent.64,68 EM reveals lipid accumulation in capillary lumens and there may be subendothelial, mesangial, and, rarely, subepithelial lipid deposition.

Treatment with bezafibrate or fenofibrate may be effective and is the initial treatment of choice.69 About three-quarters of patients with nephrotic syndrome treated with fibrates will achieve a complete or partial remission. Treatment with heparin-induced extracorporeal lipoprotein precipitation-apheresis systems also can confer a complete remission in some patients.70

A

B

C

Fig. 29.6 Fibrillary Glomerulonephritis (DNAJB9 Glomerulonephritis). (A) Glomerulus with mesangial expansion because of silver weakly positive to negative material (arrows) and rare capillary wall double contours (arrowhead). (B) Mesangial staining for DNAJB9 by immunohistochemistry. (C) Electron microscopy shows haphazardly arranged fibrils measuring 13 to 19 nm in the mesangial matrix.

Lecithin–Cholesterol Acyltransferase Deficiency

Lecithin cholesterol acyltransferase (LCAT) is a key enzyme in cholesterol metabolism. It catalyzes the esterification of free cholesterol on the surface of lipoproteins, which is necessary for cholesterol transport. LCAT deficiency is an autosomal recessive disorder associated with two clinical syndromes. Both present with very low plasma high-density lipoprotein (HDL) cholesterol levels but variable and often low frequency of cardiovascular disease in carriers[71,72] (see Chapter 20). More than 70 LCAT mutations have been reported causing total LCAT deficiency. This is termed familial LCAT deficiency (FLD), clinically manifesting with corneal opacities (misty deposits, known as “fish eye”), splenomegaly, normocytic normochromic anemia (with target cells), low HDL cholesterol, ApoA-I and ApoA-II levels, and elevated triglyceride levels. It is likely that glomerular accumulation of oxidized phospholipids and entrapment of an abnormal cholesterol-rich multilamellar particle called lipoprotein-X are pathogenic.[73] At least 18 LCAT mutations have been reported to cause the second type of LCAT deficiency called “fisheye disease” (FED) in which LCAT activity is markedly reduced but not absent. FED patients have reduced plasma HDL and corneal opacities but lack anemia, splenomegaly, or kidney disease.

In FLD, kidney disease is characterized by proteinuria, including nephrotic syndrome, and hypertension. On LM, glomeruli have irregularly thickened, bubbly appearing GBMs, which may have double contours. Mesangial regions are expanded and may have a foamy

A

B

Fig. 29.7 Lipoprotein Glomerulopathy. (A) Dilated capillary lumens contain aggregates of pale, trichromestained, mesh-like to granular material. (B) The intraluminal material stains positively with oil red O, confirming its lipid composition.

A

B

Fig. 29.8 Lecithin–Cholesterol Acyltransferase (LCAT) Deficiency. (A) Irregular, thickened and double contoured glomerular capillary walls containing clear vacuoles, which are characteristic of LCAT deficiency.
(B) Electron microscopy reveals electron dense lipid material in electron lucent lacunae (arrows) within the glomerular basement membranes.

appearance with mild hypercellularity. There may be nonspecific granular glomerular staining for C3. Ultrastructurally, the mesangial matrix and GBMs contain electron-dense lipid particles in electron lucent lacunae (Fig. 29.8). Most patients have slow, insidious progressive kidney failure, which is usually detected in the fourth decade of life. In a report of 18 patients followed for a mean of 12 years, 50% of patients developed ESKD by age 46 years.72

Supportive treatment is indicated for proteinuria and hypertension but does not prevent progression. In an LCAT deficiency mouse model,

the HDL cholesterol mimetic CER-001 eliminated circulating and kidney LpX, reducing albuminuria. A clinical trial of this agent is registered for treatment of familial hyperlipidemia and atherosclerotic disease (https://clinicaltrials.gov/ct2/show/NCT02697136). Recombinant human LCAT infusions were safe in a phase I clinical trial targeting patients with stable cardiovascular disease (ClinicalTrials.gov NCT01554800). In one patient with LCAT deficiency, it improved anemia and plasma HDL levels and possibly stabilized kidney function.74 The disease can recur in kidney transplants, and sequential kidney-liver transplantation might be curative.75

A

B

Fig. 29.9 Collagen III (Collagenofibrotic) Glomerulopathy. (A) Mesangial (arrows) and subendothelial (arrowheads) expansion due to silver negative material without hypercellularity. (B) Subendothelial fibrils are randomly oriented with an average 30 nm in diameter and are highlighted with phosphotungstic acid staining.

Collagen III Glomerulopathy

Collagen III glomerulopathy, also known as collagenofibrotic glomerulopathy, is an autosomal recessive systemic disorder with prominent kidney manifestations that may be a forme fruste of nail-patella syndrome (see Chapter 48), which has similar glomerular features.[76] However, patients with collagen III glomerulopathy lack the skeletal abnormalities associated with nail-patella syndrome. Although most cases appear to be sporadic, autosomal recessive disease has been reported in children, and LMX1B gene mutations are thought to be causative.[77] Patients present with proteinuria, hypertension, frequent microscopic hematuria, and slowly progressive kidney failure. The disease is more common in Asian populations, patients may be of any age, and there is no sex predilection. Marked elevation of serum hyaluronan concentration and N-terminal procollagen III propeptide may be found and, combined with rare autopsy reports of abnormal type III collagen fibrils seen in liver, spleen, myocardium, and thyroid by EM, suggests that this condition may be because of a systemic defect in type III collagen metabolism.[78]

Kidney biopsy is required for diagnosis. By LM, glomeruli are enlarged with weakly PAS positive, silver negative, Congo red negative material in expanded mesangial regions and widened subendothelial areas (Fig. 29.9). IF is typically negative or has nonspecific weak staining for immune reactants, although there is strong staining with antisera to collagen type III. EM shows bundles of irregularly arranged, frayed, and curvilinear fibrils showing 60 nm periodicity characteristic of type III collagen,[79] highlighted with phosphotungstic acid staining.[80] There is no effective treatment, and there is one report of this disease occurring in a living related kidney transplant.

Fibronectin Glomerulopathy

Fibronectin glomerulopathy is a rare, autosomal dominant, glomerular disease usually presenting in early adolescence with proteinuria, microhematuria, hypertension, distal (type 4) renal tubular acidosis, and slowly progressive kidney failure, reaching ESKD between the second and sixth decades of life.[81] Mutations occur in the FN1 gene, which maps to chromosome 2q32.[82] Kidney pathology demonstrates enlarged, lobular, and normocellular glomeruli with PAS positive, Congo red negative material expanding mesangial and subendothelial areas (Fig. 29.10). IF is negative or shows low-grade immunoglobulin and complement glomerular staining but is strongly positively with antifibronectin antibody. EM shows usually large finely granular to occasionally fibrillary mesangial and subendothelial deposits with randomly oriented fibrils. The pathogenesis may involve mutations affecting fibronectin tertiary structure, folding, and molecular functionality.[83] The differential diagnosis includes other disorders associated with fibril deposition (see Chapter 28). There is no effective treatment and fibronectin glomerulopathy can recur in kidney allografts.

Nephropathic Cystinosis

Cystinosis is an autosomal recessive lysosomal storage disease with mutations in the cystinosin gene (CTNS). Patients with cystinosis often have blond hair, photophobia, hypothyroidism, retinal and corneal deposits, and rickets. They also may develop myopathy, dysphagia, diabetes mellitus, pancreatic exocrine deficiency, pulmonary dysfunction, male hypogonadism, pseudotumor cerebri, and cerebral and vascular calcifications. In the infantile form, Fanconi syndrome starts in the first year of life with tubular proteinuria or nephrogenic diabetes insipidus (see Chapter 50). Before the advent of cysteamine therapy, proteinuria developed within a few years and ESKD by 10 years of age. Adolescent cystinosis, a variant of pediatric cystinosis with symptom onset into the third decade of life, causes a milder phenotype, although nephrotic syndrome may occur.84 85 Treatment of children with cysteamine has resulted in initial presentations with kidney disease in adults as late as age 50 years or beyond. A separate adult form is ocular limited. Cystinosin deficiency results in accumulation of intralysosomal cysteine crystals with subsequent monocyte/macrophage activation. There is damage to glomerular epithelial cells, which

A

B

Fig. 29.10 Fibronectin Glomerulopathy. (A) Extensive expansion of mesangial and subendothelial regions due to infiltrating silver negative material with minimal hypercellularity. (B) Electron microscopy shows large subendothelial and adjacent mesangial finely granular deposits.

Fig. 29.11 Cystinosis. The glomerulus has segmental multinucleated podocytes (arrows).

become multinucleated, more often seen in the infantile form, with podocyte foot process effacement and progression to FSGS and global glomerulosclerosis[86,87,88] (Fig. 29.11). Cysteine crystals may be found in glomerular epithelial and endothelial cells, tubular epithelial cells, and infiltrating interstitial macrophages. The treatment is long-term cysteamine administration.[89]

Miscellaneous Storage Diseases Rarely Associated With Glomerular Lesions

Diseases associated with tissue storage of abnormal lipids or carbohydrates may rarely provoke glomerular lesions, usually in infants and children. Glomerular endothelial cell inclusions may be found in Niemann-Pick disease and neuronal ceroid lipofuscinosis, whereas mesangial cell inclusions occur with gangliosidosis. Diseases with podocyte vacuolization include Hurler syndrome (type I mucopolysaccharidoses), aspartylglucosaminuria, mannosidosis, Refsum disease, nephrosialidosis and I cell disease (mucolipidosis type II). Infiltrating macrophages containing inclusions may occur in Gaucher disease, and enzyme replacement therapy has been reported to induce complete remission from Gaucher-induced nephrotic syndrome.[90]

FSGS has been reported in those with von Gierke disease (glycogen storage disease). In storage diseases for which a recombinant enzyme treatment is available, controversy exists regarding the relative benefits of enzyme replacement, substrate reduction, and/or hematopoietic stem cell transplantation. The central nervous system (CNS) is not protected by enzyme replacement therapy because of blood-brain barrier impermeability.

Juvenile malabsorption of vitamin B12 with megaloblastic anemia (Imerslund-Grasbeck syndrome; cubulin deficiency) may cause prolonged glomerular proteinuria (albuminuria), but progressive kidney disease does not develop. Patients with cubulin mutations with proteinuria but without megaloblastic anemia have also been reported.

Asphyxiating thoracic dystrophy (Jeune syndrome) is associated with glomerular, tubular, and interstitial abnormalities. Hereditary osteolysis causing wrist and ankle arthralgias and deformities can be accompanied by chronic GN.

Idiopathic (Nondiabetic) Nodular Glomerulosclerosis

Nodular glomerulosclerosis, an intercapillary nodular mesangial expansion encroaching on glomerular capillary lumens, is most commonly associated with diabetes mellitus (Kimmelstiel Wilson lesion) and proliferative diabetic retinopathy (see Chapter 31). Similar LM lesions are reported in patients with impaired glucose tolerance not meeting criteria for diabetes mellitus or may persist after marked weight loss with remission of glycemic abnormalities, masking previous type 2 diabetes. Other diseases potentially associated with a nodular glomerulosclerosis pattern include monoclonal paraproteins (light chain and heavy chain, including Waldenström macroglobulinemia; see Chapter 28);

cystic fibrosis; hepatitis C; cigarette smoking; chronic cyanotic/ischemic syndromes; chronic thrombotic microangiopathy; proteinfolding diseases such as amyloidosis, FGN, and immunotactoid GN; collagenofibrotic glomerulopathy; and fibronectin glomerulopathy.

Idiopathic nodular glomerulosclerosis was first described in 1989. Its pathogenesis is unknown, and it is a diagnosis of exclusion. It may be related to smoking, obesity, longstanding hypertension, and intermittent TMA; the term smoking-related glomerulopathy has been suggested.91 92 Recent data suggest potential contributions from a mechanism that is common to diabetic and nondiabetic nodular glomerulosclerosis and involves epigenetic changes in the annexin gene, leading to collagen type VI secretion and deposition by glomerular endothelial cells.93

The clinical features are nonspecific and nondiagnostic. The average age of patients with idiopathic nodular glomerulosclerosis is approximately 70 years; most are male and presentation with nephrotic syndrome is common. LM shows nodular glomerulosclerosis identical to the diabetes-associated Kimmelstiel-Wilson lesions, often with neovascularization within the nodules. GBMs are thickened and there may be subendothelial lucencies with capillary double contour formation. There are varying degrees of arteriolonephrosclerosis and hyalinosis. No electron-dense or organized deposits are seen on EM. The GBMs and tubular basement membranes may have pseudolinear staining for IgG and albumin on IF, similar to diabetic kidney disease.

The prognosis is poor and relates to persistence of nephrotic-range proteinuria. Most patients with idiopathic nodular glomerulosclerosis will progress to ESKD, sometimes quite rapidly, with 50% kidney survival 1 year after diagnosis in those who continue to smoke heavily. There is no known therapy other than angiotensin inhibition to reduce the proteinuria and smoking cessation where relevant.

Macrophage Activation Syndrome/Histiocytic Glomerulopathy

Macrophage activation syndrome (MAS) and hematophagocytic lymphohistiocytosis (HLH) are uncommon disorders, both characterized by massive expansion and activation of T-lymphocytes and tissue macrophages with hematophagocytic capacity, leading to overproduction of cytokines and cytokine storm. The bone marrow shows expansion of histiocytes expressing CD163, with active hemophagocytosis. By convention, HLH is a primary disease associated with causative, usually autosomal recessive, mutations. MAS, also known as secondary HLH, presents similarly, but is often associated with an underlying triggering condition. MAS occurs in approximately 15% of patients with systemic juvenile idiopathic arthritis (SJIA) and less frequently in patients with SLE, other autoimmune disorders, neoplasms, and infections (especially EBV, CMV, and SARS CoV-2). Two separate but overlapping criteria for the diagnoses of HLH and MAS are published.94 95

Typically, patients present with pancytopenia, fever, rash, coagulopathy, liver function abnormalities, adenopathy, hepatosplenomegaly, erythrophagocytosis, and/or TMA. Excessive production of cytokines (TNF-α and IL-1, -4, -6, -8, -10), extreme hyperferritinemia, marked hypertriglyceridemia, and hypofibrinogenemia are common findings often leading to the correct diagnosis. The erythrocyte sedimentation rate may be low. A clinical diagnosis should be confirmed by bone marrow biopsy.

Kidney manifestations include AKI and nephrotic syndrome. Collapsing FSGS has been reported. Histiocytic glomerulopathy is more specific to MAS and HLH, characterized by extensive glomerular capillary infiltration with macrophages with or without erythrocyte phagocytosis or foam cells and often associated with endothelial cell swelling and features of TMA[96] (Fig. 29.12). There are no immune deposits by IF.

Fig. 29.12 Histiocytic Glomerulopathy. Capillary lumens and less often mesangial regions contain many monocyte/macrophages, which stain positively for CD68 and CD163 in immunohistologic examinations.

The mortality rate of MAS is high and treatment is difficult, initially consisting of removing the triggering agent (if possible). High-dose steroids, calcineurin inhibitors, IVIG, TNF-α and IL-6 antagonists, and IL-1 receptor antagonists (anakinra) are the most commonly used therapies. Rituximab, alemtuzumab, and plasma exchange have also been used with varying degrees of success.[97] In children with a genetic mutation causing primary HLH, bone-marrow transplantation may be lifesaving.[98]

DRESS Syndrome

DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is an uncommon manifestation of severe drug hypersensitivity characterized by extensive mucocutaneous rashes, fever, lymphadenopathy, hepatitis, eosinophilia, and atypical lymphocytosis with multisystem organ injury.[99] Reactions to aromatic anticonvulsants, such as phenytoin and carbamazepine, are a common cause but several medications, including antibiotics and allopurinol, have been implicated.

AKI and proteinuria can be seen, and kidney biopsy usually reveals acute tubulointerstitial nephritis containing numerous eosinophils. Untreated, DRESS syndrome can be fatal. For severe cases, parenteral and oral steroids are indicated.[100]

Kimura Disease

Kimura disease (angiolymphoid hyperplasia with eosinophilia [ALHE]) is a rare disorder characterized by nonmalignant masses in the head and neck, lymphadenopathy, marked eosinophilia, elevation of serum IgE, and immune thrombocytopenia, predominantly in patients of Asian ancestry.[101] Kidney involvement with nephrotic syndrome because of MN, FSGS (tip lesion variant), or MesPGN is common. Steroid therapy is successful in most cases, although relapse upon tapering is common. Use of concomitant steroid-sparing agents including Tripterygium wilfordii, leflunomide, tacrolimus, vincristine, and mycophenolate have been anecdotally reported.

SELF-ASSESSMENT QUESTIONS

1. A 42-year-old man is discovered to have proteinuria, impaired kidney function (serum creatinine 2.3 mg/dL), and normocytic normochromic anemia (hemoglobin 8.2 g/dL). The physical examination shows hypertension (150/98 mm Hg), mild obesity (body mass index 31 kg/m2), bilateral corneal opacities, and 1+ edema. The albumin is 3.2 g/dL, total cholesterol 120 mg/dL, low-density lipoprotein cholesterol 80 mg/dL, high-density lipoprotein cholesterol 15 mg/dL, and triglycerides 200 mg/dL. Serum C3 is normal. A fasting blood sugar is 120 mg/dL. Urinary total protein excretion is 4.6 g/day. Which of the following is the most likely diagnosis?
A. Alport syndrome
B. Adult-onset cystinosis
C. Lecithin–cholesterol acyltransferase deficiency
D. C3 glomerulopathy
E. Obesity-related glomerulopathy

2. Which of the following can be an effective treatment of lipoprotein glomerulopathy?
A. Cyclosporine
B. Bezafibrate
C. Atorvastatin
D. Corticosteroids
E. Plasma infusions

3. A 65-year-old woman is found to have nephrotic syndrome, and kidney biopsy shows membranous nephropathy. Serum C3 is normal, and ANA is 1:80. Anti-dsDNA is negative. Immunofluorescence staining of the biopsy reveals extensive deposits of IgG4 and weak deposits of IgG1 and IgG3. Serologic studies for hepatitis B are negative. Which of the following is the most likely diagnosis?
A. Membranous lupus nephritis
B. Membranous nephropathy secondary to cancer
C. Idiopathic (primary) membranous nephropathy
D. Membranous nephropathy secondary to hepatitis C infection

4. A 46-year-old woman complains of frequent “migraine” headaches. She is found to be anemic (hemoglobin 9.8 g/dL), and serum creatinine is elevated to 1.6 mg/dL. Her blood pressure is 156/94 mm Hg. Urinalysis reveals 2+ protein and a trace of blood. The serum C3 and C4 are normal, and ANA is negative. She takes an NSAID for headache. She has had three miscarriages and is presently amenorrheic. Her physical examination is otherwise unremarkable. There are no localizing neurologic findings. Which of the following tests would be most appropriate as a next step in the diagnostic evaluation of this patient?
A. Anti-dsDNA autoantibody
B. Magnetic resonance imaging of the brain
C. Serum iron and iron-binding capacity
D. Antiphospholipid antibody test
E. Serum protein electrophoresis

REFERENCES

1. Alexopoulos E, Papagianni A, Stangou M, Pantzaki A, Papadimitriou MJNDT. Adult-onset idiopathic nephrotic syndrome associated with pure diffuse mesangial hypercellularity. Nephrol Dial Transplant. 2000;15(7):981–987.
2. Axelsen M, Pedersen RS, Heaf JG, Ellingsen TJNe. Mesangioproliferative glomerulonephritis: a 30-year prognosis study. Nephron Extra. 2014;4(1):26–32.
3. Cohen AH, Border WA, Glasscock RJ. Nephrotic syndrome with glomerular mesangial IgM deposits. Lab Invest. 1978;38(5):610–619.
4. Jennette JC, Falk Ronald J. C1Q nephropathy. In: Massry S, Glassock R, eds. Textbook of Nephrology. Vol. 1. 3rd ed. Baltimore: Williams & Wilkins; 1995:749–752.
5. Verma B, Singh A. Histological spectrum of renal disease in HIV/AIDS patients with significant proteinuria: an Indian perspective. J Fam Med Prim Care. 2019;8(3):860.
6. Sethi S, Fervenza FC, Zhang Y, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney Int. 2012;82(4):465–473.
7. Li Y, Wang J, Zhu X, Feng Q, Li X, Feng XJBn. Urinary protein markers predict the severity of renal histological lesions in children with mesangial proliferative glomerulonephritis. BMC Nephrol. 2012;13(1):29.
8. Connor TM, Aiello V, Griffith M, et al. The natural history of immunoglobulin M nephropathy in adults. Nephrol Dial Transplant. 2017;32(5):823–829.
9. Devasahayam J, Erode-Singaravelu G, Bhat Z, et al. C1q nephropathy: the unique underrecognized pathological entity. Ann Cell Pathol (Amst). 2015;2015:490413.
10. Juozapaite S, Cerkauskiene R, Laurinavicius A, Jankauskiene A. The impact of IgM deposits on the outcome of Nephrotic syndrome in children. BMC Nephrol. 2017;18(1):260.
11. Heybeli C, Oktan MA, Yıldız S, et al. Clinical significance of mesangial IgM deposition in patients with IgA nephropathy. Clin Exp Nephrol. 2019;23(3):371–379.
12. Wu H, Behera TR, Gong J, Shen Q. Coexistence of Fabry disease with IgM nephropathy: a case report. Med. 2019;98(41).
13. Tang X, Li H, Li L, et al. The clinical impact of glomerular immunoglobulin M deposition in patients with type 2 diabetic nephropathy. Am J Med Sci. 2018;356(4):365–373.
14. Vizjak A, Ferluga D, Rožič M, et al. Pathology, clinical presentations, and outcomes of C1q nephropathy. J Am Soc Nephrol. 2008;19(11):2237–2244.
15. Kim K, Son H-E, Ryu J-Y, et al. C1q nephropathy in adults is a form of focal segmental glomerulosclerosis in terms of clinical characteristics. PLoS One. 2019;14(4):e0215217.
16. Vinicki JP, Pellet SC, De Rosa G, et al. Analysis of 65 renal biopsies from patients with rheumatoid arthritis (1976–2015): change in treatment strategies decreased frequency and modified histopathological findings. J Clin Rheumatol. 2015;21(7):335–340.
17. Welton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999;106(5):13S–24S.
18. Obici L, Raimondi S, Lavatelli F, Bellotti V, Merlini G. Susceptibility to AA amyloidosis in rheumatic diseases: a critical overview. Arthritis Care Res. 2009;61(10):1435–1440.
19. Desbois AC, Cacoub P. Systemic sclerosis: an update in 2016. Autoimmun Rev. 2016;15(5):417–426.
20. Lynch BM, Stern EP, Ong V, et al. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol. 2016;34(5):106–109.
21. Woodworth TG, Suliman YA, Li W, Furst DE, Clements PJNRN. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2016;12(11):678–691.
22. Okrój M, Johansson M, Saxne T, Blom AM, Hesselstrand RJ. Analysis of

complement biomarkers in systemic sclerosis indicates a distinct pattern in scleroderma renal crisis. Arthritis Res Ther. 2016;18(1):267.

23. Steen VD, Costantino JP, Shapiro AP, Medsger Jr TA. Outcome of renal crisis in systemic sclerosis: relation to availability of Angiotensin Converting Enzyme (ACE) inhibitors. Ann Intern Med. 1990;113(5):352–357.
24. Hruskova Z, Pippias M, Stel VS, et al. Characteristics and outcomes of patients with systemic sclerosis (scleroderma) requiring renal replacement therapy in Europe: results from the ERA-EDTA Registry. Am J Kidney Dis. 2019;73(2):184–193.
25. Mathian A, Miyara M, Cohen-Aubart F, et al. Relapsing polychondritis: a 2016 update on clinical features, diagnostic tools, treatment and biological drug use. Best Pract Res Clin Rheumatol. 2016;30(2):316–333.
26. Mertz P, Belot A, Cervera R, et al. The relapsing polychondritis damage index (RPDAM): development of a disease-specific damage score for relapsing polychondritis. Joint Bone Spine. 2019;86(3):363–368.
27. Jiao Y, Xu H, Li H, Li X. Mesangial proliferative glomerulonephritis with or without IgA deposits: the morphological characters in psoriasis vulgaris. Nephron Clin Pract. 2008;108(3):c221–c225.
28. Grewal S, Wan J, Denburg M, Shin D, Takeshita J, Gelfand J. The risk of IgA nephropathy and glomerular disease in patients with psoriasis: a population-based cohort study. Br J Dermatol. 2017;176(5):1366–1369.
29. Khan A, Haider I, Ayub M, Humayun M. Psoriatic arthritis is an indicator of significant renal damage in patients with psoriasis: an observational and epidemiological study. Int J Inflamm. 2017;2017:5217687.
30. Rijnink EC, Teng YO, Kraaij T, Wolterbeek R, Bruijn JA, Bajema IM. Idiopathic non-lupus full-house nephropathy is associated with poor renal outcome. Nephrol Dial Transplant. 2017;32(4):654–662.
31. Jaunin E, Kissling S, Rotman S, Waeber G, Halfon M. Syphilis and parvovirus B19 co-infection imitating a lupus nephropathy: a case report. Medicine. 2019;98(36).
32. Sethi S, D’Costa MR, Hermann SM, Nasr SH, Fervenza FC. Immunecomplex glomerulonephritis following COVID-19 infection. Kidney Int Rep. 2021;6(4):1171–1173.
33. Joh K, Makino H. Proposal of podocytic infolding glomerulopathy as a new disease entity. Clin Exp Nephrol. 2008;12(6):417–418.
34. Shi J, Zheng R, Gao H, Zhao Z, Wu H, Zhang Z. Podocyte infolding glomerulopathy with undifferentiated connective tissue disease: a case report. Ultrastruct Pathol. 2020;44(2):245–248.
35. Joh K, Taguchi T, Shigematsu H, et al. Proposal of podocytic infolding glomerulopathy as a new disease entity: a review of 25 cases from nationwide research in Japan. Clin Exp Nephrol. 2008;12(6):421–431.
36. Zhang T, Sun W, Xue J, et al. Podocytic infolding glomerulopathy: two new cases with connective tissue disease and literature review. Clin Rheumatol. 2019;38(5):1521–1528.
37. Hughes GR. Hughes syndrome (the antiphospholipid syndrome): ten clinical lessons. Autoimmun Rev. 2008;7(3):262–266.
38. Negrini S, Pappalardo F, Murdaca G, Indiveri F, Puppo FJC, Medicine E. The antiphospholipid syndrome: from pathophysiology to treatment. Clin Exp Rheumatol. 2017;17(3):257–267.
39. Bazzan M, Vaccarino A, Stella S, et al. Patients with antiphospholipid syndrome and thrombotic recurrences: a real world observation (the Piedmont cohort study). Lupus. 2016;25(5):479–485.
40. Kanakis MA, Kapsimali V, Vaiopoulos AG, Vaiopoulos GA, Samarkos MJCER. The lung in the spectrum of antiphospholipid syndrome. 2013;31(3):452–457.
41. Bienaimé F, Legendre C, Terzi F, Canaud G. Antiphospholipid syndrome and kidney disease. Kidney Int. 2017;91(1):34–44.
42. Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15(12):1120–1124.

43. Borghi MO, Beltagy A, Garrafa E, et al. Anti-phospholipid antibodies in COVID-19 are different from those detectable in the anti-phospholipid syndrome. Front Immunol. 2020;11:584241.
44. Miyakis S, Lockshin M, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite Antiphospholipid Syndrome (APS). J Thromb Haemost. 2006;4(2):295–306.

References

45. Andreoli L, Chighizola CB, Nalli C, et al. Clinical characterization of antiphospholipid syndrome by detection of IgG antibodies against β2-glycoprotein I domain 1 and domain 4/5: ratio of anti–domain 1 to anti–domain 4/5 as a useful new biomarker for antiphospholipid syndrome. Arthritis Rheumatol. 2015;67(8):2196–2204.
46. Giannakopoulos B, Krilis S. The pathogenesis of the antiphospholipid syndrome. N Engl J Med. 2013;368(11):1033–1044.
47. Canaud G, Bienaimé F, Tabarin F, et al. Inhibition of the mTORC pathway in the antiphospholipid syndrome. 2014;371(4):303–312.
48. Lee SJ, Kim J-E, Han K-S, Kim HKJBC, Fibrinolysis. Thrombotic risk of reduced ADAMTS13 activity in patients with antiphospholipid antibodies. Blood Coagul Fibrinolysis. 2016;27(8):907–912.
49. Nuri E, Taraborelli M, Andreoli L, et al. Long-term use of hydroxychloroquine reduces antiphospholipid antibodies levels in patients with primary antiphospholipid syndrome. Immunol Res. 2017;65(1):17–24.
50. Dufrost V, Wahl D, Zuily S. Direct oral anticoagulants in antiphospholipid syndrome: meta-analysis of randomized controlled trials. Autoimmun Rev. 2020;20(1):102711.
51. Ruffatti A, Favaro M, Hoxha A, et al. Apheresis and intravenous immunoglobulins used in addition to conventional therapy to treat highrisk pregnant antiphospholipid antibody syndrome patients. A Prospect Study. Reprod Immunol. 2016;115:14–19.
52. Titeca-Beauport D, Salle V, Kontar L, Maizel J, Choukroun G. Plasma exchange in the management of catastrophic antiphospholipid syndrome. Case Rep Crit Care. 2016;2016:5375080.
53. Shapira I, Andrade D, Allen SL, Salmon JEJA. Rheumatism. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Arthritis Rhem. 64(8):2719–2723.
54. Rodriguez-Pintó I, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: the current management approach. Best Pract Res Clin Rheumatol. 2016;30(2):239–249.
55. Andeen NK, Troxell ML, Riazy M, et al. Fibrillary glomerulonephritis: clinicopathologic features and atypical cases from a multi-institutional cohort. Clin J Am Soc Nephrol. 2019;14(12):1741–1750.
56. Rosenstock JL, Markowitz GS. Fibrillary glomerulonephritis: an update. Kidney Int Rep. 2019;4(7):917–922.
57. Thomas JA, Vasin D, Lin M, Anderson AE, Alpers CE. A case of mistaken identity: fibrillary glomerulonephritis masquerading as crescentic antiglomerular basement membrane disease. Clin Nephrol. 2016;85(2):114–120.
58. Alexander MP, Dasari S, Vrana JA, et al. Congophilic fibrillary glomerulonephritis: a case series. Am J Kidney Dis. 2018;72(3):325–336.
59. Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. Kidney Int Rep. 2018;3(1):56–64.
60. Nasr SH, Dasari S, Lieske JC, et al. Serum levels of DNAJB9 are elevated in fibrillary glomerulonephritis patients. Kidney Int. 2019;95(5):1269–1272.
61. Cheungpasitporn W, Zacharek CC, Fervenza FC, et al. Rapidly progressive glomerulonephritis due to coexistent anti-glomerular basement membrane disease and fibrillary glomerulonephritis. Clin Kidney J. 2016;9(1):97–101.
62. Erickson SB, Zand L, Nasr SH, et al. Treatment of fibrillary glomerulonephritis with rituximab: a 12-month pilot study. Nephrol Dial Transplant. 2021;36(1):104–110.
63. El Ters M, Bobart SA, Cornell LD, et al. Recurrence of DNAJB9-positive fibrillary glomerulonephritis after kidney transplantation: a case series. Am J Kidney Dis. 2020;76(4):500–510.
64. Saito T, Oikawa S, Sato H, Sasaki J. Lipoprotein glomerulopathy:

renal lipidosis induced by novel apolipoprotein E variants. Nephron. 1999;83(3):193–201.
65. Yang M, Weng Q, Pan X, et al. Clinical and genetic analysis of lipoprotein glomerulopathy patients caused by APOE mutations. Mol Genet Genomic Med. 2020;8(8):e1281.
66. Katsarou M, Stratikos E, Chroni A. Thermodynamic destabilization and aggregation propensity as the mechanism behind the association of apoE3 mutants and lipoprotein glomerulopathy. J Lipid Res. 2018;59(12):2339–2348.

67. Kaur A, Sethi S. Histiocytic and nonhistiocytic glomerular lesions: foam cells and their mimickers. Am J Kidney Dis. 2016;67(2):329–336.
68. Tsimihodimos V, Elisaf MJ. Lipoprotein glomerulopathy. Curr Opin Lipidol. 2011;22(4):262–269.
69. Ieiri N, Hotta O, Taguma YJ. Resolution of typical lipoprotein glomerulopathy by intensive lipid-lowering therapy. Am J Kidney Dis. 2003;41(1):244–249.
70. Russi G, Furci L, Leonelli M, et al. Lipoprotein glomerulopathy treated with LDL-apheresis (Heparin-induced Extracorporeal Lipoprotein Precipitation system): a case report. J Med Case Rep. 2009;3(1):9311.
71. Hirashio S, Ueno T, Naito T, Masaki T. Characteristic kidney pathology, gene abnormality and treatments in LCAT deficiency. Clin Exp Nephrol. 18(2):189–193.
72. Pavanello C, Ossoli A, Arca M, et al. Progression of chronic kidney disease in familial LCAT deficiency: a follow-up of the Italian cohort. J Lipid Res. 2020;61(12):1784–1788.
73. Ossoli A, Neufeld EB, Thacker SG, et al. Lipoprotein X causes renal disease in LCAT deficiency. PLoS One. 2016;11(2):e0150083.
74. Shamburek RD, Bakker-Arkema R, Auerbach BJ, et al. Familial lecithin: cholesterol acyltransferase deficiency: first-in-human treatment with enzyme replacement. J Clin Lipidol. 2016;10(2):356–367.
75. Ahmad SB, Miller M, Hanish S, et al. Sequential kidney–liver transplantation from the same living donor for lecithin cholesterol acyl transferase deficiency. Clin Transplant. 2016;30(10):1370–1374.
76. Kurien AA, Larsen CP, Cossey LN. Collagenofibrotic glomerulopathy. Clin Kidney J. 2015;8(5):543–547.
77. Isojima T, Harita Y, Furuyama M, et al. LMX1B mutation with residual transcriptional activity as a cause of isolated glomerulopathy. Nephrol Dial Transplant. 2014;29(1):81–88.
78. Yasuda T, Imai H, Nakamoto Y, et al. Collagenofibrotic glomerulopathy: a systemic disease. Am J Kidney Dis. 1999;33(1):123–127.
79. Bao H, Chen H, Zhu X, et al. Clinical and morphological features of collagen type III glomerulopathy: a report of nine cases from a single institution. Histopathology. 2015;67(4):568–576.
80. Cohen AH. Collagen type III glomerulopathies. Adv Chronic Kidney Dis. 2012;19(2):101–106.
81. Chen H, Bao H, Xu F, et al. Clinical and morphological features of fibronectin glomerulopathy: a report of ten patients from a single institution. Clin Nephrol. 2015;83(2):93.
82. Ohtsubo H, Okada T, Nozu K, et al. Identification of mutations in FN1 leading to glomerulopathy with fibronectin deposits. Pediatr Nephrol. 2016;31(9):1459–1467.
83. dos Reis Monteiro MLG, Custódio FB, de Menezes Neves PDM, et al. A novel single amino acid deletion impairs fibronectin function and causes familial glomerulopathy with fibronectin deposits: case report of a family. BMC Nephrol. 2019;20(1):1–6.
84. Langman CB, Barshop BA, Deschênes G, et al. Controversies and research agenda in nephropathic cystinosis: conclusions from a “Kidney Disease: Improving Global Outcomes”(KDIGO) Controversies Conference. Kidney Int. 2016;89(6):1192–1203.
85. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. Orphanet J Rare Dis. 2016;11(1):47.
86. Ivanova EA, Arcolino FO, Elmonem MA, et al. Cystinosin deficiency causes podocyte damage and loss associated with increased cell motility.

Kidney Int. 2016;89(5):1037–1048.
87. Servais A, Moriniere V, Grünfeld J-P, et al. Late-onset nephropathic cystinosis: clinical presentation, outcome, and genotyping. Am J Soc Nephrol. 2008;3(1):27–35.
88. Veys KR, Elmonem MA, Arcolino FO, van den Heuvel L, Levtchenko E. Nephropathic cystinosis: an update. Curr Opin Pediatr. 2017;29(2):168–178.
89. Ariceta G, Camacho JA, Fernández-Obispo M, et al. Cystinosis in adult and adolescent patients: recommendations for the comprehensive care of cystinosis. Nefrologia. 2015;35(3):304–321.
90. Santoro D, Rosenbloom BE, Cohen AH. Gaucher disease with nephrotic syndrome: response to enzyme replacement therapy. Am J Kidney Dis. 2002;40(1):e4. 1–e4. 4.
91. Salvatore SP, Troxell ML, Hecox D, Sperling KR, Seshan SV. Smokingrelated glomerulopathy: expanding the morphologic spectrum. Am J Nephrol. 2015;41(1):66–72.

References

92. Nasr SH, D’Agati VD. Nodular glomerulosclerosis in the nondiabetic smoker. J Am Soc Nephrol. 2007;18(7):2032–2036.
93. Fujii A, Sunatani Y, Furuichi K, et al. DNA damage in human glomerular endothelial cells induces nodular glomerulosclerosis via an ATR and ANXA2 pathway. Sci Rep. 2020;10(1):1–12.
94. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–131.
95. Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International trials Organisation collaborative initiative. Arthritis Rheumatol. 2016;68(3):566–576.
96. Santoriello D, Hogan J, D’Agati VD. Hemophagocytic syndrome with histiocytic glomerulopathy and intraglomerular hemophagocytosis. Am J Kidney Dis. 2016;67(6):978–983.

97. Wang Y, Wang Z. Treatment of hemophagocytic lymphohistiocytosis. Curr Opin Hematol. 2017;24(1):54–58.
98. Ouachée-Chardin M, Elie C, de Saint Basile G, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a singlecenter report of 48 patients. Pediatrics. 2006;117(4):e743–e750.
99. Criado PR, Avancini J, Santi CG, Medrado A, Rodrigues CE, de Carvalho JF. Drug reaction with eosinophilia and systemic symptoms (DRESS): a complex interaction of drugs, viruses and the immune system. Isr Med Assoc J. 2012;14(9):577–582.
100. Funck-Brentano E, Duong T-A, Bouvresse S, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. J Am Acad Dermatol. 2015;72(2):246–252.
101. Ito S, Oda T, Matsuo A, et al. Observation of angiolymphoid hyperplasia with eosinophilia (ALHE) at three arterial sites and its association with membranous nephropathy. Intern Med. 2015;54(15):1933–1939.

30

Thrombotic Microangiopathies, Including Hemolytic Uremic Syndrome

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DEFINITIONS

Thrombotic microangiopathy (TMA) is a lesion of arteriolar and capillary vessel wall thickening with intraluminal platelet thrombosis and a partial or complete obstruction of the vessel lumina. Laboratory features of thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present. Depending on whether kidney or brain lesions prevail, two pathologically indistinguishable but clinically different entities have been described: hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Because HUS can involve extrarenal manifestations and TTP may be associated with severe kidney disease, the two can be difficult to distinguish on clinical grounds.[1] Compared with HUS, TTP is associated with more severe thrombocytopenia and less severe acute kidney injury (AKI), but changes in platelet count and kidney function largely overlap in HUS and TTP. Composite scores such as the PLASMIC score have been proposed to identify TTP patients[2]; however, there are no cut-off values that definitely discriminate the two syndromes. The identified pathophysiologic mechanisms have allowed for the differentiation of the two syndromes on a pathogenetic basis and have paved the way to specific diagnosis and treatment (Table 30.1 and Fig. 30.1).

The term HUS was introduced in 1955 by Gasser and coworkers for an acute fatal syndrome characterized by hemolytic anemia, thrombocytopenia, and severe AKI. HUS occurs most frequently in children younger than 5 years (incidence 5–6 per 100,000 children per year compared with an overall incidence of 0.5–1 per 100,000 per year). About 90% of cases are associated with infection by Shiga-like toxin (Stx) producing Escherichia coli (STEC) and, less frequently, with sepsis by Shigella dysenteriae. STEC-HUS in 90% of cases is preceded by diarrhea, often bloody. STEC-HUS occurs primarily in children, except in epidemics, when it may occur in patients with a wider range of ages. In 2011 Northern Germany experienced one of the largest STEC-HUS outbreaks ever reported, with 3816 cases of E. coli O104:H4 infection, of whom 845 developed STEC-HUS. Almost 90% of affected patients were adults, in particular women.[3] Approximately 10% of HUS cases are not caused by Stx-producing bacteria and have been classified as atypical.[4]

Atypical HUS has an annual incidence of 0.5 to 2 per million per year, can occur at any age, and is a very severe disease. Before the introduction of complement inhibition therapy, 50% of patients with atypical HUS progressed to end-stage kidney disease (ESKD), 30% had neurologic symptoms, and 25% died in the acute phase.[5] Pulmonary, cardiac, and gastrointestinal (GI) manifestations also can occur.

TTP was first described in 1925 by Moschcowitz in a teenage girl with fever, hemolytic anemia, bleeding, AKI, neurologic involvement, and a fulminant clinical course. Pathologic changes were characterized by widespread hyaline thrombosis of small vessels. TTP has an annual incidence between 1.5 and 6 cases per million in Europe and the United States.[5] TTP is more common in adults aged 40 years on average but can affect any age group and classically presents with the pentad of thrombocytopenia, microangiopathic hemolytic anemia, fever, and neurologic and kidney dysfunction. Central nervous system (CNS) involvement is seen in over 90% of patients and is characterized by thromboocclusive disease of the gray matter. Clinical features include headache, cranial nerve palsies, confusion, stupor, and coma. Up to half of patients with neurologic involvement may be left with sequelae. Up to 25% of patients exhibit creatinine clearance of less than 40 mL/

min during long-term follow-up. Cardiac involvement is common in TTP, ranging from elevation of biomarkers to heart failure, infarction, and sudden cardiac death.6

LABORATORY FINDINGS

Thrombocytopenia and microangiopathic hemolytic anemia are almost invariably present in TMA patients.4 Thrombocytopenia occurs because of platelet consumption by platelet-rich thrombi in the microcirculation evidenced by giant platelets in the peripheral smear, reduced platelet survival time, or both. Thrombocytopenia may be severe but is usually less so in patients with predominant kidney involvement. In children with STEC-HUS, the duration of thrombocytopenia is variable and does not correlate with the course of kidney disease. Microangiopathic hemolysis is likely caused by the passage of blood through the damaged capillaries and arterioles occluded by thrombi, but other explanations have been suggested.7 Hemoglobin levels are low (<10 g/dL shiftenterin >90% of patients). The peripheral smear reveals reticulocytosis, increased schistocyte numbers, with polychromasia and often nucleated red blood cells (RBCs). Detection of fragmented erythrocytes is crucial to confirm the microangiopathic hemolytic anemia—provided that valvular heart disease and other arterial abnormalities causing erythrocyte fragmentation are excluded. Other indicators of intravascular hemolysis include elevated lactate dehydrogenase (LDH), increased indirect bilirubin, and low haptoglobin levels.4 The Coombs test is negative. Serum C3 levels may be low during the acute phase of STEC and atypical HUS and in TTP. Moderate leukocytosis may be present. Bone marrow biopsy shows erythroid hyperplasia and increased megakaryocytes. The normal prothrombin time, partial thromboplastin time, fibrinogen level, and coagulation factors differentiate TMA from disseminated intravascular coagulation. Mild fibrinolysis with minimal elevation in fibrin degradation products may be observed.

Kidney involvement is present in all patients with HUS (by definition) and in about 25% of patients with TTP1,8 and manifests with hematuria, proteinuria, occasionally in the nephrotic range, and kidney failure of variable severity. Hemoglobinuria is a sensitive marker of ongoing hemolysis and monitoring for it may help early detection of disease recurrence.

Classification of Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura According to Underlying Etiology

TABLE 30.1

Clinical Presentation	Etiology
Hemolytic Uremic Syndrome	
Stx associated	Infections by Shiga toxin–producing bacteria
Atypical hemolytic uremic syndrome	Complement gene abnormalities: 60% overall CFH, 20%–30%; CFI, 4–8%; C3, 8%–10%; MCP, 8%–10%; THBD, 3%–4%; CFB, 1%–2% CFH/CFHR hybrid genes: 3%–5% DGKE: 10% of patients <1 year old anti-CFH antibodies: 5%–10%
Secondary Hemolytic Uremic Syndrome	
Streptococcus pneumoniae	Desialylation of cells by neuroaminidase Complement gene abnormalities: 20%–30%
Pregnancy associated	Complement gene abnormalities: 50%–60%
Malignant hypertension	Complement gene abnormalities: 35%–65%
Transplantation (de novo HUS)	Calcineurin inhibitors, ischemia, immune response Complement gene abnormalities: 30%
BM/HSC transplantation	Immunosuppression, chemotherapy, GVHD, radiation, infections Complement gene abnormalities: 20%–60%
Autoimmune and systemic diseases	Autoimmune endothelial damage, secondary

complement activation
Complement gene abnormalities: around 10%

Drugs

Direct toxicity to endothelial cells
Complement gene abnormalities rare: <1%

Infections

Endothelial injury, complement activation
Complement gene abnormalities: variable %

Malignancies

Unknown

Cobalamin C
deficiency

MMACHC mutations

Thrombotic Thrombocytopenic Purpura
Genetic

Homozygous or compound heterozygous mutations
in ADAMTS13 gene

Acquired

Anti-ADAMTS13 autoantibodies

BM/HSC, Bone marrow/hematopoietic stem cell; CFH, complement factor H; GVHD, graft-versus-host disease; HUS, hemolytic uremic syndrome.

PATHOLOGY

TMA manifests as widening of the subendothelial space and microvascular thrombosis. Electron microscopy (EM) shows characteristic lesions of swelling and detachment of the endothelial cells from the basement membrane and the accumulation of fluffy material in the subendothelium, intraluminal platelet thrombi, and partial or complete obstruction of vessel lumina (Figs. 30.2 and 30.3).9 These lesions are similar to scleroderma, malignant nephrosclerosis, chronic transplant rejection, and calcineurin inhibitor nephrotoxicity. Microthrombi are present primarily in the kidneys in HUS and in brain in TTP. In very young children and in those with STEC-HUS, the glomerular injury predominates (Fig. 30.4).9

Thrombi and leukocyte infiltration are common in the early phases and usually resolve after 2 to 3 weeks. Patchy cortical necrosis may be present in severe cases; crescent formation is uncommon. In idiopathic and familial forms and in adults, the injury mostly involves arteries and arterioles, with thrombosis and intimal thickening (Fig. 30.5; see also Fig. 30.3), secondary glomerular ischemia, and retraction of the glomerular tuft (Fig. 30.6). Focal segmental glomerulosclerosis may follow acute HUS and is usually seen in children with long-lasting hypertension and progressive chronic kidney disease (CKD).

The typical pathologic changes of TTP are widespread occlusive capillary and arteriolar thrombi most commonly detected in kidneys, pancreas, heart, adrenals, and brain. Compared with HUS, pathologic changes of TTP are more extensively distributed.

MECHANISMS, CLINICAL FEATURES, AND MANAGEMENT OF SPECIFIC FORMS OF THROMBOTIC MICROANGIOPATHY

Shiga Toxin–Producing Escherichia coli–Associated Hemolytic Uremic Syndrome

Mechanisms

STEC-HUS may follow GI infections by certain strains of E. coli or S. dysenteriae that produce Stxs 1 and 2 (see Fig. 30.1 and Table 30.1).10 Most patients present with bloody diarrhea that may still be present or resolved at the time of presentation of HUS. Multiple strains of E. coli isolated from human cases with diarrhea produce Stxs (STEC). Before 2007, more than 70% of US cases of STEC-HUS were ascribed to the serotype O157:H7. However, starting from 2005, the reports of cases caused by non-O157 STEC increased and during 2010 to 2017, more than half of cases have been associated with infections by about 200 non-O157 STEC, with the predominance of serogroups O26, O103, O111, O121, O145, O45, O91, O146, and O113.11 12 The natural reservoir of STEC is the GI tract of ruminants (mainly cattle). Most STEC-infected cattle remain free of disease because they lack vascular Stx receptors. Undercooked ground beef, meat patties, raw vegetables, fruit, milk, and recreational or drinking water contaminated by ruminants' excreta have been implicated in the transmission of STEC.

E. coli O157:H7 and other STECs have been responsible for multiple outbreaks worldwide.10 The very large HUS outbreak in Germany in 2011 was caused by ingestion of fenugreek sprouts contaminated by an unusual STEC strain, O104:H4 related to fecal contamination of the seeds in Egypt.3 Because no O104:H4 strains were detected in cattle feces collected in the outbreak area, infected ruminants are unlikely to be the cause of the O104:H4 STEC outbreak.

After food or water is ingested, STEC colonize the intestinal mucosa through an attaching/effacing lesion, characterized by the disruption of microvilli and attachment of the bacteria to the enterocytes.13 This promotes diarrhea and intestinal inflammation. Released Stxs damage blood vessels in the colon. Very low levels of Stxs occur in the sera of HUS patients; however, Stxs can bind to blood cells or blood-derived microvesicles, which carry Stx from the intestine to target organs. Erythrocytes, platelets, and monocytes bind Stxs via specific globotriaosylceramide (Gb3) receptors, whereas human neutrophils interact with Stxs through the toll-like receptor 4.13

In the kidney, Stxs bind mainly to specific Gb3 receptors on glomerular endothelial cells but also to podocytes, mesangial cells, and proximal tubular cells. Bound toxin is internalized and inhibits protein synthesis, causing cell death. Treatment of endothelial cells with sublethal doses of Stx increased mRNA and protein expression of chemokines and cell adhesion molecules, favoring leukocyte-dependent

Investigation, Diagnosis, and Management of Thrombotic Microangiopathies

Decreased platelet count,
Increased serum LDH
Fragmented erythrocytes
+ STEC cultures
PCR, serology

ADAMTS13 <10%
TTP

Acquired TTP

Plasma exchange,
steroids, caplacizumab,
rituximab

STEC-HUS

TMA
No identified
causes

Other causes
+ anti ADAMTS Ab

Recovery

– anti ADAMTS Ab
• Start plasma
exchange if CNS involvement
or anuria
• Start eculizumab as soon
as aHUS is suspected

Genetic TTP

ESKD
or chronic ex vivo
complement activation

Plasma exchange
or infusion

Secondary aHUS

Pneumococcal
infection

Cobalamin
deficiency

Kidney/bone
marrow Tx

Malignant
hypertension

Primary aHUS

Drugs,
cancer

Systemic
diseases

- Treat underlying condition
- Start eculizumab if ex vivo complement activation
- Consider plasma exchange or eculizumab/ ravulizumab on individual basis

Infections
(CMV, HIV)

Pregnancy

Start
eculizumab
Stop plasma
exchange

Genetic screening:
CFH, MCP, CFI, C3, CFB,
THBD, DGKE, CFH/CFHR
copy number variation

Screen for anti-CFH Ab

Fig. 30.1 Investigation, Diagnosis, and Management of Thrombotic Microangiopathies. We recommend empirical treatment with eculizumab in particular if there is evidence for in vivo complement activation (and ideally ex vivo complement activation if such diagnostic testing is available). This latter testing involves evaluating for serum-induced complement deposition on cultured endothelial cells and is done only in a few specialized centers. Ab, Antibody; aHUS, atypical hemolytic uremic syndrome; CFB, complement regulatory factor B; CFH, complement regulatory factor H; CFI, complement regulatory factor I; CMV, cytomegalovirus; CNS, central nervous system; DGKE, diacylglycerol kinase epsilon; ESKD, end-stage kidney disease; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCP, membrane cofactor protein (CD46); MLPA, multiplex ligation-dependent probe amplification; STEC-HUS, Shiga toxin–producing Escherichia coli–associated hemolytic uremic syndrome; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; Tx, transplantation.

inflammation and inducing loss of thromboresistance in endothelial cells.

Complement activation at the renal endothelial level may contribute to microangiopathic lesions in STEC-HUS. Low serum levels of C3 and increased plasma levels of C3b, C3c, and C3d occur in children with STEC-HUS. High levels of complement activation products Bb and C5b-9 indicate complement activation via the alternative pathway.13 In addition, C3 and C9 deposit on the surface of blood-derived microparticles from STEC-HUS patients. Stxs might directly contribute to complement activation on endothelial cells, which contributed to loss of thromboresistance.14 Stx2 also caused the formation of plateletleukocyte aggregates with surface-bound C3 and C9. After exposure to Stx/lipopolysaccharide (LPS), factor B–deficient mice that cannot activate the alternative pathway of complement exhibited less thrombocytopenia and were protected against glomerular abnormalities

and kidney function impairment.14 Another glomerular target for Stx-induced complement activation is the podocyte, as documented by podocyte depletion—a potential cause of proteinuria—in Stx/LPS mice, which was limited by treatment with a C3a receptor antagonist.14 Tubular epithelial and mesangial cells are also susceptible to the cytotoxic effects of Stxs. Stxs inhibit water absorption across human renal tubular epithelial cell monolayers, which may contribute to the early events underlying kidney dysfunction in STEC-HUS.

Diagnosis

Diagnosis depends on the detection of E. coli O157:H7 and other STECs and their products in stool cultures (see Fig. 30.1). When infection with STEC is suspected, physicians should ensure that stool specimens are collected promptly and specifically cultured for STEC.10 Unlike most other E. coli, serotype O157:H7 does not

Fig. 30.2 Electron Micrograph of a Glomerular Capillary in Hemolytic-Uremic Syndrome. The endothelium is detached from the glomerular basement membrane (GBM); the subendothelial space is widened and occupied by electron-lucent fluffy material and cell debris (arrow). Beneath the endothelium is a thin layer of newly formed GBM.

Fig. 30.3 Electron Micrograph of a Renal Arteriole in Hemolytic Uremic Syndrome. The vascular lumen is completely occluded by thrombi. There is marked intimal edema with consequent separation of myointimal cells.

ferment sorbitol rapidly and thus forms colorless colonies on sorbitol containing MacConkey agar (SMAC). The use of SMAC provides a simple, inexpensive, and generally reliable method of screening stools for E. coli O157. The polymerase chain reaction to detect Stxencoding genes using DNA directly isolated from stool specimens has substantially improved the identification of non-O157-H7 STEC strains. Convalescent-phase serum samples can be assayed for antibodies to O157 or other specific strain-derived LPS; however, falsepositive results may occur because of antibodies preformed during antecedent STEC exposure.10

Clinical Course

After exposure to STEC, 38% to 61% of individuals develop hemorrhagic colitis and 3% to 9% (in sporadic infections) to 20% (in epidemic forms) progress to overt HUS (Fig. 30.7).10

Fig. 30.4 Glomerulus From a Patient With Shiga Toxin–Producing Escherichia coli–Associated Hemolytic Uremic Syndrome. A marked thickening of the glomerular capillary wall occurs with many double contours (arrowhead)

STEC-induced hemorrhagic colitis without HUS is self-limiting and is not associated with a long-term risk for CKD. STEC-HUS is characterized by prodromal diarrhea followed by AKI. The average interval between E. coli exposure and illness is 3 days. Illness typically begins with abdominal cramps and nonbloody diarrhea; diarrhea may become hemorrhagic in 70% of cases, usually within 1 or 2 days.10 Vomiting occurs in 30% to 60% of cases and fever in 30%. HUS is usually diagnosed 6 to 10 days after the onset of diarrhea. Of those who develop HUS, 70% HUS require RBC transfusions, 40% to 50% need dialysis for an average duration of 10 days, and the remainder have milder kidney involvement.10 15 About 25% of patients with STECHUS have neurologic involvement, including lethargy, apnea, cortical blindness, hemiparesis, stroke, seizures, and coma. GI complications include bowel ischemia/necrosis and perforation. Rare complications include pancreatitis, diabetes mellitus, myocardial ischemia because of TMA in coronary arteries and microvasculature, and pleural and pericardial effusions16; 1% to 4% of patients die during the acute phase.

About 70% of childhood cases of STEC-HUS fully recover from the acute disease. Those who do not fully recover may have persistent proteinuria (15%–30% of patients), hypertension (5%–15%), CKD (9%–18%), or ESKD (3%).15

Compared with previous STEC epidemics, during the STEC O104:H4 German outbreak, there was a higher incidence of dialysisdependent AKI (20% vs. 6%) and death (6% vs. 1%).3 Nearly half of the patients presented with neurologic symptoms and 20% had seizures. The severe clinical phenotype was explained by the lack of previous immunity to this novel STEC strain and its exceptional virulence.3

Therapy

Typical pediatric STEC-HUS treatment relies on supportive management of anemia, kidney failure, hypertension, and electrolyte and water imbalance (see Fig. 30.1). Intravenous (IV) isotonic volume expansion as soon as an E. coli O157:H7 infection is suspected, even before culture results are available, may limit the severity of AKI and the need for kidney replacement therapy.17 Up to 80% of patients need RBC transfusions. Heparin and antithrombotic agents increase the risk for bleeding and should be avoided. Patients with severe STEC-HUS require careful monitoring, including urine output, weight, volume status, cardiovascular/respiratory function, and early signs of CNS or other organ involvement. Bowel rest (i.e., complete parenteral nutrition) is important for the enterohemorrhagic colitis associated with STEC-HUS. Antimotility agents should be avoided because they may prolong the persistence of E. coli in the intestinal lumen and therefore increase patient exposure to its toxin.

B

A

Fig. 30.5 Interlobular Artery in a Case of Hemolytic-Uremic Syndrome With Severe Vascular Involvement. (A) The vascular lumen is almost completely occluded. Changes include myointimal proliferation and reduplication of the lamina elastica. (B) Thrombotic material and erythrocytes can be seen in the lumen and within the vascular wall.

Timing of Events That May Follow
Exposure to Shiga
Toxin–Producing E. coli
E. coli O157:H7 ingested
3–4 days
Abdominal cramps, nonbloody diarrhea
1–2 days

Fig. 30.6 Glomerulus From a Patient With Atypical Hemolytic Uremic Syndrome With Predominant Vascular Involvement. Severe ischemic changes have occurred. Note the shrinkage of the glomerular tuft and marked thickening and wrinkling of the capillary wall.

Antibiotics should be restricted to the rare patients presenting with bacteremia because, at least in children with gastroenteritis, antibiotic treatment may increase the risk for HUS 17-fold, possibly related to acute release of large amounts of preformed toxin from lysed bacteria.18 Alternatively, antibiotics might give E. coli O157:H7 a selective growth advantage. Moreover, several antimicrobial drugs, particularly the quinolones, trimethoprim, and furazolidone, are potent inducers of the expression of the Stx gene. Azithromycin may be an exception because its use reduced the duration of bacterial shedding in adults in the German O104:H4 epidemic.19 In contrast to STEC-HUS, hemorrhagic colitis and HUS caused by S. dysenteriae bacteremia and sepsis should be treated with antibiotics because treatment shortens the duration of diarrhea, decreases the incidence of complications, and reduces the risk for transmission.

Careful blood pressure control and renin-angiotensin system blockade may be beneficial in the long term for patients who develop CKD after an episode of STEC-HUS.

Newer potential treatments for STEC-HUS, including Stx-binding agents and Stx-neutralizing antibodies, have been abandoned because of lack of efficacy. The only published data on the Stx-binding agent SYNSORB Pk failed to show benefits.17 Other potential therapeutics under development are designed to limit Stx receptor expression or to prevent toxin binding, trafficking, or activity within the cells.20

Bloody diarrhea
5–7 days
95%
Resolution

5%
HUS

Fig. 30.7 Timing of events that may follow exposure to Shiga toxin producing E. coli. HUS, Hemolytic uremic syndrome.

The efficacy of specific treatments in adult patients is difficult to evaluate because most information is derived from uncontrolled series that may include atypical HUS cases. No prospective randomized trials demonstrate whether plasma infusion or exchange are superior to supportive treatment alone (Table 30.2). However, comparative analyses of two large series of patients treated21 or not treated22 with plasma suggest that plasma therapy may dramatically decrease overall mortality of STEC 0157:H7–associated HUS. Plasma exchange should therefore be considered in adult patients with severe AKI and CNS involvement.

Kidney transplantation is safe for children who develop ESKD. Recurrence rates range from 0% to 10%, and graft survival at 10 years is better than in children with other causes of ESKD.

Evidence that uncontrolled complement activation may contribute to microangiopathic lesions of STEC-HUS14 led to complement inhibitor therapy with the anti-C5 monoclonal antibody eculizumab in three children with severe STEC-HUS who fully recovered. However, eculizumab therapy plus plasma exchange in the German STEC O104:H4 outbreak did not improve outcomes compared with plasma exchange alone.23 These data, however, were retrospectively collected

TABLE 30.2

HUS and TTP: Specific Therapies, Dosing, and Efficacy

Therapy

Dosing

Efficacy

Prednisone

200 mg tapered to 60 mg/day, then 5 mg reduction per wk

Prednisolone

200 mg, tapered to 60 mg/day, then 5 mg reduction per wk

Immunoglobulins

400 mg/kg/day

Probably effective in addition to plasma exchange in patients with TTP and anti-ADAMST13 autoantibodies or in aHUS with anti–factor H autoantibodies and in forms associated with autoimmune diseases. Lack of evidence from controlled trials in immune-mediated HUS or TTP.

CD20 cell depleting antibody (rituximab)

375 mg/m2/wk up to CD20 and/or CD19 cell depletion

Effective in treatment or prevention of TTP associated with immune-mediated ADAMTS13 deficiency resistant to or relapsing after immunosuppressive therapy.

Exchange

1–2 plasma volumes/day

First-line therapy in TTP.
Unproven efficacy in childhood STEC-HUS. Possibly effective in aHUS if eculizumab is not available.

Infusion

20–30 mL/kg followed by 10–20 mL/kg/day

To be considered if plasma exchange is not available.

Cryosupernatant

See plasma infusion/exchanges

To replace whole plasma in case of resistance to plasma infusion or sensitization.

Solvent-detergent–treated
plasma

See plasma infusion/exchanges

To limit the risk for infections.

Caplacizumab

10–11 mg IV loading dose, then 10–11 mg SC
daily combined with plasma exchange and
immunosuppression

Reported efficacy in acquired TTP.

Liver-kidney transplant

Perioperative plasma infusion/exchange and eculizumab

To prevent CFH-associated HUS recurrence posttransplant; about
20% mortality risk.

Complement inhibition
(eculizumab)

900 mg/wk for the first 4 wk
1200 mg every 14 days up to 6 mo in adults and chidren
with body weight >40 kg. In smaller children the dose is
adjusted on the basis of body weight.

First-line therapy in primary aHUS.

Immunosuppressives

Fresh frozen plasma

aHUS, Atypical hemolytic uremic syndrome (HUS); CFH, complement factor H; IV, intravenous; SC, subcutaneous; STEC-HUS, Shiga toxin–producing Escherichia coli–associated HUS; TTP, thrombotic thrombocytopenic purpura.

and patients given eculizumab were the most severely ill. Two doubleblind placebo controlled trials, ECUSTEC in UK (ISRCTN89553116) and ECULISHU in France (NCT02205541), in severe forms of STECHUS will be finalized soon.

Atypical Hemolytic Uremic Syndrome

The term atypical HUS (aHUS) has been used to define any form of HUS that is not caused by STEC.4 Several other classifications each carry caveats.24 Currently, the term aHUS is used when a genetic or autoimmune abnormality causing complement dysregulation is strongly suspected (see Fig. 30.1 and Table 30.1)4 25 and other causes have been excluded. Secondary HUS instead includes a broad group of patients in whom TMA occurs in the context of another condition such as malignant hypertension, autoimmune disease, certain infections, malignancy, transplantation, or drugs. However, this differentiation is not absolute because in more than 50% of patients with primary aHUS and genetic risk factors, a trigger is required for disease to manifest, such as viral and bacterial infections or pregnancy.4 25 Conversely, complement gene abnormalities have been identified in subgroups of patients with secondary HUS, indicating the relevance of genetic background for disease susceptibility.25 26 Consistently, measurement of circulating complement parameters and ex vivo assays of complement

deposition on cultured endothelial cells with serum and plasma from patients supported a role of complement activation in the etiology of several forms of secondary HUS.27

Primary aHUS4 25 is usually sporadic, and fewer than 20% of cases are familial. Although some are in siblings, suggesting autosomal recessive transmission, others occur across two or three generations, indicating an autosomal dominant mode. Incomplete penetrance of the disease in mutation carriers is a common feature that confounds the interpretation of inheritance. Indeed, many sporadic cases of aHUS inherited the genetic defect from an unaffected parent.28

Mechanisms

About 50% of aHUS patients exhibit reduced serum levels of C3 with normal C4.29 C3 consumption is documented by high levels of activated products and C3 deposits in glomeruli and other kidney vessels. The complement pathways—classic, lectin, and alternative pathways (see Fig. 17.6)—are discussed in Chapter 17. The alternative pathway (Fig. 30.8) is initiated spontaneously in plasma by C3 hydrolysis responsible for deposition of a low amount of C3b onto all plasma-exposed surfaces. On bacterial surfaces, C3b leads to phagocytosis by neutrophils and macrophages. Without regulation, a small initiating stimulus is quickly amplified to a self-harming response until complement

Alternative Pathway of Complement Activation
“Tick over” hydrolysis

Bacteria, activating surfaces

C3bBb-P
Amplification loop
C3 convertase
(surface bound)
CFD
Factor B
C3(H2O)

CFD

P

AP initiation
C3 convertase
C3(H2O)Bb

C3

inactivation

inactivation

C3b

C3a
CFH
CFI
MCP

Factor B

C3a
C3b
C3bBb

P

CFH
CFI
MCP

Factor B
CFD

C3bBb-P
Amplification loop
C3 convertase
(fluid phase)

dissociation

CFH

dissociation
CFH

C3bBbC3b
AP C5 convertase

Fig. 30.8 Alternative Pathway of Complement Activation. The alternative pathway (AP) is continuously activated in plasma by low-grade hydrolysis of C3. The latter binds factor B, to form a C3(H 2O)B complex. Factor D (CFD) cleaves factor B to form the AP initiation C3 convertase that cleaves C3 to C3b. The activation is then amplified by the covalent binding of a small amount of C3b to hydroxyl groups on cell surface carbohydrates and proteins of target cells such as bacterial cells. This C3b binds factor B to form the amplification loop C3 convertase C3bBb. C3 convertase enzymes cleave many molecules of C3, resulting in a positive feedback amplification loop. C3b also binds to the C3 convertase, forming the C5 convertase enzyme C3b2Bb. The AP is highly regulated to prevent nonspecific damage to host cells and limit the deposition of complement to the surface of pathogens. This fine regulation occurs through a number of membraneanchored and fluid phase regulators. CFH, Complement factor H (acts as cofactor for factor I for C3b cleavage and favors the decay of the C3 convertase of the AP); CFI, complement factor I (degrades C3b and C4b); CR1, complement receptor 1 (has decay accelerating activity and cofactor activity for factor I–mediated cleavage of C3b and C4b); DAF, decay accelerating factor (destabilizes the C3 and C5 convertases of the classic and alternative pathways); MCP, membrane cofactor protein (binds C3b and C4b and has cofactor activity for both the classic and alternative pathways).

components are depleted. On host cells, such a dangerous cascade is controlled by membrane-anchored and fluid-phase regulators (see Fig. 30.8). They both favor the cleavage of C3b to inactive iC3b by the plasma serine protease factor I (CFI, cofactor activity) and dissociate the C3 and C5 convertases (decay acceleration activity). Foreign targets and injured cells that either lack membrane-bound regulators or cannot bind soluble regulators are attacked by complement.

The C3 convertases of the classic/lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase requires cleavage of C3 only (see Fig. 30.8). Thus, low serum C3 levels in aHUS with normal C4 indicated selective alternative pathway activation.29

Several genetic abnormalities in members of the alternative pathway of complement have been described in aHUS, which account for about 60% of cases (see Table 30.1). Functional studies revealed that aHUS-associated mutations mainly result in complement activation that is restricted on the cell surface—which explains the normal circulating complement profile in about half of patients—and proceeds until the formation of C5b-9.27

Complement factor H. Complement factor H (CFH) regulates the alternative pathway both in the fluid phase and on the cell surface by acting as a cofactor for CFI and enhancing dissociation of C3 convertase (see Fig. 30.8). Over 120 CFH pathogenetic or likely pathogenetic variants (Database of Complement Gene Variants; www.complementdb.org) have been identified in aHUS patients (mutation frequency about 30%).28 These genetic abnormalities most commonly are associated with normal CFH levels but instead result in dysfunctional protein that cannot bind to and regulate complement on endothelial cells and platelets.30 A high degree of sequence identity between CFH and the genes CFHR1-5 for five factor H–related proteins (CFHR) located in tandem to CFH may predispose to gene conversions and genomic rearrangements.31 Hybrid CFH/CFHR1 and CFH/CFHR3 genes, coding abnormal FH proteins in which the carboxy-terminal domains that mediate complement regulation on cell surface are substituted for those of FHR1 or by the entire FHR3, occur in 3% to

5% of patients with aHUS. The resulting hybrid CFH molecules exhibit decreased complement regulatory activity on endothelial surfaces.31 Different gene conversion events between the CFH and CFHR1 genes have been reported in unrelated aHUS patients, which convert the FHR-1 C-terminus into that of CFH. The resulting FHR1 mutant strongly competes with CFH for cell surface binding.

Anti-CFH inhibitory antibodies have been reported in 5% to 10% of aHUS patients and around 25% to 50% of pediatric cases.[32] These autoantibodies predominantly target the C-terminal end, impairing complement regulation on host cell surfaces. The development of CFH autoantibodies in aHUS has a genetic predisposition, being strongly associated with the homozygous deletion of the CFHR1 and CFHR3 genes.[32] Complement gene variants identified in a quarter of patients with anti-CFH antibodies may affect disease severity and outcome.

Membrane cofactor protein. Membrane cofactor protein (MCP) is a transmembrane complement regulator widely expressed on all cells apart from erythrocytes. MCP serves as a cofactor for CFI to cleave C3b and C4b (see Fig. 30.8). MCP gene abnormalities account for 8% to 10% of aHUS cases.[28] Most are heterozygous (www.complementdb.org). The majority cluster in critical extracellular modules for regulation. Expression on blood leukocytes was reduced for about 75% of mutants. Other MCP mutants have low C3b-binding capability and decreased cofactor activity.[28]

Complement factor I. CFI is a plasma serine protease that regulates the three complement pathways by cleaving C3b and C4b in the presence of cofactor proteins (see Figs. 17.6 and 30.8). CFI pathogenetic variants affect 4% to 8% of patients. All mutations are heterozygous; 80% cluster in the serine-protease domain. Approximately 50% of mutants are not secreted in blood; however, some mutants are secreted but have impaired proteolytic activity.[28]

Complement factor B and C3. Gain-of-function mutations can affect genes encoding the alternative pathway C3 convertase components, complement factor B (CFB) and C3. CFB variants are rare (1%–2%). Some CFB mutants have excess C3b affinity and form a hyperactive C3 convertase resistant to dissociation; however, about 60% of mutants have normal activity and are likely unrelated to aHUS pathogenesis.[33]

About 9% of aHUS patients carry heterozygous variants in C3, usually with low C3 levels. Most mutations reduce C3b binding to complement regulators, severely impairing its inactivation and result in increased C3 deposition on endothelial cells.

Thrombomodulin. Heterozygous mutations in the gene THBD encoding thrombomodulin, an endothelial surface anticoagulant protein that also modulates complement on cell surfaces, have been found in 3% to 4% of patients with aHUS.[34] Cells expressing THBD variants inactivate C3b less efficiently.[34]

Determinants of disease penetrance. Incomplete penetrance of aHUS in carriers of complement gene abnormalities ranges from 20% to 50%.[28] A further mutation in one of the aforementioned genes occurs in approximately 10% of aHUS patients and increases the risk for developing the disease.[35] Common genetic risk variants (singlenucleotide polymorphisms [SNPs] and haplotype blocks) in CFH, MCP, and CFHR1 have been shown to act as susceptibility factors for the development of aHUS.[35] In a study of 103 aHUS pedigrees, the concurrent presence of two pathogenetic variants and the CFH and MCP risk haplotypes resulted in 100% penetrance.[36]

Diacylglycerol kinase ε. Homozygous or compound heterozygous mutations in DGKE, which encodes the intracellular protein diacylglycerol kinase ε, have been recently associated with infantile recessive aHUS.[37] Mutation carriers presented with aHUS before 1 year of age (see Table 30.1), with hypertension, hematuria, and severe proteinuria, often in nephrotic range. DGKE is expressed in endothelium, platelets, and podocytes; is involved in terminating diacylglycerol signaling; and is not directly linked to complement. However, a subgroup of patients exhibits systemic complement activation, with or without concomitant rare complement gene variants.

Diagnosis of Atypical Hemolytic Uremic Syndrome and Testing for Genetic Mutations

Differential diagnosis of aHUS requires exclusion of infections by STEC or concomitant diseases and conditions or ADAMTS13 deficiency or autoantibodies against ADAMTS13 (see Fig. 30.1).25 Full analysis of disease-associated genes and testing for anti-CFH antibodies is recommended because the nature of the underlying complement defect influences disease progression, the risk of relapses after kidney transplantation, and responses to therapies. Reference laboratories in several countries are equipped for genetic and antibody testing. Although new sequencing techniques have reduced cost and time, a complete evaluation still requires several weeks. Treatment of acute episodes (plasma therapy or eculizumab when available; see later discussion) should be started rapidly after clinical diagnosis, without waiting for results of genetic and anti-CFH antibody tests.

Clinical Course

Of all patients with aHUS, 60% are affected during childhood, irrespective of mutation type.28 Almost all patients with anti-CFH antibodies develop the disease before 16 years of age. Acute episodes manifest with severe hemolytic anemia, thrombocytopenia, and AKI. Extrarenal involvement (CNS or multivisceral) occurs in 20% of cases.4,28 Before the introduction of anti-C5 therapy, 50% to 70% of patients with CFH, CF, C3, CFB, or THBD mutations and 40% of children with anti-CFH autoantibodies lost kidney function, died during the presenting episode, or developed ESKD after relapses.4,28 Chronic complement dysregulation may lead to atheroma-like lesions enhancing cardiovascular morbidity and mortality. In MCP-mutation carriers, recurrences were frequent but long-term outcome was good and 80% of patients remained dialysis-free.4,28 However, rare patients with MCP mutations had severe disease, immediate ESKD, intractable hypertension, and coma, possibly because of concurrent genetic abnormalities.35

Therapy

Fresh frozen plasma. Plasma therapy (plasma exchange, 1–2 plasma volumes/day; plasma infusion, 20–30 mL/kg/day; see Table 30.2) should be started within 24 hours of diagnosis and then continued until remission or a declaration of nonresponse.4 Plasma infusion or exchange provides normal CFH to patients carrying CFH mutations.28 Long-term treatment, however, may fail as a result of development of plasma resistance. Heterozygous CFH mutation carriers usually have normal levels of CFH, half of which is dysfunctional. The beneficial effect of plasma is strongly dependent on the amount, frequency, and modality of administration, with plasma exchange being superior to plasma infusion by removing the mutant CFH that could antagonize the normal protein. Plasma exchange in association with immunosuppressive therapy (induction with corticosteroids and cyclophosphamide and maintenance with azathioprine or mycophenolate mofetil) is recommended in patients with anti-CFH antibodies to remove the inhibitory antibodies25,32 and allowed longterm dialysis-free survival in 60% to 70% of patients.32 Data on the effect of rituximab in such circumstances are scanty and inconsistent: of five patients treated with rituximab alone or with plasma exchange, only two showed disappearance of anti-CFH antibodies.32

Patients with CFI mutations showed a partial response to plasma4,28; 30% to 40% of patients with CFB mutations and 50% of those with C3 mutations responded to plasma infusion or exchange.4 Possibly these patients need frequent large-volume plasma exchange to clear the hyper-functional mutant CFB and C3.4 Because MCP is a cellassociated protein, effects of plasma are unlikely in patients with MCP mutations. Indeed, 80% of patients with an MCP mutation underwent spontaneous remission independently of plasma treatment.4,28

Kidney transplantation. Disease recurred in 60% to 80% of transplanted patients with mutations in complement-circulating proteins (CFH, CFI, CFB, and C3), and graft failure occurred in 80% to 90%.38 The risk for post-transplant aHUS recurrence in patients with anti-CFH autoantibodies is not well known.32 Recurrence of HUS was documented in 30% of cases. A reduction in autoantibody levels with plasma exchange, steroids, and/or rituximab enabled successful kidney transplantation in few patients.32

The lowest incidence of recurrence was observed in patients with MCP and DGKE mutations.37 38 MCP and DGKE are highly expressed in the kidney, and a graft that brings normal proteins corrects the defect. However, about 20% of patients with MCP mutations also carry a mutation in another complement gene. Such patients have a worse graft outcome with higher incidence of recurrences than patients with an isolated MCP mutation.35

Testing affected patients for mutations on all disease-associated genes should allow patients and clinicians to make informed decisions regarding listing for transplantation based on risk for recurrence.

Most studies have shown that plasma exchange therapy fails to prevent graft loss in patients with recurrent posttransplant aHUS.38

A preemptive plasma infusion or exchange strategy has been successful in preventing recurrent aHUS in kidney transplant recipients,39 although aHUS recurred in some when plasma therapy was tapered.

Living-related kidney donation is contraindicated given the high risk for recurrence, and it even may be risky to donors because uninephrectomy may precipitate aHUS if they are complement gene mutation carriers.

Complement inhibitors. The humanized anti-C5 monoclonal antibody eculizumab induces remission of acute episodes of aHUS and maintains long-term remission, both in native kidneys and in the kidney grafts, as documented in two prospective clinical trials of primarily adult patients with plasma-dependent or plasma-resistant aHUS40 and in a pediatric trial in 22 children, of whom 12 had no prior plasma treatment. Eculizumab is now widely used as a first-line therapy for aHUS, provided that other causes of TMA are excluded (see Fig. 30.1 and Table 30.2).25

DGKE-mediated aHUS is generally nonresponsive to eculizumab, with the exception of patients who also present with concomitant complement abnormalities.

Eculizumab prophylaxis is used to prevent aHUS relapses after kidney transplantation. In a study of 126 kidney transplants, eculizumab prophylaxis was independently associated with longer graft survival.41 However, this was a retrospective study and controlled prospective studies are required to evaluate the advantage, if any, of eculizumab prophylaxis versus eculizumab treatment at the time of overt aHUS recurrence in kidney transplant patients.39

Ravulizumab, an anti-C5 antibody engineered from eculizumab to prolong half-life, has been recently approved for the treatment of aHUS. In clinical trials, rates of remission were similar to those observed in eculizumab trials; however, fewer patients in the ravulizumab study were able to stop dialysis, possibly because of differences in patient cohorts.42

The main concern with eculizumab and ravulizumab is increased susceptibility to infection with encapsulated organisms, particularly Neisseria infections. For this reason, patients must receive meningococcal vaccination. Patients should receive vaccination against meningococcus, including type B; however, vaccination should not delay the start of eculizumab. Antibiotic prophylaxis is mandated during the first 2 weeks and is recommended for the overall treatment duration because not all serotypes are covered by vaccination.25

It is not clear how long anti-C5 therapy should be extended, a relevant issue because of the very high cost of the drug. In addition, the risk for sensitization associated with chronic eculizumab exposure or with its deposition in tissue suggest that careful tapering to withdrawal whenever possible should be attempted, under tight control of disease and complement activity. In a prospective multicenter study of eculizumab discontinuation in 55 children and adults with aHUS, 13 patients experienced a relapse and this was predicted by the presence of a rare complement gene variant.43 Different clinical courses before eculizumab therapy, and different residual complement activity while on eculizumab therapy, should be taken into consideration when strategies of chronic eculizumab therapy or discontinuation are planned.

Reliable biomarkers of early relapse are strongly needed. In this regard, abnormally elevated serum-induced C5b-9 deposition on cultured endothelial cells highlighted aHUS relapses during eculizumab tapering/discontinuation.27 At present, however, this test is available in only very few specialized centers.

Liver-kidney transplant. In patients with CFH mutations, combined liver-kidney transplant is aimed at correcting the genetic complement defect, thus preventing disease recurrence in the transplanted kidney (see Table 30.2). Liver transplantation cures aHUS without the need for specific therapies other than standard immunosuppression to prevent graft rejection. The short-term mortality risk associated with acute complement activation in the liver graft observed in initial attempts has been substantially reduced with prophylactic plasma exchange and perioperative eculizumab. Over 80% of patients with aHUS who received liver transplants to date with the previously described preparative regimen have had excellent long-term outcomes.44,45 However, the risks of kidney and liver transplantation have limited the widespread dissemination of this option.

SECONDARY HEMOLYTIC UREMIC SYNDROME

See Fig. 30.1 and Table 30.1.

Streptococcus pneumoniae–Associated HUS

Streptococcus pneumoniae accounts for 5% to 20% of reported pediatric HUS cases not associated with STEC.46 Neuraminidase produced by S. pneumoniae cleaves N-acetylneuraminic acid from the glycoproteins on the cell membrane of erythrocytes, platelets, and glomerular cells; this exposes the normally hidden Thomsen-Friedenreich antigen (T antigen), which can then react with anti-T IgM antibodies naturally present in human serum. This reaction occurs more frequently in infants and children and causes polyagglutination of RBCs in vitro, so the Coombs test is often—although not always—positive, unlike in other forms of HUS. T-antigen exposure on RBCs is detected using the lectin Hypogaea. However, T-antigen exposure alone does not seem to be sufficient in causing HUS. Desialylation of cells also triggers complement activation via the alternative pathway. Severe consumption of complement components in serum during the acute phase and the identification of complement-related gene mutations in a few patients suggest a role for complement dysregulation in this form of HUS.46

Patients, usually younger than 2 years, present with severe illness, including respiratory distress, neurologic involvement, and coma. The acute mortality rate is about 25%. The outcome hinges on the effectiveness of antibiotic therapy. In theory, plasma infusion or exchange is contraindicated because adult plasma contains antibodies against the T antigen that may accelerate polyagglutination and hemolysis. Thus, patients should be treated with only antibiotics, washed RBCs, and fluid and kidney replacement therapy. In some cases, plasma therapy with or without steroids has been associated with recovery.

Pregnancy-Associated HUS

HUS associated with pregnancy tends to occur at term or postpartum, within 3 months of delivery in most cases. This form is associated with genetic complement abnormalities in 50% to 60% of cases47 and massive ex vivo serum-induced C5b-9 formation on endothelium48 and should be included in the primary aHUS group, with pregnancy acting as a trigger on a predisposed genetic background. Consistently, around 90% of published patients with pregnancy-associated HUS underwent remission with eculizumab and the drug can be given safely during pregnancy.49

In the antiphospholipid syndrome (APS; see Chapter 29), oral anticoagulation remains the only treatment of proven efficacy to prevent and treat microvascular and macrovascular thrombosis. Rituximab may be efficacious, but further controlled studies are needed.56 Less than 1% of patients with APS develop catastrophic APS (defined as intravascular thrombosis affecting three or more systems despite any treatments). Eculizumab has been used to treat these refractory cases, and published data showed improvement or stabilization.26 Blood pressure control is fundamental in TMA associated with scleroderma crisis.

HUS and Malignant Hypertension

Drug-Induced HUS

Complement activation should also be suspected in patients with HUS in the setting of malignant hypertension.26 Variants in complement genes have been reported in 35% to 65% of patients, and ex vivo seruminduced C5b-9 deposition on endothelial cells was increased, whereas it was normal in patients with malignant hypertension alone.27,50 Blood pressure control is fundamental. Good response to eculizumab has been reported in a small series of patients. Early detection of complement activation via the endothelial assay or by elevation of plasma sC5b-9 is crucial to identify patients who would benefit from complement inhibition, especially when the disease does not improve with blood pressure control.

Drug-induced HUS may result from direct toxicity of the drug to endothelial cells or is immune mediated (see Fig. 30.1 and Table 30.1). TMA, commonly resembling HUS, occurs in 2% to 10% of cancer patients treated with mitomycin C and usually in remission from their malignancy.57 The fatality rate is about 70%; patients surviving the acute phase often remain on chronic dialysis or die later of recurrence of the tumor or metastases. Preventing the disease by corticosteroids during mitomycin treatment has been suggested and needs to be confirmed. Plasma exchange is usually attempted, but its effectiveness is unproven.

Quinine is one of the most common drugs associated with HUS.57 It is generally used to treat muscle cramps but is also contained in beverages and nutrition health products. Quinine-dependent platelet, erythrocyte, granulocyte, lymphocyte, and endothelial antibodies may contribute to the pathogenesis. Severe kidney impairment is frequent, and hemodialysis is required in most cases. High rates of death and CKD have been reported. Quinine cessation and plasma therapy should be initiated rapidly.

TMA associated with interferon alfa is characterized by predominant kidney impairment. Recovery of the disease is common in cases of early discontinuation of the drug and prompt supportive therapy.

However, kidney prognosis is usually poor, with ESKD reported in about 42% of cases.

Variants in complement genes are rare in drug-induced HUS (prevalence not different from controls) and the response after drug withdrawal was not different in patients treated with plasma, corticosteroids, or eculizumab.[26,54]

Posttransplant HUS

De novo posttransplant HUS has been reported in patients receiving kidney transplants or other solid organs and has been related to calcineurin inhibitors or humoral rejection. It occurs in 5% to 10% of kidney transplant patients receiving cyclosporine and in approximately 1% of those on tacrolimus. Withdrawal of the immunosuppressive agents is usually the first line of treatment. Underlying abnormalities in complement genes have been reported in one-third of cases. Anticomplement therapy with eculizumab is effective in some but not all cases.[51] Positive C5b-9 staining in kidney biopsy and/or complement genetic abnormalities could be indications for eculizumab.

HUS complicates 10% to 40% of allogeneic bone marrow/hematopoietic stem cell transplants and is associated with high mortality.[52]

The disease is multifactorial. Risk factors include immunosuppressive drugs, graft versus host disease, chemotherapy, radiation, and infections. In a large study, around 60% of patients with HSCT and HUS had at least one complement gene variant compared with 9% of patients without HUS,[53] and plasma sC5b-9 levels were elevated in the former. Other authors reported a lower incidence of complement gene abnormalities (20%–30%). Treatment remains controversial. Favorable outcomes with eculizumab have been described in a few cases.

HUS Associated With Autoimmune and Systemic Diseases

Several autoimmune diseases can be associated with HUS, including systemic lupus erythematosus (SLE), antiphospholipid syndrome, and scleroderma. The pathophysiology of HUS in these diseases is multifactorial. Although genetic complement abnormalities are rare in these patients,[54] complement activation via the classical or the alternative pathways occurs secondary to the underlying autoimmune disease (see Fig. 30.1 and Table 30.1).

Treatment of the concomitant disease should be the first line of intervention. Plasma therapy should always be attempted, even though its efficacy is poorly defined. In a few patients with persistent HUS despite treatment of SLE, the use of eculizumab was associated with an improvement in hematologic indices and/or kidney function.[26,55]

Infection-Associated HUS

HUS can occur in infections by viral (cytomegalovirus [CMV], Epstein-Barr virus, varicella zoster virus, parvovirus, human immunodeficiency virus [HIV], West Nile virus), bacterial, and other agents (Bordetella pertussis, Mycoplasma pneumoniae, toxoplasma gondii, plasmodium vivax).[26] Mechanisms are complex and include direct endothelial injury and complement activation involving any of the three activation pathways. The incidence of alternative pathway genetic abnormalities is low and varies according to the type of infection.[26]

In COVID-19 disease (see Chapter 59), there is increasing evidence that unrestrained complement activation induced by the virus in the lungs and other organs is one of the mechanisms of tissue injury, endothelial dysfunction, and TMA-like thrombosis.[58] Elevated levels of sC5b-9 and C5a have been reported in the plasma of severe COVID-19 patients, indicating terminal complement activation, and preliminary data of C5 or C5a inhibition in a few patients with severe COVID-19 are encouraging. More than 10 clinical trials of complement inhibition in COVID-19 are underway.[58]

Malignancy

Spontaneous TMA complicates almost 6% of cases of metastatic gastric carcinoma, which, in turn, accounts for about 50% of all malignant disease–associated TMA (see Fig. 30.1 and Table 30.1). The prognosis is extremely poor. Therapy is minimally effective.

Cobalamin C Deficiency–Associated HUS

HUS can manifest in methylmalonic aciduria and homocystinuria caused by recessive mutations in the MMACHC gene, which result in deficiency of cobalamin C type (cblC), the most common genetic functional variant of cobalamin (vitamin B12) (see Fig. 30.1 and Table 30.1). It is a rare condition, and around 40 cases of HUS associated with cblC defect have been reported. Pulmonary hypertension may accompany the disease. Diagnosis is facilitated by finding elevated plasma homocysteine and methylmalonic aciduria. HUS usually presents in early infancy, although adult onset has also been reported. Mortality is high if untreated, but metabolic therapy with hydroxocobalamin is very effective.

In summary, the term secondary HUS (or secondary TMA) includes a very heterogeneous group of conditions. Complement activity tests, like the serum-induced C5b-9 formation on endothelium, and genetic screening could allow us to reclassify each patient on etiology basis and determine whether and to what extent complement activation plays a role in the disease. Massive ex vivo C5b-9 formation on endothelium during acute episodes27 indicates complement as a driving factor and may be used to select patients for complement inhibition. Those patients also carrying genetic complement abnormalities and/or showing chronically increased C5b-9 formation in remission27 are most likely primary aHUS cases genetically predisposed to complement dysregulation, in whom the coexisting condition acted as a trigger of the acute episode (see Fig. 30.1 and Table 30.1).

Thrombotic Thrombocytopenic Purpura

In the microvasculature of patients with TTP, systemic platelet thrombi develop, mainly formed by platelets and von Willebrand factor (vWF). vWF plays a major role in primary hemostasis, forming platelet plugs at sites of vascular injury under high shear stress. vWF is synthesized in vascular endothelial cells and megakaryocytes as a high-molecularweight polymer and is stored in the Weibel-Palade bodies. On stimulation, vWF is secreted by endothelial cells as ultra-large (UL) multimers that form string-like structures attached to the endothelial cells, possibly through interaction with P-selectin. Under fluid shear stress, the UL-vWF strings are cleaved to generate the range of vWF multimer sizes that normally circulate in the blood.59 The proteolytic cleavage of vWF multimers appears to be critical to prevent thrombosis in the microvasculature.

Liver-derived ADAMTS13 is the protease responsible for cleaving vWF, creating 140- and 176-kDa fragments (Fig. 30.9). ADAMTS13 is also expressed at lower levels in renal podocytes and tubular cells, vascular endothelial cells, and platelets. The plasma concentration of ADAMTS13 is approximately 1 μg/mL (5 nmol/L). The elimination half-life of ADAMTS13 is 1 to 2 days in the circulation.

Mechanisms

ADAMTS13 is severely deficient in patients with primary TTP, leading to accumulation of UL-vWF multimers that are highly reactive with platelets.60 Exposure of UL-vWF multimers and platelets to shear stress leads to platelet aggregation. vWF and platelets have a propensity to form aggregates at the levels of shear stress found in normal arterioles and capillaries, and this needs to be constantly regulated. By cleaving UL-vWF multimers before they are activated by shear stress to cause platelet aggregation, ADAMTS13 prevents spontaneous microvascular thrombosis in the normal circulation (see Fig. 30.9). The platelet aggregation observed in patients with TTP and ADAMTS13 deficiency is thus a direct consequence of the accumulation of UL-vWF multimers. Consequently, microvascular thrombi occur in almost all organ vessels, resulting in diffuse organ ischemia and thrombocytopenia secondary to platelet consumption.

Two mechanisms for deficiency of the ADAMTS13 activity include an acquired deficiency secondary to the formation of anti-ADAMTS13 autoantibodies (acquired TTP) and a genetic deficiency resulting from homozygous or compound heterozygous mutations in ADAMTS13 (genetic TTP; see Fig. 30.1).

TTP associated with Anti-ADAMTS13 antibodies. This form accounts for the majority of acute cases (60%–90%) and is characterized by severe functional deficiency of ADAMTS13 because of transient, specific autoantibodies that tend to disappear during remission, and this is paralleled by normalization of ADAMTS13 activity (see Fig. 30.1 and Table 30.1).[60] Patients with TTP secondary to malignancies or HIV infection rarely have severe ADAMTS13 deficiency and inhibitory IgG antibodies.[61] Severe ADAMTS13 deficiency and ADAMTS13 inhibitory antibodies were detected in 80% to 90% of patients with ticlopidine-associated TTP and in a few patients with clopidogrelinduced TTP (see Table 30.1). The deficiency resolved after the drugs were discontinued. TTP diagnosed during pregnancy—most frequently during the second and third trimesters—accounts for 10% to 30% of all adult cases of TTP.[49] Most of these cases have acquired ADAMTS13 deficiency, but pregnancy also has been reported as a triggering event in patients with genetic ADAMTS13 deficiency (see later discussion).

TTP associated with genetic deficiency of ADAMTS13. This shiftenterrare inherited form of TTP is associated with homozygous or compound heterozygous mutation in the ADAMTS13 gene and accounts for about 5% of all of cases of TTP (see Table 30.1). The disease is inherited as a recessive trait in patients with and without a family history of TTP[62]; more than 120 ADAMTS13 mutations have been identified. Studies on secretion and activity of the mutated forms of ADAMTS13 showed that most of these mutations led to impaired secretion of the protease from the cells, and when the mutated protein is secreted, the proteolytic activity is greatly reduced.

Most patients are carriers of compound heterozygous mutations; only 20% of mutations have been observed in homozygous form.

Clinical Course

Compared with patients with less severe ADAMTS13 deficiency, severely deficient patients experience a higher proportion of therapyinduced remissions (82%–88% vs. 20%–75%) and lower mortality (8%–18% vs. 18%–80%).[61] The high mortality risk in non–severely deficient patients may be because of the higher proportion of secondary causes and death from underlying diseases, such as patients with hematologic malignancies.

Among patients who have a severe ADAMTS13 deficiency, those with inhibitory antibodies experience more severe disease, take a substantially longer time to achieve clinical remission, and require a higher plasma volume than patients with genetic ADAMTS13 deficiency. In patients with inhibitory antibodies, up to 50% develop relapses and undetectable ADAMTS13 activity and persistence of anti-ADAMTS13 inhibitors during remission predict recurrences.

TTP has been reported in 1 in every 1600 to 5000 patients treated with ticlopidine, and 11 cases have been reported during treatment with clopidogrel. The overall survival rate is 67% and is improved by early treatment withdrawal and plasma therapy.

Approximately 60% of patients with genetic deficiency of ADAMTS13 experience their first acute TTP episode in the neonatal period or during infancy. A second group (10%–20%) manifests the disease after the third decade of life. TTP relapses occur in 80%

of patients, but their frequency varies widely. Whereas some patients

Pathophysiology of Platelet Aggregation in Thrombotic Thrombocytopenic Purpura
Platelet
Shear

ADAMTS13

Unfolded vWF

Vessel wall
Folded vWF

Platelet rolling

Platelet adhesion

Platelet adhesion and aggregation

Vessel wall
Shear

Platelet
Platelet

Unfolded vWF
Platelet

Vessel wall

Fig. 30.9 The Pathophysiology of Platelet Aggregation in Thrombotic Thrombocytopenic Purpura. Von Willebrand factor (vWF) is synthesized and stored as ultra-large (UL) multimers in endothelial cells and megakaryocytes. On stimulation, UL-vWF multimers are secreted by endothelial cells into the circulation in a folded structure. On exposure to enhanced shear stress, UL multimers form string-like structures that adhere to endothelial cells. Normally, UL-vWF strings are cleaved by ADAMTS13 to generate vWF multimers from 500 kDa to 20 million Da and prevent thrombosis in the microvasculature (upper panel). When the ADAMTS13 proteolytic activity is defective because of the inhibitory effect of anti-ADAMTS13 autoantibodies or congenital defective synthesis of the protease, UL-vWF multimers accumulate and interact with activated platelets to facilitate platelet adhesion and aggregation, with thrombi formation and occlusion of the vascular lumen (lower panel).

with genetic ADAMTS13 deficiency depend on frequent chronic plasma infusions to prevent relapses, others remain free of disease for long periods after plasma discontinuation. The type and location of ADAMTS13 mutations may influence the age of onset of TTP and the penetrance of the disease in mutation carriers. Mutations resulting in very low residual ADAMTS13 activity (<1%) were associated with childhood onset, relapsing disease, and kidney impairment.[8] Environmental factors may contribute to induce full-blown manifestation of the disease. According to this two-hit model, deficiency of ADAMTS13 predisposes to microvascular thrombosis and TMA supervenes after a triggering event that activates microvascular endothelial cells and causes the secretion of UL-vWF multimers. Potential triggers of these phenomena are infections and pregnancy.

Therapy

In patients with acquired TTP, plasma is the cornerstone of therapy in an acute episode because it replaces defective protease activity. Plasma exchange, compared with infusion, also rapidly removes antiADAMTS13 antibodies (see Table 30.2).

Because of the potential for sudden clinical deterioration, treatment should be initiated as soon as possible after diagnosis. Treatment consists of a daily 1 to 2 plasma volume exchanges until clinical symptoms have resolved and the platelet count is stably at least 150,000/μL. Fresh-frozen plasma and cryosupernatant plasma are considered equivalent because of comparable levels of ADAMTS13.

Corticosteroids (see Table 30.2) given in combination with plasma therapy may benefit autoimmune forms of TTP by inhibiting the synthesis of anti-ADAMTS13 autoantibodies; plasma exchange will have only a temporary effect on the autoimmune basis of the disease. Two randomized clinical trials (phase 2 TITAN study and phase 3 HERCULES trial) in patients with acquired TTP found that caplacizumab, an anti-vWF humanized single variable domain immunoglobulin (nanobody), combined with plasma exchange and immunosuppressive therapy (see later), was associated with a shorter time to normalization of the platelet count than plasma exchange and immunosuppression plus placebo.[63] Caplacizumab also improved thromboembolic event rate, death rate, and relapse rate in acquired TTP.[64] Caplacizumab reduces microvascular thrombosis by inhibiting interaction between vWF multimers and platelets, but it does not affect the production of anti-ADAMTS13 autoantibodies. Thus, plasma exchange and immunosuppressive treatment are still an essential part of TTP treatment.

Prospective studies have used rituximab (see Table 30.2) in patients who failed to respond to standard daily plasma exchange and methylprednisolone and in patients with relapsed acute TTP who previously had antibodies to ADAMTS13. Treatment was associated with clinical remission, disappearance of anti-ADAMTS13 antibodies, and increase of ADAMTS13 activity to levels greater than 10%. Time to remission has been variable, from 1 to 4 weeks after the first dose. The duration of remission has ranged between 9 months and 4 years, with relapses reported in approximately 10%. Rituximab also has been used electively to prevent relapses in patients with autoantibodies.[65] Longitudinal evaluation of ADAMTS13 activity and autoantibody levels may help monitor patient responses to treatment. Retreatment with rituximab should be considered when ADAMTS13 activity decreases and inhibitors reappear into the circulation to prevent a relapse.

In genetic forms of TTP, ADAMTS13 is constitutively lacking and can be replaced by plasma therapy. During acute episodes, patients often require plasma exchange. Providing enough ADAMTS13 to achieve 5% normal enzymatic activity may be sufficient to degrade large vWF multimers—which may induce remission of the microangiopathic process—and this effect is sustained over time. Infused ADAMTS13 has a plasma half-life of 2 to 3 days in vivo, and although plasma levels fall below 5% within 3 to 7 days after plasma administration, the effect of plasma on platelet counts and clinical parameters may last up to 3 weeks, suggesting that ADAMTS13 remains available, for example, on platelets and endothelial cells. Patients with genetic ADAMTS13 deficiency tend to relapse. Patients with frequent relapses, a severe clinical course with neurologic sequelae, kidney insufficiency, and siblings who have died of TTP should be put on regular prophylactic plasma infusions every 2 to 3 weeks, which prevents episodes of acute TTP and maintains the patients in good health for years. Recombinant ADAMTS13 has demonstrated efficacy in increasing ADAMTS13 activity in a phase I/II study in patients with genetic TTP. A phase III clinical trial is ongoing (NCT03393975).

SELF-ASSESSMENT QUESTIONS

1. Which are the common clinical features characterizing patients with thrombotic microangiopathies?
A. Thrombocytopenia and nonimmune hemolytic anemia, with or without neurologic and/or renal dysfunction
B. Diarrhea and kidney dysfunction
C. Anemia, antiplatelet antibodies, and purpura
D. Disseminated intravascular coagulation
2. Which is the most common form of thrombotic microangiopathy?
A. Atypical hemolytic uremic syndrome
B. Shiga toxin E. coli–associated hemolytic uremic syndrome
C. Thrombotic thrombocytopenic purpura
D. Antiphospholipid syndrome
3. Which is the most common genetic abnormality associated with aHUS?
A. C3 mutations
B. ADAMT13 mutations
C. CFH mutations
D. CFTR mutations
4. Which of the following is not indicated for treatment of aHUS?
A. Conservative therapy
B. Eculizumab
C. Plasma exchange
D. Antibiotics
5. For which of the following is there an indication for rituximab?
A. TTP with congenital ADAMTS13 deficiency
B. Shiga-toxin producing Escherichia coli–associated HUS
C. TTP with anti-ADAMTS13 antibodies
D. aHUS associated with MCP mutations

REFERENCES

1. Remuzzi G. HUS and TTP: variable expression of a single entity. Kidney Int. 1987;32(2):292–308.
2. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017;4(4):e157–e164.
3. Ruggenenti P, Remuzzi G. A German outbreak of haemolytic uraemic syndrome. Lancet. 2011;378(9796):1057–1058.
4. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009;361(17):1676–1687.
5. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv. 2017;1(10):590–600.
6. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood. 2000;96(4):1223–1229.
7. Arvidsson I, Stahl AL, Hedstrom MM, et al. Shiga toxin-induced complement-mediated hemolysis and release of complement-coated red blood cell-derived microvesicles in hemolytic uremic syndrome. J Immunol. 2015;194(5):2309–2318.
8. Rurali E, Banterla F, Donadelli R, et al. ADAMTS13 secretion and residual activity among patients with congenital thrombotic thrombocytopenic purpura with and without renal impairment. Clin J Am Soc Nephrol. 2015;10(11):2002–2012.
9. Remuzzi G, Ruggenenti P. Thrombotic microangiopathies. In: Tisher C, Brenner B, eds. Renal Pathology. Philadelphia: J.B. Lippincott; 1994:1154–1184.
10. Mead PS, Griffin PM. Escherichia coli O157:H7. Lancet. 1998;352(9135):1207–1212.
11. CDC. National Enteric Disease Surveillance: Shiga Toxin-Producing Escherichia Coli (STEC) Annual Report. US Department of Health and Human Services; 2016. CDC April 16, 2018.
12. European Food Safety Authority and European Centre for Disease Prevention and Control (EFSA and ECDC). The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017. J Eur Food Saf Auth. 2018;16(12):e05500.
13. Buelli S, Zoja C, Remuzzi G, Morigi M. Complement activation contributes to the pathophysiology of Shiga toxin-associated hemolytic uremic syndrome. Microorganisms. 2019;7(1). https://doi.org/10.3390/microorganisms7010015.
14. Morigi M, Galbusera M, Gastoldi S, et al. Alternative pathway activation of complement by Shiga toxin promotes exuberant C3a formation that triggers microvascular thrombosis. J Immunol. 2011;187(1):172–180.
15. Spinale JM, Ruebner RL, Copelovitch L, Kaplan BS. Long-term outcomes of Shiga toxin hemolytic uremic syndrome. Pediatr Nephrol. 2013;28(11):2097–2105.
16. Khalid M, Andreoli S. Extrarenal manifestations of the hemolytic uremic syndrome associated with Shiga Toxin-Producing Escherichia Coli (STEC HUS). Pediatr Nephrol Berl Ger. 2019;34(12):2495–2507.
17. Walsh PR, Johnson S. Treatment and management of children with haemolytic uraemic syndrome. Arch Dis Child. 2018;103(3):285–291.
18. Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI. The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections. N Engl J Med. 2000;342(26):1930–1936.
19. Nitschke M, Sayk F, Hartel C, et al. Association between azithromycin therapy and duration of bacterial shedding among patients with Shiga toxin-producing enteroaggregative Escherichia coli O104:H4. J Am Med Assoc. 2012;307(10):1046–1052.
20. Forrester A, Rathjen SJ, Daniela Garcia-Castillo M, et al. Functional dissection of the retrograde Shiga toxin trafficking inhibitor Retro-2. Nat Chem Biol. 2020;16(3):327–336.
21. Dundas S, Murphy J, Soutar RL, Jones GA, Hutchinson SJ, Todd WT. Effectiveness of therapeutic plasma exchange in the 1996 Lanarkshire Escherichia coli O157:H7 outbreak. Lancet. 1999;354(9187):1327–1330.

22. Carter AO, Borczyk AA, Carlson JA, et al. A severe outbreak of Escherichia coli O157:H7-associated hemorrhagic colitis in a nursing home. N Engl J Med. 1987;317(24):1496–1500.

23. Kielstein JT, Beutel G, Fleig S, et al. Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing E. coli O104:H4 induced haemolytic-uraemic syndrome: an analysis of the German STEC-HUS registry. Nephrol Dial Transplant. 2012;27(10):3807–3815.
24. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654–666.
25. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) controversies conference. Kidney Int. 2017;91(3):539–551.
26. Palma LMP, Sridharan M, Sethi S. Complement in secondary thrombotic microangiopathy. Kidney Int Rep. 2021;6(1):11–23.
27. Galbusera M, Noris M, Gastoldi S, et al. An ex vivo test of complement activation on endothelium for individualized eculizumab therapy in hemolytic uremic syndrome. Am J Kidney Dis. 2019;74(1):56–72.
28. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010;5(10):1844–1859.
29. Noris M, Ruggenenti P, Perna A, et al. Hypocomplementemia discloses genetic predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities. Italian Registry of Familial and Recurrent Hemolytic Uremic Syndrome/ Thrombotic Thrombocytopenic Purpura. J Am Soc Nephrol. 1999;10(2):281–293.
30. Merinero HM, García SP, García-Fernández J, Arjona E, Tortajada A, Rodríguez de Córdoba S. Complete functional characterization of diseaseassociated genetic variants in the complement factor H gene. Kidney Int. 2018;93(2):470–481.
31. Venables JP, Strain L, Routledge D, et al. Atypical haemolytic uraemic syndrome associated with a hybrid complement gene. PLoS Med. 2006;3(10):e431.
32. Durey M-A.D., Sinha A, Togarsimalemath SK, Bagga A. Anticomplement-factor H-associated glomerulopathies. Nat Rev Nephrol. 2016;12(9):563–578.
33. Marinozzi MC, Vergoz L, Rybkine T, et al. Complement factor B mutations in atypical hemolytic uremic syndrome-disease-relevant or benign? J Am Soc Nephrol. 2014;25(9):2053–2065.
34. Delvaeye M, Noris M, De Vriese A, et al. Thrombomodulin mutations in atypical hemolytic-uremic syndrome. N Engl J Med. 2009;361(4):345–357.
35. Bresin E, Rurali E, Caprioli J, et al. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol. 2013;24(3):475–486.
36. Arjona E, Huerta A, Goicoechea de Jorge E, Rodríguez de Córdoba S. Familial risk of developing atypical hemolytic-uremic syndrome. Blood. 2020;136(13):1558–1561.
37. Lemaire M, Frémeaux-Bacchi V, Schaefer F, et al. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. Nat Genet. 2013;45(5):531–536.
38. Noris M, Remuzzi G. Thrombotic microangiopathy after kidney transplantation. Am J Transplant. 2010;10(7):1517–1523.
39. Noris M, Ruggenenti P, Remuzzi G. Kidney transplantation in patients with atypical hemolytic uremic syndrome: a therapeutic dilemma (or not)? Am J Kidney Dis. 2017;70(6):754–757.
40. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013;368(23):2169–2181.
41. Zuber J, Frimat M, Caillard S, et al. Use of highly Individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2019;30(12):2449–2463.

42. Menne J. Is ravulizumab the new treatment of choice for atypical hemolytic uremic syndrome (aHUS)? Kidney Int. 2020;97(6):1106–1108.
43. Fakhouri F, Fila M, Hummel A, et al. Eculizumab discontinuation in children and adults with atypical haemolytic uremic syndrome: a prospective multicentric study. Blood. 2020. https://doi.org/10.1182/blood.2020009280.
44. Saland J. Liver-kidney transplantation to cure atypical HUS: still an option post-eculizumab? Pediatr Nephrol. 2014;29(3):329–332.

References

45. Coppo R, Bonaudo R, Peruzzi RL, et al. Liver transplantation for aHUS: still needed in the eculizumab era? Pediatr Nephrol Berl Ger. 2016;31(5):759–768.
46. Scobell RR, Kaplan BS, Copelovitch L. New insights into the pathogenesis of Streptococcus pneumoniae-associated hemolytic uremic syndrome. Pediatr Nephrol Berl Ger. 2020;35(9):1585–1591.
47. Bruel A, Kavanagh D, Noris M, et al. Hemolytic uremic syndrome in pregnancy and postpartum. Clin J Am Soc Nephrol. 2017;12(8):1237–1247.
48. Timmermans SAMEG, Damoiseaux JGMC, Werion A, Reutelingsperger CP, Morelle J, van Paassen P. Functional and genetic landscape of complement dysregulation along the spectrum of thrombotic microangiopathy and its potential implications on clinical outcomes. Kidney Int Rep. 2021;6(4):1099–1109.
49. Fakhouri F, Scully M, Provôt F, et al. Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group. Blood. 2020;136(19):2103–2117.
50. Timmermans SAMEG, Abdul-Hamid MA, Potjewijd J, et al. C5b9 formation on endothelial cells reflects complement defects among patients with renal thrombotic microangiopathy and severe hypertension. J Am Soc Nephrol. 2018;29(8):2234–2243.
51. Garg N, Rennke HG, Pavlakis M, Zandi-Nejad K. De novo thrombotic microangiopathy after kidney transplantation. Transplant Rev Orlando Fla. 2018;32(1):58–68.
52. Chapin J, Shore T, Forsberg P, Desman G, Van Besien K, Laurence J. Hematopoietic transplant-associated thrombotic microangiopathy: case report and review of diagnosis and treatments. Clin Adv Hematol Oncol HO. 2014;12(9):565–573.
53. Jodele S, Zhang K, Zou F, et al. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. Blood. 2016;127(8):989–996.
54. Le Clech A, Simon-Tillaux N, Provôt F, et al. Atypical and secondary hemolytic uremic syndromes have a distinct presentation and no common genetic risk factors. Kidney Int. 2019;95(6):1443–1452.

55. Cavero T, Rabasco C, López A, et al. Eculizumab in secondary atypical haemolytic uraemic syndrome. Nephrol Dial Transplant. 2017;32(3):466–474.
56. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet Lond Engl. 2010;376(9751):1498–1509.
57. Pisoni R, Ruggenenti P, Remuzzi G. Drug-induced thrombotic microangiopathy: incidence, prevention and management. Drug Saf. 2001;24(7):491–501.
58. Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact. Kidney Int. 2020;98(2):314–322.
59. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11–18.
60. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med. 1998;339(22):1585–1594.
61. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood. 2003;102(1):60–68.
62. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001;413(6855):488–494.
63. Mazepa MA, Masias C, Chaturvedi S. How targeted therapy disrupts the treatment paradigm for acquired TTP: the risks, benefits, and unknowns. Blood. 2019;134(5):415–420.

64. Hanlon A, Metjian A. Caplacizumab in adult patients with acquired thrombotic thrombocytopenic purpura. Ther Adv Hematol. 2020;11. 2040620720902904.
65. Bresin E, Gastoldi S, Daina E, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. Thromb Haemost. 2009;101(2):233–238.

SECTION V Diabetic Kidney Disease

31

Pathogenesis, Clinical Manifestations, and Natural History of Diabetic Kidney Disease

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INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of kidney failure in high-income countries. It can develop in the course of either type 1 or type 2 diabetes mellitus (DM). Type 1 diabetes (T1D) is an autoimmune disease characterized by antibody-mediated and cell-mediated destruction of pancreatic islets. T1D may occur at any age but usually presents before the age of 30 years. Type 2 diabetes (T2D) is characterized by a combination of insulin resistance and insulin deficiency. The metabolic syndrome (insulin resistance, visceral obesity, hypertension, hyperuricemia, and dyslipidemia) is often followed by T2D. For a long period, insulin resistance is compensated by increased insulin secretion, but a gradual decline in pancreatic β-cell mass and function finally culminates in hyperglycemia, and patients with T2D may require treatment with insulin. T2D is increasingly seen in younger adults, adolescents, and even children. Other types of DM include maturity-onset diabetes of the young, gestational diabetes, diabetes secondary to various metabolic disorders, and iatrogenic diabetes resulting from corticosteroid or other immunomodulatory treatments.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

Genetic and Environmental Factors

The risk of developing DKD is equal in T1D and T2D, and only 30% to 40% of patients with T1D or T2D will ultimately develop nephropathy. The prevalence of nephropathy in diabetic patients varies among different racial and ethnic groups such that it is relatively increased in African Americans, Native Americans, Mexican Americans, Polynesians, Aboriginal Australians, and urbanized South Asian immigrants in the United Kingdom compared with Whites. Although barriers to care likely account for some of these interpopulation differences, polygenetic factors likely also contribute.

Familial clustering of DKD has been reported in T1D and T2D and in White and non-White populations. In a person with T1D who has a first-degree relative with diabetes and nephropathy, the risk for development of DKD is 83%. The frequency is only 17% if there is a first-degree relative with diabetes but without nephropathy.[1] In T2D, familial clustering has been well documented in Pima Indians.[2] A familial determinant is also suggested by higher albumin excretion rates in offspring of patients with T2D with nephropathy. The risk is particularly high in the offspring if the mother had been hyperglycemic during pregnancy, perhaps because this causes reduced formation of nephrons (“nephron underdosing”) in the offspring.[3,4] Low birthweight and nephron underdosing are also associated with hypertension, metabolic syndrome, and perhaps DKD. Nephron underdosing[5] is believed to lead to compensatory glomerular hypertrophy and increased single-nephron glomerular filtration rate (GFR), thus aggravating glomerular injury in diabetes.

The risk for DKD does not follow simple mendelian inheritance, and multiple genes are presumably involved. In patients with T1D the estimate of heritability for nephropathy was 35%; however, replication studies did not identify any single genetic variances reaching whole-genome levels of significance.[6] Nevertheless, single nucleotide polymorphisms (SNPs) in the engulfment and cell motility 1 (ELMO1) gene have been associated with risk for DKD in several ethnic groups with T2D.[7-9] Gene polymorphisms with 300,000 SNPs were analyzed in a large T1D cohort (over 6000 individuals with T1D and their relatives) and recently identified the protein coding gene ARHGAP24, associated with focal glomerulosclerosis,10 as linked to DKD. Gene polymorphisms also may contribute to familial clustering.

Environmental factors, especially diet, may be involved in the pathogenesis of diabetes and DKD. One of the strongest risk factors is the intake of soft drinks containing added sugars such as sucrose or highfructose corn syrup. Fructose increases uric acid levels, a predictor for the development of T2D and potentially also DKD,11 probably via uric acid–induced oxidative stress and endothelial dysfunction. However, a randomized study with allopurinol in patients with T1D and early to moderate DKD failed to reduce the rate of progression despite lowering uric acid levels.12 Smoking is a strong risk factor for progression of DKD and may be related to hypoxia in the kidney. Other putative associations include sleep apnea,13 higher caloric intake, and lower levels of exercise.

Hemodynamic Changes

Hyperfiltration is common in early diabetes but can be corrected with good glycemic control. Increased GFR involves glucose-dependent effects causing afferent arteriolar dilation mediated by a range of vasoactive mediators, including insulin-like growth factor 1 (IGF-1), transforming growth factor-β (TGF-β1), vascular endothelial growth factor (VEGF), nitric oxide (NO), prostaglandins, and glucagon (Fig. 31.1). Over time, vascular disease of the afferent arteriole may result in permanent alterations in kidney autoregulation that favor glomerular hypertension. Kidney injury in DKD is caused not only by hemodynamic disturbances (e.g., hyperfiltration, hyperperfusion) but also by disturbed glucose homeostasis, and the two pathways interact. For example, shear stress increases glucose transport into mesangial cells by upregulation of specific glucose transporters. Furthermore, shear stress and mechanical strain resulting from altered glomerular hemodynamics trigger autocrine and paracrine release of cytokines and growth factors in the glomerulus.

DKD is also associated with tubular abnormalities in which angiotensin II (Ang II) causes hypertrophic proximal tubular growth and increased sodium reabsorption.14 Specific inhibition of the sodium glucose cotransporter-2 (SGLT2) in proximal tubular cells slowed progression of DKD, highlighting the role of tubuloglomerular feedback and glomerular hyperfiltration in DKD (see Chapter 32).15 shiftenterInsulin itself stimulated matrix production in proximal tubular epithelial cells (TECs), and deficiency of the insulin receptor specifically in proximal TECs protected against obesity-induced kidney disease,16 implicating a key role of elevated insulin levels in kidney disease progression.

Glomerular Changes

Kidney growth occurs early after the onset of diabetes. Glomerular enlargement is associated with increased mesangial cell number, hypertrophy, and increase of capillary loops, thus enhancing the filtration surface area. Renal tubular hypertrophy is primarily the result of TEC proliferation and hypertrophy.

Experimentally, avoidance of hyperglycemia prevents kidney hypertrophy. Hyperglycemia causes hypertrophy by stimulating growth factors in the kidney, including IGF-1, epidermal growth factor (EGF), plateletderived growth factor (PDGF), VEGF, TGF-β, and Ang II. Hyperglycemia also induces thrombospondin, a potent activator of latent TGF-β. Antagonizing TGF-β in diabetic patients, however, did not confer beneficial effects on kidney function or proteinuria.17 Similarly, inhibition of VEGF prevented glomerular hypertrophy in models of DKD and reduced albuminuria.18 Urine EGF levels are linked to progression of chronic kidney disease (CKD) of multiple etiologies, including DKD.19

The pathologic hallmarks of diabetic nephropathy (DN) are mesangial expansion, nodular diabetic glomerulosclerosis (the acellular Kimmelstiel-Wilson lesion), and diffuse glomerulosclerosis. Mesangiolysis likely plays a key role in cell loss and nodule formation. Increasing evidence suggests that local NO deficiency contributes to these histologic lesions, in particular nodule formation.

The mechanisms underlying the emergence of albuminuria start with widening of the glomerular basement membrane (GBM) with accumulation of type IV collagen and net reduction in negatively charged heparin sulfate proteoglycan (see the section Kidney

Nephron Changes in Diabetes and After Administration of an ACE Inhibitor or Angiotensin Receptor Blocker

Normal

ACE Inhibitors/Angiotensin
Receptor Blockers

Diabetes

Dilated
afferent arteriole

Constricted
efferent arteriole
(increased
pressure)

Glomerular loss

of proteins

Proximal tubule

Proteins stored in
cytoplasm cause cell
activation and inflammation

Proximal tubule

Glomerulus
Podocyte

Capsular
space

Basement membrane

Lumen of
tubule

Capillary endothelium
Proteins
stored in
cytoplasm

Capillary

Fig. 31.1 Comparison of normal nephron, nephron in diabetic kidney disease (DKD), and nephron in DKD after angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) administration. Note afferent vasodilation and efferent angiotensin II–mediated vasoconstriction in DKD causing glomerular hypertension, which is relieved by an ACE inhibitor and ARB therapy. Note also protein leakage into the filtrate and tubular loading, with endocytosed protein causing an inflammatory reaction that promotes interstitial fibrosis. This is reversed by ACE inhibitor/ARB treatment.

Decreased
pressure

Pathology). The expression of one permeability-controlling protein, nephrin, is abnormally low in DKD.18 Its transcription is suppressed by Ang II and restored by renin-angiotensin system (RAS) blockers. Apoptosis of podocytes is triggered by various factors, including Ang II and TGF-β, and adhesion of podocytes to the GBM is reduced by advanced glycation end products (AGEs)-induced suppression of neuropilin-1. Podocyte loss also follows hyperglycemia-induced reactive oxygen species (ROS) generation, causing podocyte apoptosis or detachment. ROS generation in podocytes may be largely mediated by Nox4,20,21 although other contributors of ROS have also been implicated. Migration of podocytes is also attenuated by the reduction of neuropilin-1, thereby preventing surviving podocytes from covering denuded areas of GBM, which promotes development of focal segmental glomerulosclerosis (FSGS).

Crosstalk between glomerular endothelial cells and podocytes involves activated protein C (APC), the formation of which is regulated by endothelial thrombomodulin and is reduced in diabetic mice.22 In DKD, thrombomodulin-dependent APC formation inhibits podocyte apoptosis.23 In cultured podocytes, administration of the adipocytespecific hormone adiponectin prevented high glucose–induced podocyte dysfunction. Endothelial cell dysfunction associated with altered fenestrations and glycocalyx may contribute to enhanced permeability. Adiponectin levels are low in patients with the metabolic syndrome or T2D, which may contribute to the development of albuminuria20; however, once diabetes is established, elevated adiponectin levels correlate with faster progression of disease. In advanced DKD, albuminuria evolves into nonselective proteinuria with high-molecular-weight serum proteins escaping the GBM with disrupted texture, gaps, and holes.

Tubular and Inflammatory Changes

Tubulointerstitial injury ultimately determines the rate of attrition of kidney function. In vitro studies demonstrate the pathogenic role of various diabetic substrates in promoting tubule hypertrophy, extracellular matrix (ECM) production, and inflammation,18 which is a complex process with a large number of interacting pathways that lead to a chronic inflammatory infiltrate, which includes macrophages and other immune cells that release cytokines and profibrotic factors and interact with intrinsic kidney cells to create a profibrotic microenvironment. Chemokines and their receptors, in particular monocyte chemotactic protein-1 (MCP-1/CCL2), RANTES/CCL5, IL-6, and tumor necrosis factor (TNF) receptors, as well as adhesion molecules (e.g., ICAM-1), contribute to persistent inflammation that triggers a profibrotic cascade in the kidney (Fig. 31.2).18,24 Glomerular cells, TECs, macrophages/lymphocytes, and fibroblasts/myofibroblasts all contribute to matrix accumulation along the glomerular and tubular basement membranes and within the interstitium. Myofibroblasts promote progression of fibrosis in DKD by facilitating deposition of interstitial ECM (Fig. 31.3). Soluble TNF receptors appear to be a robust biomarker for progressive kidney disease in both T1D and T2D. Th17 immune cells and their effector cytokine IL-17A take part in diabetes-mediated kidney damage and could be a promising therapeutic target.25

Bardoxolone methyl, as an inducer of the KEAP1-Nrf2 pathway, exhibits antiinflammatory effects. Although the BEACON trial was terminated due to safety concerns about early heart failure, a post hoc analysis26 revealed reduction in albuminuria coupled to estimated glomerular filtration rate (eGFR) reduction. The Japanese TSUBAKI study trial showed that bardoxolone methyl increased GFR among 65 patients with T2D and stage 3 or 4 CKD versus placebo.27 The oral CCR2 inhibitor CCX140-B for 52 weeks reduced residual albuminuria in subjects with T2D.28 The FIDELIO-DKD study29 found that finerenone, a nonsteroidal blocker of the mineralocorticoid receptor (half-life ~2 hours and without metabolites), reduced the rate of progression of DKD in T2D without causing hyperkalemia. Any beneficial effects of finerenone may be mediated by reductions in inflammation, as its blood pressure lowering effects were minimal.

Clinical studies showed that even mild anemia (hemoglobin level <12.5 g/dL for men, <11.5 g/dL for women) increases the risk for progression of DKD. Anemia presumably causes kidney hypoxia. Moreover, hypoxia is exacerbated by the progressive hyalinosis of the afferent and efferent arterioles and loss of peritubular capillaries. In experimental chronic kidney injury, hypoxia is an important factor aggravating interstitial fibrosis. The transition of TECs into fibroblasts is stimulated by cellular hypoxia.30 The induction of growth factors and cytokines is mediated by hypoxia-inducible factor-1 (HIF-1), which can be amplified by Ang II. However, the TREAT trial31 showed that anemia treatment with darbepoetin-alfa initiated at a hemoglobin level of around 10.5 g/dL does not slow the rate of GFR loss in both diabetic and nondiabetic CKD.

Hyperglycemia

Role of Glucose Control

The following clinical evidence sheds light on the role of tight glycemic control in slowing the development of DKD:

✓ • ✓ In the Diabetes Control and Complications Trial (DCCT), there was a remarkable reduction in progression from normoalbuminuria to moderately increased albuminuria and other microvascular complications, specifically, retinopathy, in patients with T1D with tight glycemic control.32

✓ • ✓ Euglycemia that followed isolated pancreatic transplantation was associated with regression of diabetic glomerulosclerosis after 10 years.33

✓ • ✓ In the United Kingdom Prospective Diabetes Study (UKPDS), reducing the hemoglobin A1c (HbA1c) level by approximately 0.9% in patients with T2D reduced the risk for microvascular complications, including nephropathy.34

✓ • ✓ In the ADVANCE study, intensive glucose control with a target HbA1c level of 6.5% was associated with a long-term reduction in kidney failure, without evidence of any increased risk for cardiovascular events or death.35

✓ • ✓ In the EMPA-REG study, individuals with type 2 diabetes treated with empagliflozin with lower glycated hemoglobin levels had significant reduction in cardiovascular and kidney events, though the protective effects of the SGLT2 inhibitor are likely beyond simply glycemic control.15

✓ • ✓ In the CREDENCE trial,36 canagliflozin reduced the risk of kidney failure and cardiovascular events among 4401 individuals with type 2 diabetes with an eGFR of 30 to 90 mL/min per 1.73 m2 and albuminuria 300 to 5000 mg/g after a median follow up of 2.62 years. These benefits were consistent across eGFR subgroups, including those initiating treatment at eGFR 30 to 45 mL/min per 1.73 m2.37

✓ • ✓ In the DAPA-CKD trial,38 dapagliflozin conferred kidney and cardiovascular protection among patients with diabetic and nondiabetic CKD with eGFR 25 to 75 mL/min per 1.73 m2 and albuminuria 200 to 5000 mg/g, suggesting that the clinical benefits of SGLT2i are a class effect that extends to people with CKD. The larger EMPA-KIDNEY trial (NCT03594110), which recruited patients with eGFR down to 20 mL/min/1.73 m2 will further address the latter possibility.

A unifying theory was that hyperglycemia leads to diabetic complications through an accumulation of mitochondrial superoxide production and oxidative sequelae.39 As the kidneys are highly active metabolically and require vast amounts of adenosine triphosphate (ATP) for their normal function, they are

Diabetic milieu
High glucose
levels
Advanced
glycation
end products

Recruitment of bone
marrow–derived
monocytes

Macrophage

Kidney injury
Cytokines and
chemokines

Differentiation
of monocytes
Infiltration of
macrophages

Inflammatory responses

Release of DAMPs
DAMPs

NF-κB, MAPK and
TGF-β pathways

Adhesion
molecules

Kidney fibrosis

Activation of PRRs and
cell surface receptors

Fig. 31.2 Crosstalk Between Endothelial Cells and Podocytes Involving Protein C. Under physiologic conditions, protein C is activated by the binding of thrombin to its cofactor, thrombomodulin, on glomerular endothelial cells. The formed complex catalyzes the conversion of protein C to its catalytically activated form, which has potent anticoagulant, profibrinolytic, antiinflammatory, and cytoprotective effects. In DKD, the production of activated protein C (APC) in the glomerulus is reduced because of suppression of thrombomodulin expression. Decreased functional activity of APC affects the permeability of the glomerular capillary wall and enhances apoptosis of glomerular endothelial cells and podocytes. (From Gilbert RE, Marsden PA. Activated protein C and diabetic nephropathy. N Engl J Med. 2008;358:1628–1630.)

Hypothesis of the Development of EMT Contributing to Interstitial Fibrosis
Resident fibroblast

Adhesion molecules

Cytokines
Tubulointerstitial

fibrosis

Extracellular
matrix

Tubule

Metastable cell

Tubule

TGF-β1

EMT

Basement
membrane

A

Loss of epithelial
adhesion
Disruption of basement
membrane
Epithelial cells
Induction of
mesenchymal markers
De novo α-SMA
synthesis

≈ 36%*

TGF-β1

B

Interstitial
myofibroblasts
MMP2

C

Fig. 31.3 Hypothesis of the Development of Epithelial-Mesenchymal Transition (EMT) Contributing to Interstitial Fibrosis. Initiated by external stimuli (e.g., cytokines), tubular cells lose their cell-cell contacts (e.g., E-cadherin) (A) and start to express mesenchymal markers (e.g., α-SMA, vimentin) (B). After disruption of tubular basement membrane (by MMP2), metastable cells disengage themselves from cell connective and transdifferentiate to interstitial myofibroblasts that synthesize extracellular matrix and contribute to fibrosis (C). MMP, Matrix metalloproteinase; SMA, smooth muscle actin; TGF-β1, transforming growth factor-β1.

*Up to 36% of all interstitial myofibroblasts in diabetic kidney disease are thought to derive from EMT. (Modified from Loffler I. Pathophysiology of diabetic nephropathy. In: Wolf G, ed. Diabetes and Kidney Disease. Wiley-Blackwell; 2013.)

Formation of Advanced Glycation End-Products
Glucose + R–NH2
(Proteins, lipids)
Schiff base

Reversible
Amadori product
Inhibitors of AGE
cross-links (e.g.,
phenacylthiazolium
bromide)

Inhibitors of AGE
formation (e.g.,
aminoguanidine)

Irreversible

AGEs

AGE receptors
Cleaved
AGEs
Nephropathy

Fig. 31.4 Mechanism of formation of advanced glycation end-products (AGEs).

mitochondrially rich. Diabetes alters the delivery of substrates and oxygen to the kidneys, and changes in metabolic fuel sources to meet ATP demands result in increased oxygen consumption, which contributes to kidney hypoxia. Mitochondrial fission and fusion events enable energy demands to be met and provide mitochondrial quality control. Disruption of these events in diabetes reduces mitochondrial biogenesis, as reflected by a deficiency of the master regulator of mitochondrial biogenesis peroxisome proliferatoractivated receptor γ coactivator 1α 40 Restoring mitochondrial biogenesis and mitochondrial superoxide levels is associated with reduced inflammation, albuminuria, and fibrosis in experimental DKD.41 The protective effect of SGLT2 inhibitors may be mediated by normalizing mitochondrial function,42 and enhancing SIRT1 and hypoxia inducible factor 2α (HIF-2α) signaling43 that can explain the biologic consequences of ketonemia and erythrocytosis. Recent studies using urine metabolomics have identified that mitochondrial dysfunction plays a role in progression of DKD,44-46 and one recent clinical study47 demonstrated that SGLT2 inhibitors have beneficial effects on markers of mitochondrial function. There is likely an important role for hepatic ketone generation in response to SGLT2 inhibition, which may be a preferential fuel for kidney proximal TECs and cardiac myocytes.

Pathways Related to Glucose Metabolism

Protein kinase C (PKC) is a family of serine-threonine kinases that regulate diverse vascular functions. PKC-α mediates diabetic podocyte injury via phosphorylation of p66SHC and its inhibition by Klotho overexpression attenuated podocyte injury and proteinuria in streptozocin-treated mice.48 Protein kinase C–η mediates advanced oxidation protein product–induced mitochondrial dysfunction and oxidative stress in kidney tubular cells.49

Chronic hyperglycemia leads to nonenzymatic glycation of amino acids and proteins (Maillard or Browning reaction)50 (Fig. 31.4).

AGEs are increased in the serum, glomeruli, and tubules of DKD patients. They bind to macrophages, mesangial cells, and tubular cells and mediate cellular actions, including expression of adhesion molecules, cell hypertrophy, ECM synthesis, epithelial-mesenchymal transition (EMT), and inhibition of NO synthetase (NOS). AGEs injected in vivo induce albuminuria and glomerulosclerosis.50 AGEs induce podocyte hypertrophy, followed by apoptosis and suppression of nephrin synthesis. Among several binding sites, the most important is RAGE (receptor for advanced glycation end product), which is present in tubular cells and podocytes. Ang II stimulates upregulation of RAGE on podocytes.51 This effect is mediated by Ang II (AT2) receptors not blocked by sartanes.51 One of the actions of RAGE is activation of nuclear factor-κB (NF-κB). The soluble extracellular domain of RAGE (sRAGE) acts as a decoy receptor and experimentally ameliorates kidney lesions in diabetes.50 In T1D, sRAGE is associated with progression from severely increased albuminuria to kidney failure, though causality could not be established.52 In T2D, sRAGE is an early predictor of renovascular complications.53

Blocking the binding of AGEs to its receptor using a RAGEaptamer could inhibit tubular injury in diabetic mice partly by suppressing the AGE-RAGE-oxidative stress axis and improving insulin resistance independent of glycemic control.54 A selective RAGE inhibitor, FPS-ZM1, combined with valsartan alleviated podocyte injury in streptozocin-treated rats by restoring nephrin and synaptopodin expression and lowering albuminuria and serum cystatin C.55

The AGE/RAGE interaction upregulated myo-inositol oxygenase (MIOX), a tubule-specific enzyme modulating redox balance, to induce ROS generation and NF-κB activation to cause tubulointerstitial injury.56 Dietary supplementation of d-glucarate in diabetic mice decreased MIOX expression, attenuated tubular damage, and improved kidney function by attenuating mitochondrial fragmentation, oxidative stress, and apoptosis and restoring autophagy/mitophagy in tubular cells.57 In transgenic models, MIOX overexpression accentuated, whereas its knockdown protected the diabetic kidney in mice from tubulointerstitial injury.58

Finally, some fructose-6-phosphate is diverted into the hexosamine pathway, increasing the concentrations of N-acetylglucosamine, which modifies certain transcription factors, such as Sp1 activity. In turn, Sp1 upregulates key fibrotic mediators, such as TGF-β1 and plasminogen activator inhibitor 1.

Adenosine Monophosphate Kinase

The energy-sensing enzyme 5 -adenosine monophosphate kinase (AMPK) shiftenterpathway may contribute to DKD. Inhibition of 5 -AMP-activated protein kinase in caloric-excess states has been linked to inflammation (NF-κB, nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, monocyte chemotactic protein-1 [MCP-1] stimulation), vascular dysfunction (endothelial NOS inhibition), stimulation of hypertrophy (mammalian target of rapamycin complex [activation]), and profibrotic pathways (TGFβ signaling).59-61 Stimulation of AMPK is beneficial in both type 1 and type 2 models of DKD. Key regulators of mitochondrial healthadenosine monophosphate kinase, sirtuins, and PCG1α (peroxisome proliferator-activated receptor γ coactivator-1α) have all been shown to play significant roles in the resilience of the kidney against disease.62

Activation of Innate Immunity

Diabetes can be considered a metabolic danger signal that is effected via toll-like receptors (TLRs), a conserved family of pattern recognition

receptors that play a fundamental role in innate immunity.24 In particular, TLR-4 is overexpressed in the kidney tubules of human DN biopsies.63 64 In vitro, silencing TLR-4 ameliorated high glucose–induced tubular cell inflammation. In experimental DKD, either systemic deletion or the application of a TLR-4 antagonist conferred renoprotection.64 In addition, TLRs are also expressed in other resident kidney cell types such as podocytes and mesangial cells, as well as infiltrating macrophages, that could act in concert to bring about an inflammatory phenotype observed in DKD (Fig. 31.5). The NLRP3 inflammasome links sensing of metabolic stress in the diabetic kidney to activation of proinflammatory cascades via the induction of IL-1β and IL-18. The kallikrein-kinin system promotes inflammatory processes via the generation of bradykinins and the activation of bradykinin receptors, and activation of protease-activated receptors on kidney cells by coagulation enzymes contributes to kidney inflammation and fibrosis in DKD.

A key component of innate immunity includes the NADPH oxidase pathway, expressed primarily in the lysosomes of phagocytic cells, but also in the kidney. Enhanced Nox4 in podocytes may contribute to glomerular disease involving a pathway linking Nox to the citric acid cycle.65

Complement has been increasingly implicated in DKD. Increased levels of C5a were detected in kidney tubules from patients with biopsy confirmed DN and its intensity correlated with the progression of the disease.66 In experimental DKD, genetic deletion of C5aR1 in mice conferred protection against diabetes-induced kidney injury and in vitro, C5a/C5aR propagated injury during DKD by disrupting mitochondrial agility.67

Role of TLRs in Diabetic Kidney Disease

Fig. 31.5 Role of Toll-like Receptors (TLRs) in Diabetic Kidney Disease. Toll-like receptors in resident kidney cells could recognize and respond to the metabolic stress of diabetes or endogenous ligands activated during the diabetic state, inducing downstream signaling events to propagate the synthesis of proinflammatory cytokines and chemokines, which act as effectors to further facilitate macrophage recruitment and fibroblast proliferation, leading to a self-perpetuating cycle of kidney inflammation and subsequent tubulointerstitial fibrosis and glomerulosclerosis. AMPK, 5'-Adenosine monophosphate kinase; HMGB1, highmobility group box-1 protein; S100A8, S100 calcium binding protein A8. (Modified from Lin M, Yiu WH, Wu HJ, et al. Toll-like receptor 4 promotes tubular inflammation in diabetic nephropathy. J Am Soc Nephrol. 2012;23:86–102.)

Lipotoxicity

Lipotoxicity is increasingly implicated in the pathogenesis of DKD. In obesity, a myriad of metabolic disturbances including chronic systemic low-grade inflammation and insulin resistance are directly or indirectly associated with not only obesity, but also other metabolic diseases like metabolic syndrome, obesity-related T2D, nonalcoholic fatty liver disease, and cardiovascular disease. Animal and in vitro studies have identified saturated fatty acids as the dominant nonesterified fatty acids in the circulation of obese subjects that act as nonmicrobial agonists to trigger the inflammatory response via activating TLR4 signaling.68 Increased lipogenesis predicted DKD in T2D.69 In experimental DKD, kidney VEGF-B expression correlates with the severity of disease and inhibiting its signaling reduces kidney lipotoxicity, resensitizes podocytes to insulin signaling, inhibits the development of diabetic pathologies, and prevents kidney dysfunction.70

Epigenetics and Epigenomics

Epigenetic mechanisms involve chromatin histone modifications, DNA methylation, and noncoding RNAs.71 The first miRNA shown to have a functional role in DKD was miR-192, which acts by targeting key repressors to promote the expression of ECM and collagen and to augment the profibrotic effects of TGF-β1. Numerous miRNAs are now thought to regulate key features of DKD, such as podocyte apoptosis, ECM accumulation, glomerular and tubular hypertrophy, and fibrosis.

LncRNAs are long transcripts (>200 nucleotides and up to ~100 kb in length) that have many similarities with mRNAs but lack protein-coding (translation) potential. They have distinct cellular roles that affect various biologic mechanisms and processes. These mechanisms can respond to changes in the environment and mediate persistent expression of DKD-related genes and phenotypes induced by prior exposure to the diabetic milieu despite subsequent glycemic control, a phenomenon called metabolic memory. A number of lncRNAs could play a pivotal role in development and progression of DKD either via direct involvement or as indirect mediators of nephropathic pathways, such as TGF-β1, NF-κB, STAT3, and GSK3β signaling. Some lncRNAs may therefore become biomarkers for early diagnosis or prognosis of DKD or as therapeutic targets for DKD.

Gut Microbiome

Among patients with T2D with normoalbuminuria or moderately or severely increased albuminuria, the levels of phenyl sulfate, a gut microbiota–derived metabolite, significantly correlated with basal and predicted 2-year progression of albuminuria in patients with moderately increased albuminuria.72 In experimental diabetes, phenyl sulfate administration induced albuminuria and podocyte damage, and inhibition of tyrosine phenol-lyase, a bacterial enzyme responsible for the synthesis of phenol from dietary tyrosine before it is metabolized into phenyl sulfate in the liver, reduces albuminuria. Applying broad-spectrum oral antibiotics or fecal microbiota transplantation from healthy donors to diabetic rats decreased serum acetate levels and alleviated tubulointerstitial injury,73 suggesting that gut microbiota reprogramming might become a new strategy for DKD.

Renin-Angiotensin-Aldosterone System and Diabetic Kidney Disease

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) slow progression of DKD (see Chapter

32). Although plasma renin activity is low in DKD, it is inappropriate in relation to increased extracellular volume and exchangeable sodium, suggesting activation of the RAS.74 In experimental diabetes, sites of local RAS activation have been identified in glomeruli and TECs.74 High glucose and AGEs stimulate angiotensinogen and renin expression in various kidney cells, mainly through ROS.74 Proteinuria further activates the local RAS of tubular cells.

Ang II has many nonhemodynamic effects and mediates cell proliferation, hypertrophy, ECM expansion, and cytokine (TGF-β, VEGF) synthesis.74 Therefore, ACE inhibitors and ARBs presumably act via hemodynamic and nonhemodynamic actions.

Aldosterone accelerates progression in kidney damage models independently of Ang II. In DKD, aldosterone escape has been linked to progression of proteinuria (see Chapter 32). Aldosterone synthesis is stimulated in DKD, and this steroid hormone stimulates the synthesis of other proinflammatory and profibrogenic cytokines (MCP1, shiftenterTGF-β).75 The beneficial effects of the mineralocorticoid receptor blocker finerenone is likely mediated via its antiinflammatory action.

Other vasoactive agents involved in the pathogenesis of DKD include endothelin, NO, the kallikrein-kinin system, and natriuretic peptides. The SONAR trial76 showed that the selective endothelin-A receptor antagonist atrasentan, administered to 1325 T2D patients with eGFR 25 to 75 mL/min/1.73 m2 and albuminuria 300 to 5000 mg/g creatinine versus 1323 placebo control subjects reduced the risk of kidney events after a median follow-up of 2.2 years, though at an increased risk of fluid retention and anemia.

Uric Acid and Fructose

An elevated uric acid level can predict the development of DKD. Uric acid is generated during the metabolism of fructose when it induces mitochondrial oxidative stress. In addition to dietary fructose from added sugars, there is increasing evidence that in diabetes, fructose is generated in the kidney, where it is metabolized to uric acid that may mediate kidney injury. Thus, both dietary and endogenous production of fructose may be involved in the development of diabetes and its complications.77 Lowering of serum urate levels with allopurinol among 267 individuals with T1D with DKD versus 263 placebo control subjects in the PERL12 (Preventing Early Renal Function Loss) trial, however, did not affect kidney outcomes.

EPIDEMIOLOGY

The US Renal Data System 2020 Annual Report (www.USRDS.org) revealed in 2018 that DKD was the most frequent primary diagnosis accounting for 47.1% of incident patients being started on kidney replacement therapy. The China Kidney Disease Network (CKD-NET) 2016 Annual Data Report78 published in 2020 revealed DKD to be the top cause of CKD, accounting for 26.7% of CKD.

The proportion of diabetes among patients with kidney failure varies considerably among countries, but in many countries DKD is the leading cause of kidney failure.79 Classic features of DKD were observed in about 60% of diabetic patients (i.e., normal kidney size despite kidney failure; proteinuria >1 g/2 h with or without retinopathy); 13% had an atypical presentation with ischemic nephropathy, and in 27% a known primary kidney disease coexisted with diabetes. An important mode of presentation has become irreversible acute kidney injury (AKI), for example, after administration of nonsteroidal antiinflammatory drugs (NSAIDs), cardiac events, and septicemia. Many patients also lose the clinical manifestations

Current and Projected Cases of Diabetes by Region
750
700

55%

South and Central America

650

143%

Africa

600

33%

North America/Caribbean

96%

Middle East/North Africa

15%

Europe

74%

Southeast Asia

31%

Western Pacific

550
500
(In millions)

450
400
350
300
250
200
150
100
50
0
2019
2045

Fig. 31.6 Predicted Increase in Diabetes Prevalence by Geographic Region Over the Next Two Decades. The rate of increase is greatest in the developing world. (Modified from Saeedi P, Petersohn I, Salpea P, et al.; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes

Res Clin Pract. 2019;157:107843.)

of overt diabetes (e.g., hyperglycemia) because of CKD-associated weight loss, impaired kidney gluconeogenesis, or increased insulin half-life in CKD.

The proportion of patients with T1D and T2D who develop proteinuria and elevated serum creatinine concentration is related to the duration of diabetes. Diabetes and its complications caused an estimated 4.2 million deaths worldwide in 2019, of which half occurred in patients below the age of 60, and more than half were caused by increased risks for cardiovascular and other diseases. There is a more rapid increase in the prevalence of T2D in lower-income versus higher-income regions: 4 out of 5 people with diabetes live in low- and middle-income countries, and these countries are predicted to experience the greatest surge in diabetes over the next 25 years (Fig. 31.6).80

For example, the prevalence of diabetes from 2019 is predicted to increase by 143% in Africa, 74% in Southeast Asia, and 55% in South and Central America by 2045 versus 33% in North America, 15% in Europe, and 31% in the Western Pacific. In Africa and the Middle East/ North Africa, 75% and 50% of deaths due to diabetes were in people younger than 60 years, respectively. In Asia, high mortality from diabetes is most prominent in patients aged 50 to 60 years, which translates to a reduction in life expectancy of more than a decade. Up to 60% of Asian patients with diabetes have elevated albuminuria, compared with 30% to 40% reported in Western diabetic populations in crosssectional surveys.81

CLINICAL MANIFESTATIONS AND NATURAL HISTORY

Diabetic kidney disease is part of a generalized microvascular and macrovascular disease.

Obesity, Metabolic Syndrome, and Kidney Disease

The metabolic syndrome—defined by the presence of three or more of certain factors (increased waist circumference, elevated triglycerides, decreased high-density lipoprotein, elevated blood pressure [BP], and elevated fasting blood glucose concentration)—is increasingly recognized as a major contributor to cardiovascular diseases with a negative impact on kidney function.82 83 Obesity is often defined as body mass index greater than 30, although different values define obesity in other countries (e.g., China, India, Japan). Obese individuals have large kidneys and glomerulomegaly, with increased kidney blood flow, increased filtration fraction, and glomerular hyperfiltration.84 Obese patients have moderate albuminuria even in the absence of hypertension. The resemblance of obesity-related kidney disease to early DKD is striking. In addition, sleep apnea, which is common in obese individuals, leading to hypoxic episodes, may contribute to kidney impairment. Visceral adipocytes are a potent source of deleterious factors85 and could have an impact on kidney function (Ang II, leptin, TNF-α). By contrast, the secretion and

31.1). Williams[87] proposed a scheme of the natural history and pathophysiology of nephropathy typically observed in T2D over a period of 20 years (Fig. 31.7).

Mogensen[88] proposed a scheme of the different stages of DKD that is largely valid in T1D but less reliable in T2D. In the latter, CKD may occur in the absence of albuminuria, possibly as a result of macrovascular disease. Of note, with improved glycemic and BP control there is a growing population of patients with T1D with normoalbuminuria who have progressive DKD.[87] In this cohort, progressive kidney function decline, not albuminuria, is the predominant clinical feature. The putative mechanisms that initiate and sustain progressive kidney function decline in T1D are not well known. In clinical practice, annual eGFR decline is expected to be within 5 mL/min/1.73 m2 while on a RAS blocker, and further investigation and more frequent monitoring are warranted for attrition rates above this level.

plasma concentration of adiponectin, an adipokine with cardiovascular protective, antidiabetic, and antiinflammatory properties, are markedly decreased in obesity and its related pathologies (see the section Glomerular Changes). Thus, kidney changes may occur years before the manifestation of T2D during obesity and the development of the metabolic syndrome.

Evolution of Diabetic Kidney Disease

One of the earliest changes of kidney function in patients with T1D and many with T2D is an increase in GFR, or hyperfiltration, which is accompanied by an increase in kidney size. The next observable change is the development from normal (<30 mg albumin/24 h) to moderately increased albuminuria (30-300 mg albumin/24 h or 30 to 300 mg/g or 3 to 30 mg/mmol creatinine, graded as A2 by the Kidney Disease: Improving Global Outcomes [KDIGO] nomenclature[86]), previously termed microalbuminuria. This may progress to severely increased albuminuria (>300 mg albumin/24 h or >300 mg/g or >30 mg/mmol creatinine; graded as A3 by KDIGO), previously termed macroalbuminuria (Table

TABLE 31.1

Hypertension and Diabetic Kidney Disease

In patients with T2D, hypertension often precedes the onset of diabetes by years. At diagnosis of T2D, an abnormal BP and an abnormal circadian BP profile are found in 80% of patients. Prediabetic hypertension increases the risk for onset and progression of DKD. The onset of DKD in T2D further increases BP, though this relationship is generally much less than in T1D. The pathogenesis of hypertension in T2D is complex and involves RAS activation, direct sympathetic nerve activation, and macrovascular changes.[89] Furthermore, genetic factors defining primary hypertension as well as diabetes are clustered (Fig. 31.8).

In DKD, nocturnal BP decrease is frequently attenuated, and this nondipping phenomenon may precede the onset of moderately increased albuminuria.[89] Furthermore, BP responses to exercise tend to be exaggerated. Stiffening of the aorta increases the peak systolic pressure and decreases the diastolic pressure, resulting in increased BP amplitude, which explains why isolated systolic hypertension is so common in patients with T2D.[90] Low diastolic pressure increases

Classification of Albuminuria

URINE ALBUMIN EXCRETION

<30
30–300

<30
30–300

<3
3–30

A1
A2

>300

>300

>30

A3

Natural History of Diabetic Nephropathy
Onset of
diabetes
Primary
prevention

Secondary
prevention

Tertiary
prevention
Proteinuria (albuminuria)

GFR

Kidney
failure

160
Hyperfiltration
GFR (mL/min)

Condition
Normoalbuminuria
Moderately
increased
albuminuria
Severely increased
albuminuria

SPOT URINE
24-hr
Urine
(mg/mmol
(mg/day) (mg/g Cr) Cr)
Category

110

6
5
4

Onset of

nephropathy

3

Azo

60

tem

Moderately
increased albuminuria

20
0

5

2

ia

1
10

15

20

25

Urine protein excretion (g/24 h)

Categories

371

30

Years of diabetes

Fig. 31.7 Natural History of Diabetic Nephropathy. Changes in glomerular filtration and proteinuria over time from the onset of diabetes. Proteinuria reduction is shown as a tertiary prevention. GFR, Glomerular filtration rate. (From Krolewski AS. Progressive renal decline: the new paradigm of diabetic nephropathy in type 1 diabetes. Diabetes Care. 2015;38[6]:954–962.)

Potential Mechanisms Leading to Hypertension in Type 2 Diabetes

Exogenous factors

Genetic factors

Obesity

Type 2 diabetes

Insulin resistance,
hyperleptinemia

Hyperglycemia

Sympathic
activation

Microvasculopathy

Proportion of Type 2 Diabetic Patients With Progression of Nephropathy According to Categories of Blood Pressure

100
80

Dyslipidemia

Macrovasculopathy

Angiotensin II

Progression (%)

60
40
20
0

Hypertension

Fig. 31.8 Overview of Potential Mechanisms Leading to Hypertension in Patients With Type 2 Diabetes. Genetic susceptibility factors for primary hypertension and diabetes may be clustered so that an individual patient may have a higher incidence of both diseases. Obesity and metabolic syndrome lead to insulin resistance and hyperleptinemia associated with sympathetic nerve activation. Hyperglycemia directly activates the renin-angiotensin system and, in addition, stimulates development of hypertension through kidney microvasculopathy. Dyslipidemia leads to stiffness of vessels and hypertension through macrovasculopathic alteration.

the risk for coronary events because coronary perfusion occurs during diastole only.91 Augmented pulse pressure and impaired nocturnal BP decline are independent predictors of nephropathy progression in T2D (Fig. 31.9). The increased prevalence of sleep apnea in DKD also contributes to hypertension.92

Associated Extrarenal Microvascular and Macrovascular Complications

Diabetic retinopathy is present in virtually all patients with T1D and albuminuria from DN. In contrast, only 50% to 60% of proteinuric patients with T2D have retinopathy.93 94 Consequently, the absence of retinopathy does not exclude the diagnosis of DN in patients with T2D.94 In patients with DN, retinopathy tends to progress more rapidly, hence more frequent ophthalmologic monitoring is needed.

Many patients with DN also have polyneuropathy. Sensory polyneuropathy is an important cause of the diabetic foot, which correlates with loss of kidney function. Because cardiac innervation is defective, pain and angina are frequently absent when the patient has coronary heart disease and myocardial infarction. Further consequences of autonomic polyneuropathy are gastroparesis and diarrhea or constipation (see Chapter 89). Erectile impotence and detrusor paresis with delayed and incomplete emptying of the bladder are common urologic problems.

The major macrovascular complications associated with DKD are stroke, coronary heart disease, and peripheral vascular disease,95 96 with a fivefold higher frequency than diabetic patients without DKD.

<85.0

Diasto

lic nigh

t:day B

≥85.0
P ratio

(%)

.5
≥57
g)
5
.
7
mH
<5
P (m
P
24 h

Fig. 31.9 Proportion of Patients With Type 2 Diabetes With Progression of Nephropathy According to Categories of Blood Pressure (BP). Progression risk according to categories of nighttime to daytime diastolic BP (median value <85% or ≥85%) and 24-hour ambulatory pulse pressure (PP) (median value <57.5% or ≥57.5%). (From Knudsen ST, Laugesen E, Hansen KW, et al. Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients. Diabetologia. 2009;52:698–704.)

Survival in Patients With Diabetic Kidney Disease

The presence of DKD greatly increases mortality in patients with both T1D and T2D. Compared with the general population, mortality in patients with T1D and no proteinuria is elevated by two- to threefold, which increased to 20-fold to 200-fold with proteinuria.97 98

The major increase in risks occurs not only with the onset of albuminuria (Fig. 31.10) but also in the upper normal range of albuminuria (Fig. 31.11). Urinary albumin excretion is a good predictor of cardiovascular events.98 Albuminuria likely reflects generalized endothelial cell dysfunction with an increased risk for atherosclerosis98 and other associated cardiovascular risk factors, such as elevated BP, dyslipoproteinemia, increased platelet aggregation, and increased C-reactive protein concentration. Other biomarkers for progressive DKD have been described including soluble TNFR1 or TNFR2,99 and other urine metabolites such as aconitic acid and 3-hydroxyisobutyrate.45

KIDNEY PATHOLOGY

After the onset of diabetes, kidney weight increases by an average of 15%. Kidney size remains increased until overt nephropathy is established. Most patients with T1D have a sustained increase in glomerular volume and glomerular capillary luminal volume. These changes are accompanied by hypertrophy of the interstitium.100

In patients having diabetes for more than 10 years, regardless of whether nephropathy is present, GBM thickening up to three times the normal range of 270 to 359 nm is common (Fig. 31.12). In advancing DKD, there is a consistent correlation between GBM thickness and fractional mesangial volumes with albuminuria.

Mortality (all causes)

<16 mg
Albuminuria/24 h

0.99
0.98
>16 mg
Albuminuria/24 h
Baseline UAE

0.97
0.96
0.95
0.94

1.0

Low UAE

Normoalbuminuria

0.9

High UAE

0.93

0.8

Moderately
increased albuminuria

0.7

Severely increased
albuminuria

0.6
0.5

1.00

0

1

3
4
5
6
Years

Fig. 31.10 Influence of Microalbuminuria and Macroalbuminuria on Mortality. The influence of microalbuminuria and macroalbuminuria on mortality was evaluated prospectively in 328 White patients with non–insulin-dependent diabetes mellitus observed for 5 years. Microalbuminuria and macroalbuminuria led to a significant increase in total mortality compared with that in patients who remained normoalbuminuric. (From Gall MA, Borch-Johnsen K, Hougaard P, et al. Albuminuria and poor glycemic

control predict mortality in NIDDM. Diabetes. 1995;44:1303–1309.)

A

2

Follow-up UAE

Impact of Moderately and Severely Increased Albuminuria on Mortality

Cardiovascular Morbidity and Mortality After Follow-up Screening in the PREVEND Study

CV event–free survival (%)

Nodular glomerular intercapillary lesions in advanced DKD were described in 1936 by Kimmelstiel and Wilson (Fig. 31.13C).101 The nodules are located in the central regions of peripheral glomerular lobules as well-demarcated eosinophilic and periodic acid–Schiff–positive masses (see Fig. 31.13C–D). When they are not acellular, nodules contain pyknotic nuclei. It is suggested that nodules result from microaneurysmal dilation of the associated capillary followed by mesangiolysis and laminar organization of the mesangial debris with lysis of the center of the lobule. Foam cells often surround the nodules. These appearances, reported in only 10% to 50% of biopsy specimens in both T1D and T2D, are also seen in diseases with a membranoproliferative glomerulonephritis pattern (see Chapter 22), in amyloidosis and light-chain deposition disease (see Chapter 28), and specific stains and immunofluorescence findings, respectively, will clarify the diagnosis.

0

400

800
1200
Follow-up (days)
Fig. 31.11 Event-Free Survival for Cardiovascular (CV) Morbidity and Mortality After Follow-up Screening in the PREVEND Study. Individuals are stratified according to the presence of a high or low urinary albumin excretion (UAE). High and low UAE are defined by either the UAE measurement from the baseline screening (orange and purple lines) of approximately 4.2 years before follow-up screening or the repeated UAE measurement at time of the follow-up screening (blue and green lines). To allow comparison, the survival curves for the 6800 individuals with either the baseline or follow-up measurement of UAE are plotted in the same graph. A high UAE (dashed lines) is defined as a UAE ≥16.2 mg/24 h, being the 75th percentile of UAE with use of the UAE measurement of the baseline screening. (From Brantsma AH, Bakker SJ, de Zeeuw D, et al; PREVEND Study Group. Extended prognostic value of urinary albumin excretion for cardiovascular events. J Am Soc Nephrol. 2008;19:1785–1791.)

B
Fig. 31.12 Electron Microscopy of Structural Changes in Diabetic Nephropathy. (A) Glomerular basement membranes are diffusely thickened. (B) The expanded mesangium encroaches on the capillary spaces (arrows).

A

B

C

D

Fig. 31.13 Light Microscopy of Glomerular Changes in Diabetic Kidney Disease. (A) Normal glomerulus. (B) Diffuse glomerular lesion. Widespread mesangial expansion. (C) Nodular lesion and mesangial expansion. There is a typical Kimmelstiel-Wilson nodule at the top of the glomerulus (arrow). (D) Nodular lesion. Methenamine silver staining shows the marked nodular expansion of mesangial matrix. (A–C, Periodic acid–Schiff reaction.)

5μm
5μm

Normal Rat
Diabetic Rat

Fig. 31.14 Electron Micrograph of External Surface of Glomerular Tufts From Rats After Removal of Bowman's Capsule by Freeze Fracture. Left, Normal rat kidney with podocyte cell body; the primary processes and terminal foot processes resting on the glomerular capillary basement membrane are seen clearly. Right, In the diabetic rat kidney, the decrease in the density of foot processes and the denuded glomerular capillary basement membrane are apparent. (From Marshall SM. The podocyte: a major player in the development of diabetic nephropathy? Horm Metab Res. 2005;37[suppl 1]:9–16.)

Diffuse glomerular lesions occur more often than nodular lesions, seen in 90% of patients with T1D greater than 10 years and in 25% to 50% of T2D patients. They consist of an increase of mesangial matrix extending to involve the capillary loops (see Fig. 31.13B). In contrast to nodular lesions, which are of little functional significance, the degree of diffuse glomerulosclerosis and in particular mesangial matric expansion correlates with worsening kidney function.102 In more severe disease, capillary wall thickening and mesangial expansion lead to capillary narrowing (see Fig. 31.12B) and hyalinization, with accompanying periglomerular fibrosis.

Podocytes are involved early in the course of DKD in T1D and T2D (Fig. 31.14), and an increase in foot process width is already observed with only slight increases in albuminuria.103 104 Longitudinal studies demonstrated a reduction in podocyte number that closely correlated with proteinuria.103

Arteriolar lesions are prominent in diabetes. Hyaline material progressively replaces the entire wall structure and involves both the afferent and efferent vessels, which is highly specific for diabetes.

A new classification of DN was introduced in 2007. This classification considers not only glomerular changes (Fig. 31.15) but also pathologic alterations of the tubulointerstitium and vasculature.105

Immunohistologic examination is usually negative, but linear immunoglobulin G (IgG) can be seen occasionally because of passive trapping in the GBM (Fig. 31.16).

Tubulointerstitial fibrosis and tubular atrophy may be the best pathologic correlates for progressive decline in GFR. Tubulointerstitial fibrosis and renal arteriolosclerosis are more prevalent in T2D than

A

B

C

D

E

F

G

H

Fig. 31.15 Pathologic Classification of Diabetic Kidney Disease (DKD). Representative examples of the morphologic lesions in DKD. (A) Glomerulus showing only mild ischemic changes, with splitting of Bowman's capsule. No clear mesangial alteration. (B) Electron micrograph of this glomerulus. The mean width of the glomerular basement membrane was 671 nm (mean taken over 55 random measurements). Electron microscopy provides the evidence for classifying the biopsy with only mild light microscopy changes into class I.

(C–D) Class II glomeruli with mild and moderate mesangial expansion, respectively. In part C, the mesangial expansion does not exceed the mean area of a capillary lumen (IIa), whereas in part D it does (IIb). (E–F) A class III Kimmelstiel-Wilson lesion is seen in part F. The lesion in part E is not a convincing Kimmelstiel-Wilson lesion; therefore, on the basis of the findings in this glomerulus, the finding is consistent with class IIb. For the purpose of the classification, at least one convincing Kimmelstiel-Wilson lesion (as in F) needs to be present. (G) Example of glomerulosclerosis that does not reveal its cause (glomerulus from same biopsy as H).

(H) Signs of class IV DKD consist of hyalinosis of the glomerular vascular pole and a remnant of a KimmelstielWilson lesion on the opposite site of the pole. For the purpose of the classification, signs of DKD should be histopathologically or clinically present to classify a biopsy with global glomerulosclerosis in more than 50% of glomeruli as class IV. (From Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21:556–563.)

Fig. 31.16 Immunofluorescence for Glomerular Immunoglobulin G (IgG) in Diabetic Nephropathy.
Faint staining of the glomerular basement membrane (GBM) for IgG results from passive trapping of IgG in the expanded GBM. (Courtesy Prof. Peter Furness, Leicester, UK.)

T1D. In fact, kidney structure is heterogeneous in patients with T2D; only a subset of patients with T2D have typical diabetic glomerulopathy, whereas others have more advanced tubulointerstitial and vascular rather than glomerular lesions or have normal or near-normal kidney structure,[105] or even features suggestive of glomerular ischemia.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of DKD is based on the detection of proteinuria. In addition, most patients also have hypertension and retinopathy. The main evaluation procedures in the patient with suspected DKD include:

- Measurement of urinary albumin or protein
- Measurement of serum creatinine concentration and estimation of GFR
- Measurement of BP
- Ophthalmologic examination

Measurement of Albuminuria or Proteinuria

There is substantial individual day-to-day variation in albumin excretion (coefficient of variation, 30%–50%) and day and night differences (Fig. 31.17). Even in the upper quantiles of so-called normoalbuminuria, the risk for progression and cardiovascular events is elevated. At concentrations of 30 to 300 mg/24 h, albumin is normally not detected by conventional dipsticks for proteinuria. Albumin can be detected by special dipsticks for moderately increased albuminuria or by a suitable laboratory assay. A first-void morning urine sample is preferred. The normal range is less than 20 µg/mL.

The detection of urinary albumin is a specific indicator of DN only if confounding factors such as fever, physical exercise, urinary tract infection, nondiabetic kidney disease, hematuria from other causes, heart failure, uncontrolled hypertension, and uncontrolled hyperglycemia have been excluded.[106]

The main advantage of testing for moderately increased albuminuria early is that it predicts a high kidney and cardiovascular risk and thus allows targeted intervention. The American Diabetes Association, KDIGO, and others recommend annual testing of albumin-tocreatinine ratio (more costly) or protein-to-creatinine ratio.

By definition, there is clinically overt DKD (or severely increased albuminuria) if the rate of albumin excretion exceeds 300 mg/day. At this point, serum proteins other than albumin are usually excreted in the urine as well (nonselective proteinuria).

Measurement of Blood Pressure

The following points should be noted:

- In overweight T2D patients, the size of the cuff should be adapted to the upper arm circumference. When this exceeds 32 cm, cuffs of 18 cm width are indicated.
- Patients with severe autonomic neuropathy tend to develop orthostatic hypotension, defined as a decrease of systolic BP by more than 20 mm Hg in the upright position.
- The circadian BP profile tends to be abnormal in the early stages, and even a paradoxical increase in nocturnal BP is not rare. In DKD patients, increase in nocturnal BP is independently associated with a 20-fold higher mortality and a higher risk for kidney failure.

Ambulatory BP recordings are useful to assess the efficacy of antihypertensive treatment.

✓•✓ In diabetic patients with sclerosis or calcification of the radial and brachial arteries, there may be pseudohypertension characterized by spuriously elevated BP despite normotension upon intraarterial BP measurements with a discrepancy between mild target organ damage (e.g., left ventricular hypertrophy) and very high measured BP values. Such patients tend to develop marked hypotension even with modest antihypertensive therapy.

Measurement of Serum Creatinine and Estimation of Glomerular Filtration Rate

Serum creatinine concentration may be inaccurate in cachexic patients with low muscle mass. This problem is particularly frequent in elderly patients with T2D. KDIGO recommends reporting estimated GFR in adults using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.

Differential Diagnosis

Although hematuria is one of the atypical features indicating the presence of nondiabetic kidney disease in patients with diabetes, it may be present in DKD. Moreover, a study identified hematuric patients with pathologically defined DKD, who had significantly lower kidney function than nonhematuric patients with DKD.107 The prevalence of nephrotic

1000

1000

100

100

First day 24 h (μg/min)

Night UAE (μg/min)

Circadian Variation of Urinary Albumin Excretion

10

10

1

1
1

10

100

1000

1

Day UAE (μg/min)

10

100

1000

Second day 24 h (μg/min)
Primary hypertension

Type 1 diabetes

Fig. 31.17 Circadian Variation of Urinary Albumin Exretion (UAE). UAE is lower in resting conditions at night (left) than during daytime activity (right). Relationship between UAE assessed on two different days 1 week apart in patients with type 1 diabetes (open circles) and primary hypertension (closed circles). There is substantial individual day-to-day variation of albumin excretion and also between day and night collections.
(From Redon J. Measurement of microalbuminuria: what the nephrologist should know. Nephrol Dial Transplant. 2006;21:573–576.)

Pathologic Diagnoses Other Than Diabetic Nephropathy
30.0
24.8%

25.0
21.0%
Cases (%)

20.0
15.3%

15.0

12.9%

10.0

8.9%

8.0%
5.6%

5.0
0

FSGS

MCD

Pauci

MGN

SLE

IgAN

4.0%

Mes

Other

Fig. 31.18 Pathologic Diagnoses Other Than Diabetic Nephropathy Are Found in More Than Half of Patients With Type 2 Diabetes With Proteinuria. A total of 233 patients were studied; 53.2% (124 patients) had a diagnosis of nondiabetic kidney disease. FSGS, Focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; Mes, mesangial immune complex glomerulonephritis; MGN, membranous nephropathy; Pauci, ANCA-positive pauci-immune glomerulonephritis; SLE, systemic lupus erythematosus. (From Pham TT, Sim JJ, Kujubu DA, et al. Prevalence of nondiabetic renal disease in diabetic patients. Am J Nephrol. 2007;27:322–328.)

syndrome and retinopathy was significantly higher in hematuric patients than in nonhematuric patients with diabetic glomerulosclerosis.

On the other hand, other forms of kidney disease may be found in patients with T2D. Younger patients with diabetes, shorter duration of diabetes, and proteinuria without retinopathy may suggest nondiabetic kidney disease.108 Membranous nephropathy, FSGS, acute interstitial nephritis, postinfectious GN, and IgA nephropathy have all been described in patients with T2D in whom DKD was clinically suspected (Fig. 31.18).

Clinical Evaluation of Diabetic Kidney Disease
Diabetes and proteinuria

Exclude urinary tract infection
Signs and symptoms of nondiabetic kidney disease
Urine microscopy: Red cells, white cell casts (?)
Quantitate proteinuria
Kidney ultrasound
Serology if glomerulonephritis suspected ANCA,
double-stranded DNA antibodies, C3, C4
Serum protein electrophoresis if age >50 y

Typical diabetic kidney disease
Type 1 diabetes for >10 years
Retinopathy
Previous moderately increased
albuminuria
No macroscopic hematuria
No red cell casts
Enlarged kidneys on ultrasound

Atypical
Type 1 diabetes for <10 years
No retinopathy
Nephrotic-range proteinuria
without progression through
moderately increased
albuminuria
Macroscopic hematuria
Red cell casts

No kidney biopsy

Kidney biopsy

Atypical
Azotemia with proteinuria <1 g/day
Papillary necrosis (pyuria,
hematuria, scarring)
Tuberculosis (pyuria, hematuria)
Renovascular disease (other
occlusive vascular disease)

No kidney biopsy

Fig. 31.19 Clinical evaluation of diabetic kidney disease. ANCA, Antineutrophil cytoplasmic antibody.

Indications for Kidney Biopsy

Further investigation, including kidney biopsy, should be considered in the following situations[109] (Fig. 31.19):

✓•✓ If retinopathy is not present in T1D with proteinuria or moderately impaired kidney function (absence of retinopathy does not exclude DKD in T2D).

✓•✓ If the onset of proteinuria has been sudden and rapid, and the duration of T1D less than 5 years. Alternatively, if the evolution has been atypical, for example, without transition through the usual stages, particularly the development of nephrotic syndrome without previous moderately increased albuminuria.

✓•✓ If there is macrohematuria or an active nephritic urinary sediment including acanthocytes or red blood cell casts; the sediment in DKD typically is not more than occasional erythrocytes.

- If the decline in kidney function is exceptionally rapid after excluding reversible causes of AKI such as infection, drugs, and obstruction, or if kidney dysfunction is found without significant proteinuria (first, renovascular disease must be excluded) (Fig. 31.20).
- If there are signs and symptoms suggestive of a nondiabetic cause for kidney disease.

If kidney ultrasound reveals small kidneys or a significant size difference, it is prudent not to perform a kidney biopsy. Recent initiatives by the National Institutes of Health (NIH)-funded Kidney Precision Medicine Project are assessing biopsies from patients with DN to determine whether a multiomic approach with single cell transcriptomics, proteomics, and spatial metabolomics could provide new insights in humans.

Approach to the Diabetic Patient With Impaired Kidney Function

When seeing a diabetic patient with CKD, the nephrologist should:

- Assess the cause of CKD (acute vs. chronic kidney impairment; DKD vs. alternative causes of kidney damage).

Fig. 31.20 Glomerulonephritis Superimposed on Diabetic Kidney Disease (DKD). A glomerulus showing a cellular crescent with rupture of the Bowman’s capsule superimposed on nodular DKD. The patient, known to have diabetic nephropathy, presented with rapidly deteriorating kidney function and red cell casts in the urine.

- Assess the magnitude of proteinuria and the rate of progression.
- Search for typical extrarenal microvascular and macrovascular complications of diabetes.

The majority of diabetic patients with heavy proteinuria or kidney failure have DKD. Kidney ischemia (atherosclerotic kidney artery stenosis or cholesterol embolism) is common in diabetic patients, and many patients with T2D have small kidneys and low GFR without albuminuria, possibly from macrovascular disease.

If urinary tract infection occurs, it is more severe in the diabetic than the nondiabetic patient. Purulent papillary necrosis and intrarenal abscess formation have now become rare.

Diabetic patients with nephropathy are particularly prone to development of AKI after administration of NSAIDs or radiocontrast media or after cardiovascular events or septicemia. Preventive measures for

AKI are discussed in Chapter 74. AKI superimposed on preexisting DKD carries a poor kidney prognosis.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements about diabetic nephropathy is correct?
A. The pathophysiology for diabetic nephropathy is different in T1D and T2D.
B. Glomerulosclerosis, tubular atrophy, and tubulointerstitial lesions are typical pathologic findings in diabetic nephropathy.
C. Development of diabetic nephropathy is always associated with microalbuminuria.
D. Development of diabetic nephropathy is always associated with hypertension.
2. Which of the following is not a risk factor for the development of diabetic kidney disease?
A. Genetic background
B. Hyperglycemia
C. Smoking

D. Anemia
E. Type of diabetes
3. Which of the following findings may suggest a nondiabetic origin of the kidney disease?
A. Proteinuria greater than 2 g/day
B. Large kidneys on ultrasound
C. Increased serum creatinine
D. Acanthocytes in urine sediment
4. Which of the following observations suggests inflammation is a feature in diabetic kidney disease?
A. Increased transforming growth factor-β levels
B. Inflammasome activation in the diabetic kidney
C. Markedly elevated C-reactive protein and ferritin levels
D. Peripheral leukocytosis
E. Presence of urinary red and white cell casts

REFERENCES

1. Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease: evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med. 1989;320:1161–1165.
2. Nelson RG, Knowler WC, Pettitt DJ, et al. Diabetic kidney disease in Pima Indians. Diabetes Care. 1993;16:335–341.
3. Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes. 1998;47:1489–1493.
4. Amri K, Freund N, Van Huyen JP, et al. Altered nephrogenesis due to maternal diabetes is associated with increased expression of IGF-II/mannose-6-phosphate receptor in the fetal kidney. Diabetes. 2001;50:1069–1075.
5. Zandi-Nejad K, Luyckx VA, Brenner BM. Adult hypertension and kidney disease: the role of fetal programming. Hypertension. 2006;47:502–508.
6. Sandholm N, Van Zuydam N, Ahlqvist E, et al. FinnDiane Study Group., Tuomilehto J, Lyssenko V, McKeigue PM, et al; DCCT/EDIC Study Group., Florez JC, Hirschhorn JN, Maxwell AP; GENIE Consortium., Dunger D, Cobelli C, Colhoun HM, et al; SUMMIT Consortium.. The Genetic Landscape of Renal Complications in Type 1 Diabetes. J Am Soc Nephrol . 2017;28:557–574.
7. Mehrabzadeh M, Pasalar P, Karimi M, et al. Association between elmo1 gene polymorphisms and diabetic nephropathy in an iranian population. J Diabetes Metab Disord. 2016;15:43.
8. Bodhini D, Chidambaram M, Liju S, et al. Association of rs11643718 SLC12A3 and rs741301 elmo1 variants with diabetic nephropathy in south indian population. Ann Hum Genet. 2016;80(6):336–341.
9. Wu HY, Wang Y, Chen M, et al. Association of elmo1 gene polymorphisms with diabetic nephropathy in Chinese population. J Endocrinol Invest. 2013;36(5):298–302.
10. Haukka J, Sandholm N, Valo E, FinnDiane Study Group, et al. Novel linkage peaks discovered for diabetic nephropathy in individuals with type 1 diabetes. Diabetes. 2021;70(4):986–995.
11. Mauer M, Doria A. Uric acid and risk of diabetic kidney disease. J Nephrol. 2020;33(5):995–999.
12. Doria A, Galecki AT, Spino C, PERL Study Group, et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382(26):2493–2503.
13. Dong M, Guo F, Zhou T, Wei Q. Association of diabetic nephropathy with the severity of obstructive sleep apnea-hypopnea syndrome in patients with type 2 diabetes mellitus. Endocr J. 2020;67(5):515–522.
14. Satriano J, Vallon V. Primary kidney growth and its consequences at the onset of diabetes mellitus. Amino Acids. 2006;31:1–9.
15. Wanner C, Inzucchi SE, Lachin JM, et al. Empa-reg outcome investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–334.
16. Lee HJ, Mariappan MM, Norton L, et al. Proximal tubular epithelial insulin receptor mediates high-fat diet-induced kidney injury. JCI Insight. 2021;6(3):e143619.
17. Voelker J, Berg PH, Sheetz M, et al. Anti-tgf-β1 antibody therapy in patients with diabetic nephropathy. J Am Soc Nephrol. 2017;28(3):953–962.
18. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest. 2014;124(6):2333–2340.
19. Ju W, Nair V, Smith S, ERCB, C-PROBE, NEPTUNE, and PKUIgAN Consortium, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med. 2015;7(316):316ra193.
20. Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest. 2008;118(5):1645–1656.
21. Jha JC, Thallas-Bonke V, Banal C, et al. Podocyte-specific Nox4 deletion affords renoprotection in a mouse model of diabetic nephropathy. Diabetologia. 2016;59(2):379–389.

22. Isermann B, Vinnikov IA, Madhusudhan T, et al. Activated protein C protects against diabetic nephropathy by inhibiting endothelial and podocyte apoptosis. Nat Med. 2007;13:1349–1358.

23. Gilbert RE, Marsden PA. Activated protein C and diabetic nephropathy. N Engl J Med. 2008;358:1628–1630.
24. Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020;16(4):206–222.
25. Lavoz C, Matus YS, Orejudo M, et al. Interleukin-17A blockade reduces albuminuria and kidney injury in an accelerated model of diabetic nephropathy. Kidney Int. 2019;95(6):1418–1432.
26. Rossing P, Block GA, Chin MP, et al. Effect of bardoxolone methyl on the urine albumin-to-creatinine ratio in patients with type 2 diabetes and stage 4 chronic kidney disease. Kidney Int. 2019;96(4):1030–1036.
27. Nangaku M, Kanda H, Takama H, et al. Randomized clinical trial on the effect of bardoxolone methyl on GFR in diabetic kidney disease patients (TSUBAKI study). Kidney Int Rep. 2020;5(6):879–890.
28. de Zeeuw D, Bekker P, Henkel E, et al. CCX140-B diabetic nephropathy study group. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. Lancet Diabetes Endocrinol. 2015;3(9):687–696.
29. Bakris GL, Agarwal R, Anker SD, et al. Fidelio-dkd investigators. effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–2229.
30. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17:17–25.
31. Pfeffer MA, Burdmann EA, Chen CY, et al. Treat Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–2032.
32. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986.
33. Fioretto P, Steffes MW, Sutherland DE, et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med. 1998;339:69–75.
34. UK Prospective Diabetes Study (UKPDS) Group. Intensive bloodglucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–853.
35. Wong MG, Perkovic V, Chalmers J, et al. Advance-on collaborative group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: advance-on. Diabetes Care. 2016;39(5):694–700.
36. Perkovic V, Jardine MJ, Neal B, et al. Credence trial investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–2306.
37. Jardine MJ, Zhou Z, Mahaffey KW, et al. Credence study investigators. Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: a secondary analysis of the CREDENCE randomized trial. J Am Soc Nephrol. 2020;31(5):1128–1139.
38. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapa-Ckd trial committees and investigators. dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446.
39. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–820.
40. Forbes JM, Thorburn DR. Mitochondrial dysfunction in diabetic kidney disease. Nat Rev Nephrol. 2018;14(5):291–312.
41. Miyamoto S, Zhang G, Hall D, et al. Restoring mitochondrial superoxide levels with elamipretide (MTP-131) protects db/db mice against progression of diabetic kidney disease. J Biol Chem. 2020;295(21):7249–7260.
42. Afsar B, Hornum M, Afsar RE, et al. Mitochondrion-driven nephroprotective mechanisms of novel glucose lowering medications.

Mitochondrion. 2021;58:72–82.

43. Packer M. Role of impaired nutrient and oxygen deprivation signaling and deficient autophagic flux in diabetic ckd development: implications for understanding the effects of sodium-glucose cotransporter 2-inhibitors. J Am Soc Nephrol. 2020;31(5):907–919.

44. Sharma K, Karl B, Mathew AV, et al. Metabolomics reveals signature of mitochondrial dysfunction in diabetic kidney disease. J Am Soc Nephrol. 2013;24(11):1901–1912.

45. Kwan B, Fuhrer T, Zhang J, et al. CRIC study investigators. Metabolomic markers of kidney function decline in patients with diabetes: evidence from the chronic renal Insufficiency cohort (CRIC) study. Am J Kidney Dis. 2020;76(4):511–520.
46. Liu JJ, Liu S, Gurung RL, et al. Urine tricarboxylic acid cycle metabolites predict progressive chronic kidney disease in type 2 diabetes. J Clin Endocrinol Metab. 2018;103(12):4357–4364.
47. Mulder S, Heerspink HJL, Darshi M, et al. Effects of dapagliflozin on urinary metabolites in people with type 2 diabetes. Diabetes Obes Metab. 2019;21(11):2422–2428.
48. Jiang W, Xiao T, Han W, et al. Klotho inhibits PKCα/p66SHCmediated podocyte injury in diabetic nephropathy. Mol Cell Endocrinol. 2019;494:110490.
49. Li X, Xu L, Hou X, et al. Advanced oxidation protein products aggravate tubulointerstitial fibrosis through protein kinase C-dependent mitochondrial injury in early diabetic nephropathy. Antioxid Redox Signal. 2019;30(9):1162–1185.
50. Bohlender JM, Franke S, Stein G, Wolf G. Advanced glycation end products and the kidney. Am J Physiol Renal Physiol. 2005;289:F645–F659.
51. Rüster C, Bondeva T, Franke S, et al. Angiotensin II upregulates rage expression on podocytes: role of AT2 receptors. Am J Nephrol. 2009;29:538–550.
52. Wadén JM, Dahlström EH, Elonen N, et al. Finndiane study group. soluble receptor for age in diabetic nephropathy and its progression in finnish individuals with type 1 diabetes. Diabetologia. 2019;62(7):1268–1274.
53. Farhan SS, Hussain SA. Advanced glycation end products (AGEs) and their soluble receptors (sRAGE) as early predictors of reno-vascular complications in patients with uncontrolled type 2 diabetes mellitus. Diabetes Metab Syndr. 2019;13(4):2457–2461.
54. Sotokawauchi A, Matsui T, Higashimoto Y, et al. DNA aptamer raised against receptor for advanced glycation end products suppresses renal tubular damage and improves insulin resistance in diabetic mice. Diab Vasc Dis Res. 2021;18(1).
55. Sanajou D, Ghorbani Haghjo A, Argani H, et al. FPS-ZM1 and valsartan combination protects better against glomerular filtration barrier damage in streptozotocin-induced diabetic rats. J Physiol Biochem. 2018;74(3):467–478.
56. Sharma I, Tupe RS, Wallner AK, Kanwar YS. Contribution of myoinositol oxygenase in age:rage-mediated renal tubulointerstitial injury in the context of diabetic nephropathy. Am J Physiol Renal Physiol. 2018;314(1):F107–F121.
57. Zhan M, Usman IM, Sun L, Kanwar YS. Disruption of renal tubular mitochondrial quality control by Myo-inositol oxygenase in diabetic kidney disease. J Am Soc Nephrol. 2015;26(6):1304–1321.
58. Sharma I, Deng F, Liao Y, Kanwar YS. Myo-inositol oxygenase (MIOX) overexpression drives the progression of renal tubulointerstitial injury in diabetes. Diabetes. 2020;69(6):1248–1263.
59. Declèves AE, Mathew AV, Cunard R, Sharma K. AMPK mediates the initiation of kidney disease induced by a high-fat diet. J Am Soc Nephrol. 2011;22:1846–1855.
60. Eid AA, Ford BM, Block K, et al. AMP-activated protein kinase (AMPK) negatively regulates Nox4-dependent activation of p53 and epithelial cell apoptosis in diabetes. J Biol Chem. 2010;285:37503–37512.
61. Lee MJ, Feliers D, Mariappan MM, et al. A role for amp-activated protein kinase in diabetes-induced renal hypertrophy. Am J Physiol Renal Physiol. 2007;292:F617–F627.
62. Clark AJ, Parikh SM. Targeting energy pathways in kidney disease: the roles of sirtuins, ampk, and PGC1α. Kidney Int. 2020;(20):31412–31415.

S0085-2538.
63. Verzola D, Cappuccino L, D’Amato E, et al. Enhanced glomerular Tolllike receptor 4 expression and signaling in patients with type 2 diabetic nephropathy and microalbuminuria. Kidney Int. 2014;86(6):1229–1243.
64. Lin M, Yiu WH, Wu HJ, et al. Toll-like receptor 4 promotes tubular inflammation in diabetic nephropathy. J Am Soc Nephrol. 2012;23(1):86–102.

65. You YH, Quach T, Saito R, et al. Metabolomics reveals a key role for fumarate in mediating the effects of nadph oxidase 4 in diabetic kidney disease. J Am Soc Nephrol. 2016;27(2):466–481.
66. Yiu WH, Li RX, Wong DWL, et al. Complement C5a inhibition moderates lipid metabolism and reduces tubulointerstitial fibrosis in diabetic nephropathy. Nephrol Dial Transplant. 2018;33(8):1323–1332.
67. Tan SM, Ziemann M, Thallas-Bonke V, et al. Complement C5a induces renal injury in diabetic kidney disease by disrupting mitochondrial metabolic agility. Diabetes. 2020;69(1):83–98.
68. Li B, Leung JCK, Chan LYY, Yiu WH, Tang SCW. A global perspective on the crosstalk between saturated fatty acids and Toll-like receptor 4 in the etiology of inflammation and insulin resistance. Prog Lipid Res. 2020;77:101020.
69. Afshinnia F, Nair V, Lin J, et al. Increased lipogenesis and impaired βoxidation predict type 2 diabetic kidney disease progression in American Indians. JCI Insight. 2019;4(21):e130317.
70. Falkevall A, Mehlem A, Palombo I, et al. Reducing VEGF-B signaling ameliorates renal lipotoxicity and protects against diabetic kidney disease. Cell Metab. 2017;25(3):713–726.
71. Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol. 2019;15(6):327–345.
72. Kikuchi K, Saigusa D, Kanemitsu Y, et al. Gut microbiome-derived phenyl sulfate contributes to albuminuria in diabetic kidney disease. Nat Commun. 2019;10(1):1835.
73. Hu ZB, Lu J, Chen PP, et al. Dysbiosis of intestinal microbiota mediates tubulointerstitial injury in diabetic nephropathy via the disruption of cholesterol homeostasis. Theranostics. 2020;10(6):2803–2816.
74. Wolf G. Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway. Kidney Int. 2006;70:1914–1919.
75. Huang XR, Chen WY, Truong LD, Lan HY. Chymase is upregulated in diabetic nephropathy: implications for an alternative pathway of angiotensin II–mediated diabetic renal and vascular disease. J Am Soc Nephrol. 2003;14:1738–1747.
76. Heerspink HJL, Parving HH, Andress DL, et al. SONAR Committees and Investigators. atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019;393(10184):1937–1947.
77. Hovind P, Rossing P, Tarnow L, et al. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes. 2009;58:1668–1671.
78. Zhang L, Zhao MH, Zuo L, et al. CK-net work group. china kidney disease network (CK-net) 2016 annual data report. Kidney Int Suppl. 2011;10(2):e97–e185. 2020 Dec.
79. Tang SCW, Yu X, Chen HC, et al. Dialysis care and dialysis funding in asia. Am J Kidney Dis. 2020;75(5):772–781.
80. Saeedi P, Petersohn I, Salpea P, et al. IDF diabetes Atlas committee. global and regionacl diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International diabetes federation diabetes atlas. Diabetes Res Clin Pract. 2019;157:107843. 9th ed.
81. Parving HH, Lewis JB, Ravid M, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. demand investigators. Kidney Int. 2006;69:2057–2063.
82. Nguyen NT, Magno CP, Lane KT, et al. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the national health and nutrition examination survey, 1999 to 2004.

J Am Coll Surg. 2008;207:928–934.
83. Wolf G. After all those fat years: renal consequences of obesity. Nephrol Dial Transplant. 2003;18:2471–2474.
84. Chagnac A, Herman M, Zingerman B, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transplant. 2008;23:3946–3952.
85. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. J Clin Endocrinol Metab. 2008;93(suppl 1):S64–S73.
86. de Boer IH, Caramori ML, Chan JCN, et al. Executive summary of the 2020 kdigo Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney Int. 2020;98(4):839–848.

87. Krolewski AS. Progressive renal decline: the new paradigm of diabetic nephropathy in type 1 diabetes. Diabetes Care. 2015;38(6):954–962.
88. Mogensen CE. How to protect the kidney in diabetic patients with special reference to niddm. Diabetes. 1997;56(suppl 2):104–111.
89. Mourad JJ, Le Jeune S. Blood pressure control, risk factors and cardiovascular prognosis in patients with diabetes: 30 years of progress. shiftenterJ Hypertens. 2008;26:S7–S13.
90. Muxfeldt ES, Cardoso CR, Salles GF. Prognostic value of nocturnal blood pressure reduction in resistant hypertension. Arch Intern Med. 2009;169:874–880.
91. Winer N, Sowers JR. Diabetes and arterial stiffening. Adv Cardiol. 2007;44:245–251.
92. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. Diabetes Care. 2013;36(11):3718–3725.
93. Girach A, Vignati L. Diabetic microvascular complications: can the presence of one predict the development of another? J Diabetes Complications. 2006;20:228–237.
94. Wolf G, Müller N, Mandecka A, Müller UA. Association of diabetic retinopathy and renal function in patients with types 1 and 2 diabetes mellitus. Clin Nephrol. 2007;68:81–86.
95. Knudsen ST, Laugesen E, Hansen KW, et al. Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients. Diabetologia. 2009;52:698–704.
96. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes Obes Metab. 2007;9:781–791.
97. Gall MA, Borch-Johnsen K, Hougaard P, et al. Albuminuria and poor glycemic control predict mortality in niddm. Diabetes. 1995;44:1303–1309.

98. Brantsma AH, Bakker SJ, de Zeeuw D, et al. Extended prognostic value of urinary albumin excretion for cardiovascular events. prevend Study group. J Am Soc Nephrol. 2008;19:1785–1791.
99. Niewczas MA, Gohda T, Skupien J, et al. Circulating tnf receptors 1 and 2 predict esrd in type 2 diabetes. J Am Soc Nephrol. 2012;23(3):507–515.
100. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in niddm patients with microalbuminuria. Diabetologia. 1996;39:1569–1576.
101. Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. Am J Pathol. 1936;12:83–98.
102. Fioretto P, Steffes MW, Sutherland DE, et al. Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression. Kidney Int. 1995;48:1929–1935.
103. Wolf G, Chen S, Ziyadeh FN. From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy. Diabetes. 2005;54:1626–1634.
104. Marshall SM. The podocyte: a major player in the development of diabetic nephropathy? Horm Metab Res. 2005;37(suppl 1):9–16.
105. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21:556–563.
106. Redon J. Measurement of microalbuminuria: what the nephrologist should know. Nephrol Dial Transplant. 2006;21:573–576.
107. Akimoto T, Ito C, Saito O, et al. Microscopic hematuria and diabetic glomerulosclerosis: clinicopathological analysis of type 2 diabetic patients associated with overt proteinuria. Nephron Clin Pract. 2008;109:c119–c126.
108. Pham TT, Sim JJ, Kujubu DA, et al. Prevalence of nondiabetic renal disease in diabetic patients. Am J Nephrol. 2007;27:322–328.
109. Liew A, Bavanandan S, Prasad N, et al. Asian pacific society OF nephrology clinical practice guideline ON diabetic kidney disease - executive summary. Nephrology. 2020;25(suppl 2):3–11. https://doi.

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Prevention and Treatment of Diabetic Kidney Disease

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INTRODUCTION

The development of diabetic kidney disease (DKD) signifies a generalized microvascular syndrome that is frequently accompanied by macrovascular disease (see Chapter 31). We use the terms DKD (and formerly diabetic nephropathy) to encompass the spectrum of vascular, glomerular, and tubulointerstitial components of chronic kidney disease (CKD) attributed to diabetes. Classically, DKD evolves through several stages based on urine albumin excretion and measured as urine albumin-to-creatinine ratio in a spot urine sample (UACR): normoalbuminuria (<30 mg/g), moderately increased albuminuria (previously called microalbuminuria, 30–300 mg/g), and severely increased albuminuria (previously called macroalbuminuria or overt nephropathy, >300 mg/g).[1] Furthermore, a substantial proportion of patients with diabetes mellitus have a nonproteinuric phenotype with progressive loss of estimated glomerular filtration rate (eGFR). DKD classification and staging are based on eGFR and degree of albuminuria, as in other causes of CKD. The level of UACR and eGFR are both independently associated with the risk of adverse kidney outcomes and cardiovascular (CV) morbidity and mortality. Normoalbuminuria is arbitrarily defined by UACR less than 30 mg/g, a threshold far above the normal albumin excretion in most healthy individuals. Thus, even in individuals with normoalbuminuria, increments in albuminuria are associated with increased cardiorenal risk.

In patients with established DKD, the goals of treatment are albuminuria regression and preservation of kidney function. Strict blood pressure (BP) and glycemic control early in the disease course are vital. Aggressive lipid-lowering and lifestyle modifications, including adherence to a low-protein and low-sodium diet, exercise, weight loss, and smoking cessation all are beneficial and likely to improve kidney and CV outcomes. Such multifactorial therapy lowered the risk for cardiovascular disease (CVD), nephropathy, retinopathy, and autonomic polyneuropathy in the Steno 2 trial in patients with type 2 diabetes (T2D), and even delayed mortality.[2] Most patients with advancedstage DKD, however, are likely to die of CVD or progress to end-stage kidney disease (ESKD), even though treatment may slow progression.

This chapter reviews the management of patients with type 1 diabetes and kidney disease and focuses on strategies that promote kidney protection and cardioprotection in patients with T2D. The recent introduction of highly effective medications to ameliorate CV and kidney outcomes in patients with T2D and DKD has revolutionized the approach to clinical care, and management strategies are rapidly changing as new pharmaceuticals become available and as their indications and use in the lower eGFR ranges widen. Fig. 32.1 is from the Kidney Disease: Improving Global Outcomes (KDIGO) DKD 2022 Guideline.[2a] In general, the pyramidal peak describes the overall treatment goals, which are to optimize glycemic, blood pressure, and lipid control in patients with T2D. Treatment approaches begin with the foundational goals of smoking cessation and encouraging exercise. In addition, patients should be encouraged to eat a healthy diet, especially targeting lipid, sodium, and modest protein restriction, encouraging fruits and vegetables, and achieving an optimal body weight. For patients with hypertension, hyperlipidemia, and CV disease complicating T2D, the KDIGO guidelines recommend first-line therapy to control glycemia with metformin (for patients with eGFR > 30 mL/min/1.73 m2); a sodium-glucose transporter inhibitor (SGLT2i, for patients with underlying CV and/or kidney involvement and eGFR > 20 mL/min/1.73 m2); blood pressure and proteinuria modulation with renin-angiotensin system (RAS) inhibition or angiotensin receptor blockade; and control of hyperlipidemia with a statin. For those in need of additional or alternative medication approaches to achieve glycemic, blood pressure, proteinuria, CV, and/or lipid goals, secondline therapies including glucagon-like peptide 1 (GLP-1) receptor agonists may be used to address hyperglycemia, proteinuria, renal function decline, and CV complications. A nonsteroidal aldosterone antagonist may be added to further reduce proteinuria, slow the rate of loss of eGFR, and reduce CV complications. Finally, antiplatelet agents may be used to address atherosclerotic CV disease.

One obstacle to achieving adherence is the complexity of these regimens. Therefore, prevention and treatment of patients with DKD must be individualized and require consideration of the cost, side effects, and convenience of the drug regimen measured against the anticipated benefits. A comprehensive approach incorporating multidisciplinary teams, along with patient participation in shared decision-making, is best for managing patients with DKD. Special considerations are indicated in the management of the diabetic patient with advanced CKD (see Chapter 33). Many therapeutic issues discussed here are not specific for DKD and may be relevant for CKD in general (see Chapter 82). The paragraphs below expand on specific considerations in using particular medications or medication classes.

DIABETIC KIDNEY DISEASE IN TYPE 1 DIABETES

In patients with T1D, strict glycemic control decreases the risk for developing DKD. The Diabetes Control and Complications Trial (DCCT) compared the effects of intensive glucose control with conventional treatment on the long-term complications of T1D (Fig. 32.2). Over 9 years, patients with mean hemoglobin A1c (HbA1c) of 7% who received intensive therapy had a 35% to 45% lower risk for development of moderately increased albuminuria compared with the control group (mean HbA1c, 9%).3 In the DCCT follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, the long-term risk for developing impaired glomerular filtration rate (GFR) was 50% lower in patients assigned to tight control compared with those treated with conventional therapy. This effect was not evident until more than 10 years after randomization.4

The appearance of moderately increased albuminuria typically precedes hypertension in patients with T1D. When hypertension occurs, control is imperative. Higher BP is associated with increasing

Regular
risk factor
reassessment
(every 3–6
months)

Lipid management

Glycemic
control

GLP-1 RA
(T2D)

Metformin
(T2D)

Diet

Additional
risk factor
control

Additional
drugs with
heart and
kidney
protection

Blood
pressure control

Antiplatelet therapies
(ASCVD)

SGLT2 inhibitor
(T2D)

Exercise

First-line
drug
therapy

ns-MRA
(T2D)

RAS blockade
(HTN)

Smoking cessation

Lifestyle
and selfmanagement

Statin

Weight

Diabetes with CKD

Fig. 32.1 Treatment Algorithm for Diabetic Kidney Disease (DKD) in Patients With Type 2 Diabetes (T2D). The Kidney Disease: Improving Global Outcomes (KDIGO) Executive Summary describes a recommended approach for the management of DKD, beginning with foundational lifestyle recommendations. Built upon these are the sequential incorporation of first- and second-line glycemic lowering medications, with preferential consideration of each drug’s potential for cardioprotection and renoprotection above and beyond their capacity to improve glycemic control. At the top of the pyramid are overarching goals of risk factor modification, including optimization of glycemic, hypertensive, and lipid management. ASCVD, Atherosclerotic cardiovascular disease; HTN, hypertension; SGLT2, sodium-glucose transporter 2. (From Rossing P, Caramori ML, Chan JCN, et al. Kidney Disease: Improving Global Outcomes [KDIGO] Executive Summary of the KDIGO 2022 Clinical Practice Guideline for diabetes management in chronic kidney disease. An update based on rapidly emerging new evidence. Kidney Int. 2022;102:990–999.)

albuminuria, more rapid progression, and increased risk for kidney failure, as well as increased risk for fatal and nonfatal CV events.[5] Thus, effective treatment of hypertension is arguably the single most important strategy in the treatment of established DKD (Fig. 32.3). Antihypertensive therapies, regardless of the agent used, reduce UACR, delay progression of nephropathy, postpone loss of GFR, and improve survival.

Lower rates of ESKD among patients with T1D attributable to BP and tight glycemic control, along with antiproteinuric strategies (see section on RAAS blockade), are now reported from many countries around the world, and ESKD, when it does occur, occurs at an older age.[6] These encouraging data underscore the need for early glycemic and BP control in T1D.

DIABETIC KIDNEY DISEASE IN TYPE 2 DIABETES

Glycemic Control

Several major studies demonstrate a lower risk for nephropathy with stricter glycemic control in patients with T2D. In a design similar to the DCCT, the Kumamoto study found a 60% reduction in moderately increased albuminuria in relatively young, nonobese patients with T2D receiving intensive glycemic treatment (HbA1c 7.1%) compared with conventional treatment (HbA1c 9.4%).[7] In the United Kingdom Prospective Diabetes Study (UKPDS) trial, newly diagnosed patients with T2D were assigned to intensive management (HbA1c 7.0%) with a sulfonylurea or insulin or to conventional management (HbA1c 7.9%) with diet alone. After 9 years of intensive therapy, the risk of developing moderately increased albuminuria was reduced by 24%.[8] After termination of the study, patients were observed for a further 10 years. The differences in HbA1c were lost within 1 year, but a 24% lower relative risk of microvascular disease and myocardial infarction (−15%) persisted. Allcause mortality was also reduced by 13%. This phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control even if followed by a return to less intensive metabolic control has been termed metabolic memory or legacy effect. It emphasizes the importance of early glycemic control in the primary prevention of microvascular and macrovascular complications in diabetic patients.

Most of the evidence favoring strict glycemic control comes from studies of patients with normoalbuminuria or early stages of DKD. Fewer studies addressed intensive glycemic control in patients with more advanced DKD stages, in whom it may be difficult to show

Cumulative incidence of moderately
increased albuminuria (%)

Intensive Glucose Control Reduces
Development of Moderately
Increased Albuminuria
50
40

Conventional insulin therapy
Intensive insulin therapy

30

P < .05

20
10
0
0

1

2

3

4
5
6
7
8
9
Years of study
Fig. 32.2 Moderately Increased Albuminuria Risk Reduction With
Intensive Versus Conventional Insulin Therapy. Intensive glucose
control was associated with a decreased risk for the subsequent development of
moderately increased albuminuria in patients with type 1
diabetes. (Modified from Diabetes Control and Complications Trial
Research Group. The effect of intensive treatment of diabetes on the
development and progression of long-term complications in insulindependent
diabetes mellitus. N Engl J Med. 1993;329:977–986.)

Control of Blood Pressure Slows
Progression of Type 1
Diabetic Kidney Disease
Glomerular filtration rate (GFR)
(mL/min per 1.73 m2)

105
ΔGFR = 0.94 mL/min/mo

95

(ADVANCE) study showed that intensive glycemic control (HbA1c 6.5% vs. 7.3%) yielded a 10% relative reduction in major macroand microvascular events, in particular a 21% relative reduction in nephropathy.9 However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, very tight glycemic control (lowering HbA1c to a median of 6.4% vs. 7.5% with conventional control) led to a 22% increase in mortality from any cause and did not significantly reduce major CV events.10 A third major study of tight glucose control in patients with T2D, the Veterans Affairs Diabetes Trial (VADT), found no significant reduction in CV deaths or events over 7.5 years in high-risk patients treated aggressively for glycemic control (median HbA1c 6.9%) compared with standard therapy (median HbA1c 8.4%).11 A meta-analysis showed that tight glycemic control reduced microvascular complications, including kidney and eye events.12

We interpret the data to suggest that glycemic control must be individualized, considering the patient's age, duration of diabetes, presence of CVD, presence of CKD, and microvascular risks and complications, as well as previous glycemic control and susceptibility to and awareness of hypoglycemia. In younger patients with short diabetes duration, longer life expectancy, low hypoglycemia risk, and no prior CV events, strict glycemic control can reduce DKD risk and other microvascular complications. A more cautious approach to glycemic control is recommended in the frail or elderly patient with long-standing diabetes or preexisting CV problems or in patients who are susceptible to hypoglycemic episodes. In these patients, the HbA1c goal may be set higher. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 clinical practice guidelines recommend lowering HbA1c to a goal ranging from less than 6.5% to less than 8.0%.13 The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) similarly endorse tight glycemic control at the onset of diabetes in patients with few comorbidities as a preventive strategy and less stringent control in patients with more advanced comorbidities.14

Antihyperglycemic Therapeutic Options in Type 2 Diabetes and Kidney Disease

85
ΔGFR = 0.29 mL/min/mo

benefit because the results are confounded by the effects of concomitant hypertension and CVD. Even so, there is evidence to support glycemic control in reducing the risk for worsening albuminuria and kidney functional decline.

Options for antihyperglycemic treatment in patients with T2D have expanded over the past decade, and several confer CV and kidney protection substantially beyond their glycemic effects. Despite specific indications and relative contraindications for some newer drug classes discussed below, most patients can safely be prescribed at least one, if not more, classes of the newer antiglycemic agents as needed. These newer agents have been shown to confer a level of CV and kidney protection that far surpasses the protection conferred by RAS inhibition alone. Importantly, the severity of CKD has implications for the efficacy and safety of glycemic treatments. Dosing adjustments and careful monitoring for adverse effects are required for patients with advanced CKD or with kidney failure (see Chapter 33). Fig. 32.4 represents a treatment strategy combining lifestyle recommendations and a hierarchical medication prescribing approach recommended in the KDIGO DKD Guideline2a to address glycemic control and CV and renoprotection in patients with T2D. The following paragraphs expand on the particular pharmacologic considerations of medication use in each of the drug classes.

Glycemic Targets

Metformin

HbA1c is widely used to monitor glycemic control, and testing should be performed routinely in all patients with diabetes as part of continuing care, combined with patient self-monitoring of blood glucose or continuous glucose monitoring in selected patients. The HbA1c assay has limitations in patients with advanced CKD, as the result can be influenced by conditions that affect red cell turnover (see Chapter 33). Several major trials tested whether strict glycemic targets reduced CVD risk in patients with T2D. The Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation

Metformin is a biguanide which has been used for over 60 years and is the preferred initial antihyperglycemic drug for T2D because of its low cost, high efficacy, and low risk for hypoglycemia. Metformin also has weight- and lipid-lowering properties, and beneficial effects on CV and all-cause mortality.15 It is primarily eliminated by the kidney, and the risk of lactic acidosis in patients with kidney impairment or acute illness is a concern. However, the lowest eGFR safety threshold for metformin has been reconsidered in recent years, as data demonstrating an increased risk of lactic acidosis in CKD is limited. Currently, it is

75

ΔGFR = 0.10 mL/min/mo
65

Commencing
antihypertensive therapy

55
−2

−1

0

1

2
Years

3

4

5

6

Fig. 32.3 Control of blood pressure reduces the risk for progression in type 1 diabetes and diabetic kidney disease. (Modified from Parving HH, Andersen AR, Smidt VM, et al. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. Br Med J (Clin Res Ed). 1987;294[6585]:1443–1447.)

Regular
risk factor
reassessment
(every 3–6
months)

Lifestyle
Healthy diet

First-line
drug therapy

SGLT2i
(Initiate eGFR ≥20;
continue until dialysis
or transplant)

Physical activity

Metformin
(if eGFR ≥30)

Smoking cessation

Weight management

RAS inhibitor at maximum
tolerated dose (if HTN*)

Moderate-or
high-intensity statin

Regular reassessment
of glycemia, albuminuria,
BP, CVD risk, and lipids
Additional
risk-based
therapy

GLP-1 RA if needed to
achieve individualized
glycemic target

Nonsteroidal MRA † if
ACR ≥30 mg/g and
normal potassium

Other glucose-lowering
drugs if needed to
achieve individualized
glycemic target

Dihydropyridine CCB
and/or diuretic* if
needed to achieve
individualized
BP target

Steroidal MRA if
needed for resistant

hypertension
if eGFR ≥45

Antiplatelet
agent for
clinical ASCVD

Ezetimibe, PCSK9i,
or icosapent ethyl if
indicated based on
ASCVD risk and lipids

T2D only
All patients
(T1D and T2D)

Fig. 32.4 Treatment algorithm for glycemic control in patients with type 2 diabetes and diabetic kidney disease. ACR, Albumin/creatinine ratio; ASCVD, atheroslerotic cardiovascular disease; BP, blood pressure;CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RA, receptor agonist; RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes. (From Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. Kidney Int. 2022;102:990-999.)

recommended to decrease the dose of metformin to 500 mg twice daily at eGFR less than 45 mL/min/1.73 m2 and discontinue use at eGFR less than 30 ml/min/1.73 m2 2a

Sodium Glucose Cotransporter-2 Inhibitors

The magnitude of the effect size of SGLT2i for kidney protection in T2D is approximately 2.5 times the protective effect of RAS inhibitor when added to a maximally tolerated dose of RAS inhibitor. No drug class currently exists with this degree of renoprotection. Empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin are now widely approved antihyperglycemic therapies with kidney benefits conferred at least in part via glycosuric and tubuloglomerular feedback mechanisms. They induce osmotic diuresis, which in turn confers natriuretic effects contributing to plasma volume contraction, have decreased weight, and have decreased systolic BP by 4 to 6 mm Hg and diastolic BP by 1 to 2 mm Hg. SGLT2 inhibition is associated with an acute reduction of more than 10% in eGFR in about a third of all individuals with T2D and CVD. However, this initial decline is fully reversible after stopping SGLT inhibition. Albuminuria is reduced by 30% to 40%. These effects mirror preclinical observations suggesting that proximal tubular natriuresis activates renal tubuloglomerular feedback through increased macula densa sodium and chloride delivery, leading to afferent vasoconstriction. Glycosuric effects are attenuated in patients with

eGFR less than 60 mL/min/1.73 m2, but BP, eGFR, and albuminuria lowering effects are preserved.

There is solid evidence for CV and kidney protection of SGLT2 inhibitors in patients with T2D. The Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTCOME) trial in patients with T2D and established CVD reported a 14% reduction in the primary composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, and more than 30%

reductions in CV mortality, overall mortality, and heart failure hospitalizations.16 The Canagliflozin Cardiovascular Assessment Study (CANVAS) showed a similar magnitude of CV event reduction using canagliflozin in patients with T2D and a high risk of CVD. In terms of kidney protection, the EMPA-REG OUTCOME study reported a 39% reduction in incident or worsening kidney disease that included doubling of serum creatinine (relative risk reduction, 44%) and kidney-replacement therapy (relative risk reduction, 55%) in the empagliflozin group, whereas the CANVAS-Renal trial similarly reported an impressive 40% reduction in the composite kidney outcome (defined as a sustained 40% reduction in the rate of eGFR decline, need for kidney replacement therapy, or death from kidney causes).17 18 The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was halted early after a planned interim analysis indicated significant 30% reduction in composite outcome (ESKD, doubling of the serum creatinine, or death from kidney or CV causes) in the canagliflozin group compared with the placebo group.19 Similarly, dapagliflozin was shown to reduce heart failure and fatal myocardial outcomes in patients with T2D and CV risk factors in the DECLARE study.19a and the DAPA-HF study19b Of great significance, the DAPA-CKD study showed that treatment with dapagliflozin improved all of the components of the composite kidney endpoint of sustained eGFR decline, ESKD, and CV or renal death in patients with and without DKD with a relative risk reduction of 39%.20 In 2022, similar findings of CV and renoprotection were reported for empagliflozin20a in patients with and without T2D. Corroborating all of the results of these individual studies, a meta-analysis20b reported that SGLT2 inhibitors reduced the risk of kidney disease progression by 37%, the risk of acute kidney injury by 23%, and the risk of cardiovascular death or hospitalization for heart failure by 23%, with similar effects in those with and without diabetes. SGLT2 inhibitors also reduced the CV death risk but did not reduce the risk of non-CV death. The authors concluded that the absolute effects of SGLT2 inhibitors outweighed the small risks of ketoacidosis or amputation, the latter having been observed in only one trial with canagliflozin. The risk for genital and urinary tract infections, especially with Candida species, is generally increased, and hygiene measures are recommended.20

Collective evidence from clinical studies demonstrated that SGLT2 inhibitor use does not predispose to clinically significant AKI.

GLP-1 Receptor Agonists

GLP-1 receptor agonists are a newer class of antihyperglycemic treatment with demonstrated CV and kidney benefits in patients with T2D. They lower glucose levels and reduce body weight and BP. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that fewer patients in the liraglutide group died from CV causes (relative risk reduction, 22%), and the rate of death from any cause was also lower (15%). Fewer patients reached a kidney endpoint (23%), which consisted mainly of a lower frequency of heavy albuminuria.21 Similarly impressive CV benefits were demonstrated for semaglutide in the SUSTAIN-6 and PIONEER-6 studies.22 Both the 2020 ADA guideline and the 2022 KDIGO guideline now recommend the use of GLP-1 receptor agonists with proven CV benefits in patients with T2D who have established CVD or are at high risk. Notably, the 2020 ADA guidelines recommend using these agents for the reduction of CV risk independent of glycemic control,14 and the 2022 KDIGO guidelines recommend these as adjunctive therapies after consideration of metformin and SGLT2 inhibitors.2a Cost concerns and the need for injection remain barriers to using GLP-1 receptor agonists. Additional research is needed to fully characterize subgroups among patients with T2D who will particularly benefit from GLP-1 receptor agonists and to determine if the CV and kidney benefits extend to patients with T1D.

Dipeptidyl Peptidase-4Inhibitors

Like the GLP-1RA, the dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e., gliptins) are incretin-based antihyperglycemic agents effective in lowering blood glucose in patients with T2D. By inhibiting DPP-4, a regulator of GLP-1 degradation, these agents increase GLP-1 levels. Thus, combined use of DPP-4 inhibitors and GLP-1 RA is not recommended. As a class, DPP-4 inhibitors are generally well tolerated and can be used even in patients with advanced CKD. Treatment with DPP-4 inhibitors reduces albuminuria. So far, clinical trials of DPP-4 inhibitors have demonstrated no additional CV outcome benefit compared with placebo.23

Blood Pressure Control

As many as 40% of patients with T2D have known hypertension before the diagnosis of DKD. Once severely increased albuminuria develops, hypertension is almost universal and is associated with volume expansion and salt sensitivity. The absence of hypertension in an untreated patient with T2D and DKD should raise suspicion for underlying cardiac disease. The optimal BP target in DKD remains unclear. Guidelines published before the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial suggested a BP target in diabetic patients of less than 130/80 mm Hg. However, this BP target was challenged by the ACCORD BP trial. Among patients with T2D and high CV risk, randomized to goal systolic BP of under 120 mm Hg or standard therapy aiming for under 140 mm Hg, there was no difference in the risks for composite major CV events. The risks for hyperkalemia and kidney dysfunction were increased at lower BP goals in ACCORD.24 In contrast, the large Systolic Blood Pressure Intervention Trial (SPRINT) showed that for nondiabetic patients, lowering systolic BP below 120 mm Hg, compared with the standard goal below 140 mm Hg, significantly lowered event rates and mortality without a significant increase in adverse events.25 Unfortunately, data are more limited in patients with diabetes or advanced stage CKD. In the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive lowering of systolic BP to 120 mm Hg was associated with improved kidney and patient survival, an effect independent of baseline kidney function.26 Mortality increased with systolic BP below 120 mm Hg, although a cause-andeffect relationship could not be inferred. Low diastolic BP is poorly tolerated, and the incidence of myocardial infarction and mortality increases at values less than 70 mm Hg, at least in patients with coronary heart disease, presumably because coronary perfusion occurs during diastole. Indeed, in the IDNT study, CV mortality increased not only with higher systolic BP but also with low diastolic BP. The KDIGO 2021 Hypertension Guideline remained somewhat agnostic about the blood pressure target in patients with diabetes. Citing SPRINT, the workgroup report stated “The working group feels that cardiovascular benefits of intensive BP lowering cannot be excluded in patients with concomitant diabetes and CKD and that a large randomized trial addressing this issue is warranted.”27 Thus, a solid evidence-based recommendation for a BP target in patients with diabetes remains elusive, but based on KDIGO 2021, it appears appropriate to target a BP less than 140/90 mm Hg for all diabetic patients and less than 130/80 mm Hg as tolerated for patients with CKD and/or UACR greater than 30 mg/g.27 The American College of Cardiology/American Heart Association (ACC/AHA) 2017 hypertension guideline similarly set a BP target below 130/80 mm Hg for individuals with CKD and others at elevated CV risk. For diabetic patients at highest risk for cerebrovascular accidents, lower systolic BP goals (i.e., <120 mm Hg) may provide greater protection against stroke, but the potential risks for adverse events and the burden of antihypertensive therapy must be considered.

RAAS BLOCKADE

Renin-Angiotensin-Aldosterone System Inhibition in the Prevention of Diabetic Kidney Disease

We do not recommend the use of renin-angiotensin system (RAS) inhibition in normotensive, normoalbuminuric diabetic patients for the primary prevention of DKD. Most patients with diabetes do not develop DKD, even after long periods of uncontrolled hyperglycemia, and there are hazards using RAS inhibitors, including their potential teratogenicity. In a post hoc analysis of the multicenter Diabetic Retinopathy Candesartan Trials (DIRECT) program, which included patients with normotensive and normoalbuminuric T1D and normoalbuminuric T2D with or without hypertension, candesartan had no effect on the development of moderately increased albuminuria.28
In hypertensive, normoalbuminuric patients, an angiotensinconverting enzyme (ACE) inhibitor or angiotensin receptor blocker

(ARB) are both effective as first-line antihypertensive agents. The

Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), which randomized patients with hypertension, normoalbuminuria, and T2D to placebo, verapamil, trandolapril, or a combination of verapamil plus trandolapril, showed less progression to moderately increased albuminuria in those receiving trandolapril either alone or with verapamil.29 Results with verapamil alone were similar to placebo. There were similar findings in smaller studies with other RAS inhibitors, implicating a class effect. Longer-term studies would be required to demonstrate the effects of RAS inhibitors on the clinically important outcomes of death, dialysis, and doubling of serum creatinine level in normoalbuminuric patients.

Renin-Angiotensin System Inhibition in the Treatment of Diabetic Kidney Disease

In patients with established DKD, RAS inhibition confers kidney protection that is independent of BP reduction. The mitigation of intraglomerular hemodynamic and nonhemodynamic kidney effects of angiotensin II best explain the observed protection. Supporting this hypothesis, in vitro models of DKD show cellular effects of RAS inhibition that are consistent with benefits independent of BP effects (see Chapter 31).

Type 1 Diabetes

In patients with T1D with moderately increased albuminuria, ACE inhibitors reduce the risk for progression to overt nephropathy. In a meta-analysis in normotensive patients with T1D and moderately increased albuminuria treated with ACE inhibitors, the majority for more than 2 years, treatment was associated with a 60% reduction in progression to severely increased albuminuria and a threefold increase in regression to normoalbuminuria.30 Changes in BP do not entirely explain the antiproteinuric effect of ACE inhibition.

In patients with severely increased albuminuria or overt nephropathy, captopril reduced albuminuria, slowed loss of GFR, and delayed the onset of kidney failure compared with placebo.31 The beneficial effect of captopril was greater in patients with reduced GFR at baseline largely because one of the components of the composite endpoint, a doubling of baseline serum creatinine level, was achieved more quickly in these patients.

Data are insufficient to demonstrate the efficacy of ARBs in T1D and DKD. Nevertheless, based on the shared properties of ACE inhibitors and ARBs in inhibiting the RAS, ARBs are probably effective in the treatment of T1D and DKD.

Type 2 Diabetes

In patients with T2D, more data are available on the kidney-protective effect of ARBs compared with ACE inhibitors. In the stage of moderately increased albuminuria, the IRMA 2 study showed that irbesartan reduced progression to overt nephropathy by 70% in patients with hypertension and T2D during a 2-year follow-up period.32 In the MARVAL trial, valsartan produced a greater reduction in UACR than did amlodipine (44% vs. 8%), with the same degree of BP reduction, suggesting that the antiproteinuric effect of ARBs is BP independent.

In patients with T2D with severely increased albuminuria and decreased GFR, the large randomized controlled trials (RCTs) IDNT and RENAAL showed that ARBs are effective in lowering proteinuria and decreasing the relative risk for reaching the composite endpoint of death, dialysis, and doubling of serum creatinine level.33,34 However, the risk reduction for reaching the composite endpoint was only 18% to 20% in these studies in patients with T2D and nephropathy, compared with the more robust risk reduction of about 50% in patients with T1D receiving captopril. ARBs did not decrease CV death in these trials but did decrease the incidence of heart failure.

Compared with ARBs, data on the efficacy of ACE inhibitors in T2D and DKD are less strong, largely because of small sample size or short follow-up. In general, ACE inhibitors and ARBs have similar effects on patient outcomes. In a small RCT of patients with T2D with early DKD and 5-year follow-up, telmisartan was not inferior to enalapril in providing long-term kidney protection.35

Aldosterone Blockade in Diabetic Kidney Disease

The beneficial effect of ACE inhibitors and ARBs in slowing progressive kidney disease did not differentiate between the relative contributions of the RAS inhibition versus aldosterone system blockade (see Chapter 82). In fact, plasma aldosterone levels are elevated in a subset of patients despite ACE inhibitor and ARB therapy (also known as aldosterone breakthrough; see Chapter 82). In studies that defined aldosterone breakthrough as any increase from an individual’s baseline serum aldosterone level (i.e., before RAS inhibition), the incidence ranged from 40% over 10 months to 53% over 12 months.36 In addition to its classic effects of promoting sodium retention and enhancing potassium and magnesium excretion, aldosterone promotes tissue inflammation and fibrosis. Small studies demonstrated faster decline in GFR in patients who experienced aldosterone breakthrough (median, −5.0 mL/min/y) than in those who did not (median, −2.4 mL/min/y). However, current evidence is not strong enough to support widespread testing for aldosterone breakthrough. In selected patients, the addition of a mineralocorticoid receptor antagonist (MRA) may represent optimal therapy for patients who no longer show maximal antiproteinuric effects with RAS inhibitors.

The steroidal MRAs spironolactone and eplerenone reduce proteinuria when used alone. They have an additive effect on proteinuria when combined with an ACE inhibitor or ARB.37 However, the risk for hyperkalemia, AKI, and other adverse effects, including gynecomastia, erectile dysfunction, and dysmenorrhea, frequently limit the use of combined MRA with ACE inhibitors or ARBs, especially in patients with reduced eGFR. Finerenone, a new nonsteroidal MRA, has greater receptor selectivity and affinity compared with steroidal MRAs (e.g., spironolactone and eplerenone) and has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with T2D to reduce CV morbidity and mortality and slow the rate of progressive renal functional decline. Recently published results from the two phase III finerenone studies, FIGARO and FIDELIO, demonstrated that finerenone reduced the relative risks of CKD progression and CV morbidity and mortality in patients with T2D CV risk and CKD.38,38aAdverse events were similar between the finerenone and placebo group. Hyperkalemia leading to finerenone discontinuation was uncommon (2.3%) compared with placebo (0.9%). The success of. finerenone to confer CV and kidney benefits and a low incidence of underlies the recommendation in the KDIGO DKD Guidelines to consider utilizing finerenone in a triple combination drug therapy strategy of ACE inhibitors or ARBs, SGLT2 inhibitors, and the nonsteroidal MRAs to provide optimal CV and kidney protection for most patients with T2D and DKD. Trials of several additional novel MRAs (esaxerenone, apararenone, KBP-5074) are underway. Recently, a phase III study of esaxerenone in patients with T2D showed albuminuria reduction compared to placebo.53 Esaxerone is approved in Japan for the treatment of hypertension.

Combination
Inhibitors

Therapy

With

Renin-Angiotensin

System

Combination therapy with an ACE inhibitor and an ARB is not recommended for DKD based on the results of several large trials in which the combination failed to improve clinical outcomes but which did engender hyperkalemia and/or AKI.39 Similar untoward events were observed when an ACE inhibitor or ARB was combined with the direct renin inhibitor aliskerin.40

Dosing and Adverse Effects Associated With ACE Inhibitors and ARBs

In individual patients, proteinuria may respond to ACE inhibitor or ARB dose escalations beyond those recommended for BP control.41 Unfortunately, maximal dosing of ACE inhibitors or ARBs may be limited by side effects, including hyperkalemia, hypotension, and AKI.
In women of reproductive age, counseling about pregnancy prevention and contraceptive use should begin before a RAS inhibitor is started.
Serum creatinine concentration may increase up to 30% in proteinuric patients with kidney impairment after starting a RAS inhibitor.
This rise in creatinine is associated with long-term kidney protection, and therapy should not necessarily be stopped in these patients.
Increases in serum creatinine concentration above 30% after initiation of a RAS inhibitor should raise the suspicion of renal artery stenosis.
Aggressive dose increments of ACE inhibitors or ARBs, especially in conjunction with diuresis, can precipitate AKI, so caution is appropriate.
Interestingly, a retrospective cohort study showed that discontinuing RAS inhibition in patients with eGFR less than 30 mL/min/1.73 m2 was associated with 39% and 37% higher risks for all-cause mortality and major adverse cardiovascular events (MACE), respectively, over 5 years of follow-up compared with continuation.42 No significant difference in the risk of progression to ESKD was found. A randomized clinical trial of RAS inhibition withdrawal in patients with advanced kidney disease (STOP-ACE) is currently underway. In practice, the addition of diuretic therapy and potassium binders can reduce the incidence of hyperkalemia in patients with severe CKD and offer the potential to enhance the therapeutic effects of RAS inhibitors.

TREATMENT OF DYSLIPIDEMIA

Most patients with DKD have dyslipidemia characterized by low levels of high-density lipoprotein (HDL) cholesterol, high triglyceride (TG) levels, and a shift from larger toward smaller low-density lipoprotein (LDL) cholesterol. Dyslipidemia in diabetic patients may contribute to the development of glomerulosclerosis and progressive kidney disease.43 In the Diabetes Atherosclerosis Intervention Study (DAIS), patients with T2D taking fenofibrate had a significantly lower rate of progression from normoalbuminuria to moderately increased albuminuria at 3 years compared with the placebo group.44
Statins have the strongest evidence for reducing atherosclerotic CVD risk and are the first-choice hypolipidemic agent. Treatment emphasis is placed on assessing a patient’s global risk for CVD and using maximum tolerated statin intensity for primary and secondary prevention of CVD. For diabetic patients ages 40 to 75 years without atherosclerotic CVD, the ACC/AHA guidelines recommend moderateintensity statin therapy. Younger patients with elevated CVD risk factors may reasonably be treated with a statin as well. In diabetic patients with atherosclerotic CVD, maximally tolerated dose of high-intensity statin is recommended, aiming to lower LDL cholesterol by 50% or more.45 Follow up fasting lipid measurements should be done 4 to 12 weeks after starting a statin and should be repeated every 3 to 12 months as needed. The addition of a nonstatin hypolipidemic agent (e.g., ezetimibe) may be considered in high-risk patients who have not achieved a LDL cholesterol reduction goal on statin therapy. Once a patient has ESKD and is placed on dialysis, statin therapy may not improve CV outcomes (see Chapter 33).46
In patients with T2D, LDL cholesterol is not the sole lipoprotein

that defines CV risk. As major statin trials have demonstrated, lowering

of LDL cholesterol does not prevent the majority of adverse CV events and does not bring the CV risk in T2D down to the level of nondiabetic patients (referred to as residual CV risk). Atherogenic dyslipidemias, specifically elevated TG, low HDL cholesterol, elevated apolipoprotein B, and elevated apolipoprotein C III, are thought to be key factors associated with residual CV risk in diabetic patients.47 In the UKPDS, elevated TG was independently associated with albuminuria in patients with T2D. Thus, interventions aimed at improving all lipid targets are recommended. However, it is not clear whether this is best achieved by intensification of statin therapy or supplementation of statin therapy with other hypolipidemic therapeutics or omega-3 fatty acids. In the ACCORD Lipid trial, routine use of combination therapy with a statin plus a fibrate did not reduce CV risk in patients with T2D.48

NONPHARMACOLOGIC INTERVENTIONS

For all patients with diabetes mellitus, emphasis should be placed on lifestyle modification to lower the risk for DKD and CV events, including dietary restriction of salt and saturated fat, weight reduction and exercise as appropriate, and smoking cessation.

Dietary protein restriction may alleviate uremic symptoms in patients at or approaching ESKD. Small trials have shown low-protein diets (≤0.8 g/kg/day) reduce proteinuria significantly with increased plasma albumin in patients with T2D with severely increased albuminuria. A recent meta-analysis concluded that a low-protein diet (≤0.8 g/kg/day) slows the decline in eGFR and improves proteinuria in patients with DKD.49 Even patients with mild DKD appear to benefit from dietary protein restriction with decreased proteinuria. However, nutritional counseling is advised for all patients to avoid proteinenergy malnutrition and to receive education on salt, potassium, and phosphate restriction, as well as choice of carbohydrates and fats (see Chapter 90). The efficacy of low-protein diets in reducing the rate of kidney function loss in patients taking SGLT2 inhibitors has not been systematically studied.

Smoking cessation and weight reduction can provide additive kidney benefits and lower the risk for CV events in patients with DKD. Smoking is an independent risk factor for the development of nephropathy in T2D and is associated with accelerated loss of kidney function. Smoking cessation attenuates albuminuria and improves kidney prognosis.50 Weight reduction also may improve kidney outcome. The Look-AHEAD trial found intensive lifestyle interventions consisting of diet and exercise plans achieved greater weight loss compared with diabetes support and education (mean 1-year weight loss of 8.6% vs. 0.7%) and reduced the incidence of CKD (0.63% vs. 0.91%) in obese patients with T2D.51 Furthermore, results of prospective cohort studies and emerging evidence from randomized clinical trials show bariatric surgery may prevent or slow the progression of DKD over medical intervention in obese patients with T2D.52

EMERGING TREATMENTS FOR DIABETIC KIDNEY DISEASE

Genetic and epigenetic factors, glomerular hypertension and hyperfiltration, overactive RAS, accumulation of advanced glycation end products, oxidative stress, kidney inflammation, and fibrosis contribute to DKD and are potential therapeutic targets.

A number of treatments, some experimental and others in clinical use for other indications, have been tried to prevent or treat DKD.

Unfortunately, many investigational drugs failed to meet primary clinical endpoints, had unacceptable side effects, or were abandoned by pharmaceutical companies for financial reasons. Bardoxolone methyl

TABLE 32.1

Selected Investigational Drugs for Diabetic Kidney Disease

Drug

Mechanism of Action

Clinical Trials and Comments

Finerenone, esaxerenone,
apararenone, KBP-5074

Selective nonsteroidal MRAs

Atrasentan, avosentan

Endothelin A receptor blocker

Paricalcitol

Vitamin D receptor activators

Allopurinol, febuxostat,
topiroxostat

Purine analog and inhibitor of
xanthine oxidase that decreases
uric acid formation
Nonselective phosphodiesterase
inhibitors

In FIDELIO-DKD, finerenone reduced kidney progression and CV events in T2D with advanced CKD.38
A phase III trial of esaxerenone in T2D with moderately elevated albuminuria showed that it is effective in reducing albuminuria. Esaxerenone is approved in Japan for the treatment of hypertension.
In a phase III trial (SONAR), atrasentan reduced kidney endpoints by 35% in patients with T2D; significant risk for fluid retention and anemia occurred in the atrasentan group.55
A phase III trial of avosentan (ASCEND) showed a reduction in albuminuria in the short term, but the trial was terminated early due to fluid retention in the avosentan group.54
An RCT (n = 281) found addition of paricalcitol to RAS inhibition nonsignificantly lowered albuminuria in patients with T2D and DKD.57
The PERL and CKD-FIX trials concluded that allopurinol did not reduce the progression of DKD.58,59

Pentoxifylline, CTP-499

CCX-140, NOX-E36

Selonsertib (GS-4997)

ASP-8232
Bardoxolone methyl (RTA-402)

C-C chemokine receptor 2 antagonist and chemokine ligand 2 inhibitor
Selective ASK1 inhibitor
Vascular adhesion protein 1 inhibitor
Inducer of Nrf2 pathway

In a small trial (n = 169) of patients with T2D, the addition of pentoxifylline to a RAS inhibitor had additive antiproteinuric effect and slowed kidney disease progression after the first year of treatment and maintained statistical significance with placebo after 24 months.60

Phase II trials of several chemokine inhibitors have shown kidney protective effects of chemokine inhibitors in T2D with DKD.

A phase II trial of selonsertib showed no effect on albuminuria compared with placebo, though post hoc analyses suggest that it may slow DKD progression.56

Ongoing phase II trial to evaluate the efficacy and safety of ASP-8232 in patients with T2D and DKD.

A phase III trial of bardoxolone methyl in DKD was halted because of excess serious adverse events in the treated group. A separate phase II study in Japan showed significant improvement in eGFR, with an associated increase in UACR, in the bardoxolone methyl group compared with placebo. There is an ongoing phase III trial in Japanese patients with T2D and CKD.

ASCEND, Avosentan on Doubling of Serum Creatinine, ESKD and Death; ASK1, apoptosis signal-regulating kinase 1; CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; RCT, randomized controlled trial; SONAR, Atrasentan and Renal Events in Patients with Type 2 Diabetes and Chronic Kidney Disease; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

(an inducer of the Nrf2 pathway), ruboxistaurin (a protein kinase C inhibitor), pirfenidone (an antifibrotic agent), pimagedine/aminoguanidine/pyridoxamine (advanced glycation end product formation inhibitors), baricitinib (janus kinase inhibitor), palosuran (a vasopeptidase inhibitor), probucol (an antioxidant), and sulodexide (a glycosaminoglycan) are examples. Ongoing trials exploring new DKD treatments include endothelin receptor antagonists, drugs that target oxidative stress, xanthine oxidase inhibitors, and other antiinflammatory and antifibrotic agents (Table 32.1).

ENDOTHELIN RECEPTOR ANTAGONISTS

The kidney endothelin system is activated in experimental and clinical DKD. The antiproteinuric effect of an endothelin A receptor blocker was shown in the Avosentan on Doubling of Serum Creatinine, ESKD and Death (ASCEND) phase III clinical trial. However, fluid retention led to early termination of the ASCEND trial.54 Another endothelin A receptor blocker, atrasentan, is more selective than avosentan and was shown in the Atrasentan and Renal Events in Patients with Type

2 Diabetes and Chronic Kidney Disease (SONAR) trial to reduce the incidence of primary composite endpoints of serum creatinine doubling or onset of ESKD. Serious adverse events included fluid retention and anemia, which occurred more frequently in the atrasentan group.

There were no CV benefits.55 Whether atrasentan will be approved for DKD treatment remains unclear.

SELECTIVE APOPTOSIS SIGNAL-REGULATING KINASE 1 INHIBITOR

Apoptosis signal-regulating kinase 1 (ASK1) activation from oxidative stress in glomerular and tubular cells has been implicated in the pathogenesis of DKD. Selonsertib is a selective ASK1 inhibitor developed as a once-daily oral agent for the treatment of DKD. In a phase II trial evaluating selonsertib’s safety and efficacy, selonsertib failed to reduce UACR compared with placebo, though post hoc analyses suggest that it may slow DKD progression.56 A phase IIb trial enrolling patients with moderate-advanced DKD is currently underway.

Vitamin D Receptor Activators

Vitamin D receptor activation reduced albuminuria in small trials of DKD. A cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES, 2001–2006) data showed that there was an independent association between vitamin D deficiency and insufficiency with the presence of nephropathy. The largest phase II RCT investigating the effect of paricalcitol (a vitamin D analog) 1 or 2 µg/day in patients with T2D failed to meet its primary endpoint (change in albuminuria), but post hoc analysis showed lowered albuminuria compared with placebo in patients with high sodium intake and on a higher dose of paricalcitol.57 However, only 58% of the patients assigned to 2 μg/day of paricalcitol received the full dose during the study, and the follow-up period of 24 weeks was brief. The use of vitamin D analogs in clinical applications of DKD demands further RCTs in larger patient series with adequate follow-up.

Xanthine Oxidase Inhibitors

Epidemiologic studies suggest an independent association between asymptomatic hyperuricemia and increased risk for arterial hypertension, CKD, albuminuria, CV events, and mortality. Whereas some smaller clinical trials have shown improvements in BP control and slowing of CKD progression using urate-lowering therapy, two recent RCTs did not. In one trial treating patients with CKD at high risk of progression, urate-lowering treatment with allopurinol did not slow the decline in eGFR compared with placebo.58 Similarly, in another trial, clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with T1D and early to moderate DKD could not be detected.59 Although both studies had some weaknesses in design (e.g., including subjects who were not hyperuricemic), the use of allopurinol for this indication is currently unsupported.

Phosphodiesterase Inhibitors

Pentoxifylline (PTF) is a nonselective phosphodiesterase (PDE) inhibitor used for symptomatic relief of claudication. It has vasodilatory and antihypertensive effects and may have beneficial kidney hemodynamic effects. PTF also inhibits the synthesis of inflammatory cytokines. In a small trial in patients with T2D, the addition of PTF to RAS inhibition had additive antiproteinuric effects and slowed kidney disease progression after the first year of treatment. Statistical significance was maintained for 24 months.60 A key problem for the clinical development of PTF as a DKD treatment is the low cost of the drug. A more selective PDE inhibitor, PF-489791, was discontinued despite early promising phase II results.

Novel Therapeutic Approaches

Novel investigational agents, including CCX-140, NOX-E36, DMX200 (chemokine inhibitors), LY3016859 (an epidermal growth factor receptor inhibitor), GKT137831 (a NADPH oxidase inhibitor), ASP8232 (a vascular adhesion protein 1 inhibitor), SER150 (a thromboxane A2 receptor antagonist), and several drugs currently in clinical use for other indications (e.g., N-acetylcysteine, colchicine), are being evaluated for treatment of proteinuric kidney disease, including DKD. A new formulation of bardoxolone methyl, RTA 402 (an inducer of Nrf2 pathway), is being tested for safety and efficacy in Japanese patients with T2D with CKD. The role of micro-RNAs in the pathogenesis of DKD is an emerging field and may also provide additional novel treatment approaches. New insights into the molecular mechanisms that underlie the origin and progression of DKD are emerging from large-scale genetic and molecular studies in experimental models and humans.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO). Chapter 1: definition and classification of CKD. Kidney Int Suppl. 2013;3:19.

2. Gaede P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the steno-2 randomised trial. Diabetologia. 2016;59(11):2298–2307.

2a. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. Kidney Int. 2022;102:990–999.

3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986.

4. Diabetes control and complications trial/epidemiology of diabetes interventions and complications research group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med. 2011;365:2366–2376.

5. Parving HH, Andersen AR, Smidt VM, et al. Effect of anti-hypertensive treatment on kidney function in diabetic nephropathy. BMJ. 1987;294:1443–1447.

6. Helve J, Sund R, Arffman M, et al. Incidence of end-stage renal disease in patients with type 1 diabetes. Diabetes Care. 2018;41:434–439.

7. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the kumamoto study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23(suppl 2):B21–B29.

8. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–853.

9. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572.

10. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559.

11. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–139.

12. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participants data from randomized controlled trials. Lancet Diabet Endocrinol. 2017;5:431–437.

13. Kidney Disease Improving Global Outcomes (KDIGO). 2020 Clinical practice guidelines for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4):S1–S115.

14. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020:43.

15. Anfossi G, Russo I, Bonomo K, et al. The cardiovascular effects of metformin: further reasons to consider an old drug as a cornerstone in the therapy of type 2 diabetes mellitus. Curr Vasc Pharmacol. 2010;8(3):327–337.

16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcome, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128.

17. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375:323–334.

18. Neal B, Perkovic V, Mahaffey KW, CANVAS ProgramCollaborative Group, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657.

19. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–2306.

19a. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7:606–617.

19b. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995–2008.
20. Heerspink H, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease (DAPA-CKD). E Engl J Med. 2020;383:1436–1446.
20a. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2022. Online ahead of print.
20b. The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists’ Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400:1788–1801. Online ahead of print.
21. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322.
22. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844.
23. Mannucci E, Mosenzon O, Avogaro A. Analyses of results from cardiovascular safety trials with DPP4 inhibitors: cardiovascular outcomes, predefined safety outcomes, and pooled analysis and metaanalysis. Diabetes Care. 2016;39(2):S196–S204.
24. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–1585.
25. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–2116.
26. Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol. 2005;16:3027–3037.
27. Cheung AK, Chang TI, Cushman WC, et al. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3):559–569.
28. Bilous R. DIRECT-renal: The Effect of the Angiotensin Type 1 Receptor Blocker Candesartan on the Development of Microalbuminuria in Type 1 and Type 2 Diabetes. Philadelphia: American Society of Nephrology (ASN) 41st Annual Meeting and Scientific Exposition; 2008.
29. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med. 2004;351:1941–1951.
30. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med. 2001;134:370–379.
31. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Collaborative Study Group: the effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–1462.
32. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345:870–878.
33. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–869.
34. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–860.
35. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351:1952–1961.
36. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol. 2007;3:486–492.

37. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006;1:940–951.
38. Bakris GL, Agarwal R, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219–2229.
38a. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385:2252–2263.

39. Ontarget Investigators. telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547–1559.
40. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal endpoints in a trial of aliskiren in type 2 diabetes. N Engl J Med. 2012;367:2204–2213.
41. Rossing K, Schjoedt KJ, Jensen BR, et al. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005;68:1190–1198.
42. Qiao Y, Shin JI, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimate glomerular filtration rate. JAMA Intern Med. 2020;180(5):718–726.
43. Tonolo G, Velussi M, Brocco E, et al. Simvastatin maintains steady patterns of GFR and improves AER and expression of slit diaphragm proteins in type II diabetes. Kidney Int. 2006;70:177–186.
44. Ansquer JC, Foucher C, Rattier S, et al. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). Am J Kidney Dis. 2005;45:485–493.
45. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. J Am Coll Cardiol. 2019;74(10):e177–e232.
46. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. Kdigo clinical practice guidelines for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259–305.
47. Fruchart JC, Sacks F, Hermans MP, et al. The Residual risk reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol. 2008;102:1K–34K.
48. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–1574.
49. Li Q, Wen F, Wang Y, et al. Diabetic kidney disease benefits from intensive low-protein diet: updated systematic review and meta-analysis. Diabetes Therapy. 2020. https://doi.org/10.1007/s13300-020-00952-5.
50. Phisitkul K, Hegazy K, Chuahirun T, et al. Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy. Am J Med Sci. 2008;335:284–291.

51. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look ahead randomized clinical trial. Lancet Diabetes Endocrinol. 2014;2(10):801–809.
52. Cohen R, Pereira TV, Aboud CM, et al. Effect of gastric bypass vs best medical treatment on early-stage chronic kidney disease in patients with type 2 diabetes and obesity: a randomized clinical trial. JAMA Surg. 2020;155(8):e200420.
53. Ito S, Kashihara N, Shikata K, et al. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN). Clin J Am Soc Nephrol. 2020;15(12):1715–1727.
54. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21:527–535.
55. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double blind, randomized, placebo-controlled trial. Lancet. 2019;393(10184):1937–1947.
56. Chertow GM, Pergola PE, Chen F, et al. Effects of Selonsertib in patients with diabetic kidney disease. J Am Soc Nephrol. 2019;30(10):1980–1990.
57. De Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin d receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomized controlled trial. Lancet. 2010;376:1543–1551.
58. Badve SV, Pascoe EM, Biostat M, et al. Effects of allopurinol on the

progression of chronic kidney disease. CKD-FIX study). 2020;382:2504–2513.

59. Doria A., Galecki A.T., Spino C., et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes (PERL study). 382:2493–2503

60. Navarro-Gonzalez JF, Mora Fernandez C, Muros de Fuentes FM, et al. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the predian trial. J Am Soc Nephrol. 2015;26:220–229.

33

Management of Patients With Diabetes and Chronic Kidney Disease

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Type 2 diabetes mellitus (T2D), and to a lesser extent type 1 (T1D), are rapidly increasing in incidence and remain the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the Western world.1 This chapter reviews the diagnostic and management considerations of the patient with diabetes and CKD, referred to as diabetic kidney disease (DKD), focusing on strategies with the potential to improve clinical outcomes.

DIAGNOSTIC CONSIDERATIONS

Diabetic kidney disease is usually a clinical diagnosis in patients with diabetes and CKD, with kidney biopsy reserved for atypical presentations such as frank hematuria amid negative urologic investigations, nephrotic range albuminuria in the presence of normal glomerular filtration rate (GFR), or an accelerated progression of albuminuria or decline in GFR.2 In such populations, one-half to two-thirds of patients have nondiabetic kidney disease.3 4 The presence of diabetic retinopathy increases the pretest probability of DKD, but its absence is less helpful in ruling it out.4 5

GENERAL MANAGEMENT CONSIDERATIONS

Patients with DKD are at risk of premature mortality from cardiovascular (CV) disease.6 7 The Kidney Disease: Improving Global Outcomes (KDIGO) guideline on Diabetes Management in CKD recommends lifestyle changes, identification and treatment of kidney-heart risk factors, patient self-management, and team-based integrated care programs to complement targeted pharmacotherapy (Fig. 33.1).8 Key lifestyle changes include smoking cessation, salt restriction to less than 5 g/day (sodium <2 g/day); adoption of diets high in fruits, vegetables, unsaturated fats, and plant-based proteins while avoiding processed meats and carbohydrates; and moderate-intensity physical activity for at least 150 minutes weekly. Self-management education programs empower patients to actively participate in this comprehensive care model, aiming to slow DKD progression, reduce CV and treatment-related complications, and improve satisfaction with and adherence to treatment plans.9 Future aims include halting the disease process and reversing damage.

A multidisciplinary approach is pivotal. It should include nephrologists, primary care providers, endocrinologists/diabetologists, cardiologists, nephrology/diabetes nurse specialists, podiatrists, ophthalmologists, and dieticians, as needed. Regular clinical monitoring improves outcomes in CKD patients,10 with current recommendations for follow-up ranging from yearly to quarterly depending on the level of GFR level and its rate of decline.

MONITORING DIABETIC KIDNEY DISEASE

Beyond methods for measuring glycemic control (see later), albuminuria (typically quantified by albumin-to-creatinine ratio [ACR]) and estimated GFR (eGFR) constitute the mainstay of monitoring in DKD.

Measures of Glycemic Control

Hemoglobin A1c

Hemoglobin A1c (HbA1c) arises from nonenzymatic glycation of blood hemoglobin11 and reflects average glycemia over approximately 10 to 12 weeks. Advantages are its accessibility and low intrasubject variability.12 Limitations include inability to provide measures of short-term serum glucose levels or glycemic variability and reduced correlation with blood glucose levels in advanced CKD stages, due largely to increased red blood cell turnover (see Chapter 86).[13] Despite this, elevated HbA1c (>8% [>64 mmol/mol]) has been associated with higher all-cause and CV mortality in people with advanced DKD, including those treated with dialysis or kidney transplantation.[14-18] Guidelines of the KDIGO recommend an individualized HbA1c target ranging between less than 6.5% and 8.0% or less in people with nondialysis DKD. Fig. 33.2 shows factors guiding decisions on individual HbA1c targets in DKD. In dialysis patients, the optimal glycemic target is unknown.

Self-Monitoring of Blood Glucose

In contrast to HbA1c, direct glucose measurements are not affected by severe CKD. Self-monitoring of blood glucose (SMBG) using a fingerstick and glucometer may facilitate maintenance of glycemic control. Self-monitoring is especially valuable in patients receiving insulin or other agents that may cause hypoglycemia. Because SMBG is at the discretion of the patient, episodes of hypoglycemia or hyperglycemia may be missed. Additionally, glucose variability cannot be readily assessed.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) devices measure interstitial glucose using subcutaneous sensors. Depending on the system used, glucose measurements can be programmed to be performed continuously or at specific intervals (typically every 5–15 minutes). Some models allow for visualization of glucose levels or trends in real time. Devices can generate reports that display glucose trends over time (specifying time within, above, and below the target glucose range) in addition to measures of glucose variability. A typical target range is a glucose level of 70 to 180 mg/dL (3.9–10.0 mmol/L) in more than 70% of readings.[19]

Continuous glucose monitoring facilitates meeting glycemic targets and encourages self-management, with newer models offering linkage with insulin delivery systems or smartphone integration. This type

Risk Reduction Strategy in Diabetic CKD

Regular
risk factor
reassessment
(every 3–6
months)

Lipid management

Glycemic
control

Additional
drugs with
heart and
kidney
protection

Blood
pressure control

GLP-1 RA

Antiplatelet therapies

ns-MRA

(T2D)

(ASCVD)

(T2D)

Metformin
(T2D)

Diet

Additional
risk factor
control

SGLT2 inhibitors
(T2D)

Exercise

RAS blockade
(HTN)

First-line
drug
therapy
Lifestyle
and selfmanagement

Statin

Smoking cessation

Weight

Diabetes with CKD

Fig. 33.1 Chronic Kidney Disease and Diabetes. Patients with diabetes and chronic kidney disease (CKD) Should be treated with a comprehensive strategy to reduce risks of kidney disease progression and adverse cardiovascular outcomes. Lifestyle and risk factor modification form the foundation of therapy, with pharmacotherapy targeted to appropriate patients using evidence from clinical trials. RAS, Renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2. (From Kidney Disease: Improving Global Outcomes [KDIGO] Diabetes Work Group. KDIGO 2022 clinical practice guidelines for diabetes management in chronic kidney disease. Kidney Int. 2022;102:S1-S127.)

Individualization of Glycemic Targets in Diabetic CKD
< 6.5%
CKD G1
Absent/minor

HbA1c
Severity of CKD
Macrovascular complications

Few

Comorbidities

Long

Life expectancy

Present
Available
Low

Hypoglycemia awareness
Resources for hypoglycemia management
Propensity of treatment to cause hypoglycemia

< 8.0%
CKD G5
Present/severe
Many
Short
Impaired
Scarce
High

Fig. 33.2 Glycemic Targets Should be Individualized for Patients with Diabetes and Chronic Kidney Disease (CKD). Clinical factors affecting benefits and risks, depicted here, should be assessed to inform shared decision making. CKD G1, Estimated glomerular filtration rate (eGFR) ≤90 mL/min/1.73 m2; CKD G5, eGFR <15 mL/min/1.73 m2. HbA1c, Hemoglobin A1c. (From Kidney Disease: Improving Global Outcomes [KDIGO] Diabetes Work Group. 2022 clinical practice guidelines for diabetes management in chronic kidney disease. Kidney Int. 2022;102:S1-S127.)

Management of Diabetic Chronic Kidney Disease
Physical activity
Nutrition
Weight loss

Lifestyle therapy

Metformin
eGFR
< 45

First-line therapy

SGLT2 inhibitor

eGFR
< 30

Reduce dose Discontinue

eGFR
< 20

+
Discontinue

Do not initiate

GLP-1 receptor agonist
(preferred)

Additional drug therapy as
needed for glycemic control

DPP-4 inhibitor

Insulin

Sulfonylurea

TZD

Discontinue

- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 mL/min per 1.73 m2 or treated with dialysis
- See Figure 33.4

Alpha-glucosidase inhibitor

Fig. 33.3 Most patients with type 2 diabetes and chronic kidney disease should be treated with lifestyle therapy, metformin, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor, depending on clinical factors and estimated glomerular filtration rate. Additional drug therapy may be needed to control glycemia if metformin and SGLT2 inhibition are not tolerated or contraindicated. DPP-4, Dipeptidyl peptidase-4; eGFR, estimated

glomerular filtration rate; GLP-1, glucagon-like peptide 1; TZD, thiazolidinedione. (From Kidney Disease: Improving Global Outcomes [KDIGO] Diabetes Work Group. 2022 clinical practice guidelines for diabetes management in chronic kidney disease. Kidney Int. 2022;102:S1-S127.)

of monitoring is especially valuable for people who have highly variable glucose levels, are at risk for experiencing severe hypoglycemia, and those for whom HbA1c levels do not align with measured blood glucose. Disadvantages of CGM include skin irritation related to the device patch and potentially high cost.

Albuminuria

Albuminuria is classified as normoalbuminuria (<30 mg albumin/24 h), moderately increased albuminuria (30–300 mg/24 h), and severely increased albuminuria (>300 mg/24 h). The terms microalbuminuria and macroalbuminuria should be abandoned. Any albuminuria is associated with an increased risk of DKD progression and cardiovascular disease (CVD).20 21 Moderately increased albuminuria was long viewed a first step in DKD, leading to worsening albuminuria, eGFR loss, and ESKD.22 However, reduced GFR in the absence of albuminuria is common, particularly in T2D, with up to 57% of patients in certain CKD cohorts presenting in this manner.23-25 These latter patients are still at increased risk of progression, albeit with slower rates of eGFR decline than albuminuric DKD.26 Additionally, albuminuria in patients with moderately increased albuminuria may not progress to severely increased albuminuria and even undergo spontaneous remission.27 28

Glomerular Filtration Rate

Measured and estimated GFR are important predictors of kidney prognosis, particularly when combined with albuminuria. In healthy persons the annual age-related eGFR decline is 0.5 to 1 mL/min/1.73 m2 29
A large cohort of participants with T1D (mean duration of 5.5 years) had median decline in eGFR of 3 mL/min/1.73 m2 over 3 years, with 25% experiencing a 3-year decline of 14 mL/min/1.73 m2 or greater.30
In more contemporary DKD cohorts, albuminuria is still associated with rapid eGFR decline even in the presence of renin-angiotensin system (RAS) inhibition. For example, the high kidney-risk CREDENCE

trial participants with T2D and DKD experienced an annual eGFR decline of 4.71 ± 0.15 mL/min/1.73 m2 per year.31 Limitations of using GFR to monitor disease progression include nonlinear trajectories in GFR decline, including the occurrence of hyperfiltration early in the disease course and treatment-induced hemodynamic changes in kidney function, imperfect correlations between estimated and measured GFR, and potential underestimation of eGFR decline in clinical trial settings when compared with real-world clinical scenarios.

Models to Predict Kidney Failure Risk

The Kidney Failure Risk Equation (KFRE) is a widely used prediction instrument that has been validated in several cohorts and CKD etiologies, including DKD (see https://kidneyfailurerisk.com).32 The KFRE uses patient age, sex, eGFR, and ACR to offer 2-year and 5-year risk estimates of developing ESKD. In addition to helping nephrologists quickly convey prognostic information to patients, KFRE-derived risk estimates are routinely used to anticipate and plan for the initiation of kidney-replacement therapies.

MANAGEMENT OF GLYCEMIA

Insulin is the primary treatment for T1D, with dosing schedules iteratively refined based on observed blood glucose concentrations at all levels of kidney disease. In T2D, oral antihyperglycemic agents are preferred as foundational therapy because of their lower risks of hypoglycemia and, for some drug classes, reduction in the risk of progressive

CKD or CV events. For patients with T2D and CKD, lifestyle treatments, metformin, and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are recommended as first-line therapy, with some restrictions according to eGFR (Fig. 33.3). Additional or alternate agents should be selected according to patient preferences, comorbidities, and other characteristics when needed to achieve glycemic goals (Fig. 33.4).

Personalized Management of Diabetic CKD
-su table medication
s
Less
TZD

ble medicat
e-su ta
ions
Mor
GLP1RA

SU, AGI

Pr
ef

r

eGFR < 15
mL/min/1.73
m2 or treatment
with dialysis

GLP1RA,
DPP4i,
insulin

GLP1RA,
insulin

Potent
glucose-lowering
Avoid
hypoglycemia

Low cost
SU, TZD,
AGI

DPP4i,
TZD, AGI

ti

DPP4i
insulin,
TZD

GLP1RA

,
rb d ty or other
mo
ch
o
c
ar
ac
e

te
ri
Heart
High-risk
failure
ASCVD

Weight
loss

GLP1RA

SU, insulin, TZD

Avoid
injections

GLP1RA,
DPP4i,
TZD, AGI

SU,
insulin

DPP4i, TZD, SU, AGI,
oral GLP1RA

GLP1RA, insulin

Fig. 33.4 For patients with type 2 diabetes and chronic kidney disease (CKD) who have not achieved individualized glycemic targets despite use of metformin and sodium-glucose cotransporter-2 inhibitor treatment, or who are unable to use those medications, patient preferences, comorbidities, and other characteristics should be used to select additional or alternate glucose-lowering medications. In general, glucagon-like peptide 1 receptor agonists (GLP1RA) may be preferred because of their beneficial cardiovascular effects, and possible beneficial effects on CKD progression. AGI, Alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; SU, sulfonylurea; TZD, thiazolidinedione. (From Kidney Disease: Improving Global Outcomes [KDIGO] Work Group. 2022 clinical practice guidelines for diabetes management in chronic kidney disease. Kidney Int. 2022;102:S1-S127.)

Hypoglycemia and Hyperglycemia

Episodes of hypoglycemia are more common in patients with severe CKD or requiring dialysis due to reduced insulin clearance and impaired renal gluconeogenesis. Hypoglycemic episodes may result in increased short-term mortality, and these risks may be further elevated in patients who are elderly or have multiple comorbidities.[33] In stage III CKD, regular review of the oral antihyperglycemic regimen or insulin dosing is essential. With progression of CKD, medications that have a higher risk of inducing hypoglycemia should be dose reduced or replaced based on the following considerations.

Oral Hypoglycemic Agents

Many oral agents for the treatment of T2D require dose adjustments with reduced GFR (Table 33.1). Also, in advanced CKD, drug-drug

interactions increase together with further complications of diabetes. For example, gastroparesis affects the pharmacokinetics of oral medications.

Biguanides

Metformin decreases hepatic glucose production, increases insulin sensitivity and insulin-mediated utilization of glucose in peripheral tissues, and decreases intestinal glucose absorption. Metformin is recommended as the first-line agent for management of T2D in combination with SGLT2i and lifestyle measures (Fig. 33.3).34 In addition to effectively improving glycemic control, metformin modestly reduces the risk of CV events and death in T2D.35 Metformin dosage should be reduced when eGFR drops below 45 mL/min/1.73 m2, and such patients should be instructed to temporarily stop metformin in states

TABLE 33.1

Daily Dosing for Selected Oral Hypoglycemic Agents

Class

Drug

CKD1 and 2: eGFR CKD3a: eGFR
>60 mL/min/1.73 45–59 mL/
m2
min/1.73 m2

Biguanides

Metformin IR

No adjustment

No adjustment

Metformin ER

No adjustment

No adjustment

Canagliflozin

No adjustment

100 mg once daily

Dapagliflozin

No adjustment

No adjustment

850 mg or 1000
mg once daily
1000 mg once
daily
100 mg once
daily
No adjustment

Empagliflozin

No adjustment

No adjustment

No adjustment

Exenatide IR

No adjustment

No adjustment

No adjustment

Avoid initiation with
eGFR <25 mL/
min/1.73 m2a
Avoid initiation with
eGFR <20 mL/
min/1.73 m2a
Avoid

Exenatide ER
Dulaglutide
Semaglutide
(injection or oral)
Liraglutide
Linagliptin

No adjustment
No adjustment
No adjustment

No adjustment
No adjustment
No adjustment

Avoid
No adjustment
No adjustment

Avoid
No adjustment
Limited experience

Avoid
Avoid
Limited experience

No adjustment
No adjustment

No adjustment
No adjustment

No adjustment
No adjustment

Limited experience
No adjustment

Limited experience
No adjustment

Sitagliptin
Saxagliptin

No adjustment
No adjustment

No adjustment
No adjustment

25 mg once daily
2.5 mg once daily

25 mg once daily
2.5 mg once daily

Pioglitazone
Gliclazide
Glipizide
Glimepiride
Repaglinide
Acarbose

No adjustment
40 mg once daily
No adjustment
No adjustment
No adjustment
No adjustment

No adjustment
40 mg once daily
20 mg once daily
1 mg once daily
No adjustment
No adjustment

50 mg once daily
2.5 mg once
daily
No adjustment
40 mg once daily
20 mg once daily
1 mg once daily
No adjustment
No adjustment

No adjustment
40 mg once daily
20 mg once daily
1 mg once daily
No adjustment
Avoid

No adjustment
Avoid
Avoid
Avoid
Limited experience
Avoid

SGLT-2i

Incretin mimetics
(GLP-1 receptor
agonists)

Gliptins (DPP-4
inhibitors)

Thiazolidinediones
Sulfonylureas

Meglitinides
α-Glucosidase
inhibitors

CKD3b: eGFR
30–44 mL/
min/1.73 m2

CKD4: eGFR 15–29
mL/min/1.73 m2

CKD5: eGFR <15
mL/min/1.73 m2
or Dialysis

Avoid

Avoid

Avoid

Avoid

Avoid initiation

Avoid
Avoid

Avoid

Avoid

[a] Threshold levels of eGFR for drug initiation are based on published clinical trials. Regulatory guidance may vary by agency, over time, and according to specific indication.

CKD, Chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ER, extended release; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide-1; IR, immediate release; SGLT-2, sodium-glucose cotransporter-2.

Listed dosages reflect the maximum daily recommendations based on manufacturer recommendations and expert opinion. Drug initiation and uptitration should be done slowly and cautiously with declining eGFR. Available formulations and pharmacologic guidelines vary by country.

of dehydration, before the administration of radiocontrast media, and other situations where there is an increased risk for acute kidney injury (AKI). Metformin is not recommended for people with eGFR less than 30 mL/min/1.73 m2 because of the risk for lactic acidosis. However, a Cochrane review[36] found no evidence that advanced CKD was associated with increased risk for lactic acidosis in patients receiving appropriate doses of metformin.[35,37]

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT2i block kidney proximal tubular glucose reabsorption. Resulting reductions in blood glucose are greater with higher concentrations of blood glucose and higher GFR. Along with metformin, SGLT2i are first-line antihyperglycemic therapy in DKD, given their cardioprotective and renoprotective effects (Fig. 33.3). In the EMPA-REG OUTCOME trial in patients with T2D and eGFR above 30 mL/min/1.73 m2, empagliflozin reduced the risk of CV mortality, all-cause mortality, and hospitalization for congestive heart failure with favorable effects on weight and systolic blood pressure. The EMPA-REG OUTCOME trial also reported a reduced progression of kidney failure and albuminuria.[38] The CREDENCE trial enrolled patients with

T2D, eGFR 30 to 90 mL/min/1.73 m2, and macroalbuminuria and demonstrated reduced CKD progression and incident kidney failure with canagliflozin.31 Additional randomized controlled trials (RCTs; CANVAS, DECLARE-TIMI 58, VERTIS, DAPA-CKD, DAPA-HF, EMPEROR-Reduced, SCORED, SOLOIST) have consistently demonstrated substantial long-term CV and kidney benefits of SGLT2i across eGFR despite reduced antihyperglycemic effects (Table 33.2).39-46

The mechanisms underlying kidney benefits of SGLT2i are incompletely understood. Effects have been attributed in part to restoration of tubuloglomerular feedback and reduction of glomerular hyperfiltration via increased distal sodium delivery to the macula densa. Other mechanisms may include improvements in energy metabolism, with a shift from carbohydrate to ketone metabolism inducing an energyefficient mitochondrial oxygen consumption that reduces kidney hypoxia.47 Reduced glomerular hyperfiltration is thought to account for the acute decline in eGFR observed with SGLT2i initiation.

Text continues on p. 397

TABLE 33.2 Summary of Selected Large Clinical Trials of Recently Established and Potential
New Therapeutics in Diabetic Kidney Disease
Study

Treatment Arms

Duration

Patient Cohort

Outcome

Canagliflozin 100 mg
daily vs. placebo

2.6 years

4401 T2D patients with
stage 2 or 3 CKD and
macroalbuminuria and on
an ACE inhibitor or ARB

Empagliflozin vs. placebo

3.1 years

7020 participants with T2D
at high CV risk

Primary: 30% reduction in ESKD,
S-creatinine doubling, renal/CV death
Secondary: 20% reduction in CV death,
nonfatal MI, nonfatal stroke; 39% reduction
in hospitalization for CHF; 34% reduction in
composite renal endpoint (ESKD, doubling
of serum Cr, renal death)
14% reduction in composite; death from CV
causes, nonfatal MI, or nonfatal stroke

Canagliflozin vs. placebo

3.6 years

10,142 participants with
T2D and high CV risk

Dapagliflozin and
Cardiovascular Outcomes in
Type 2 Diabetes (DECLARETIMI 58),40 NCT01730534

Dapagliflozin vs. placebo

4.2 years

17,160 participants
with T2D at risk for
atherosclerotic CVD

Cardiovascular Outcomes

with Ertugliflozin (VERTIS),41
NCT01986881

Ertugliflozin vs. placebo

3.5 years

8246 participants with T2D
and atherosclerotic CVD

Dapagliflozin in Patients with
Heart Failure and Reduced
Ejection Fraction (DAPAHF),43 NCT03036124
Cardiovascular and Renal
Outcomes with Empagliflozin
in Heart Failure (EMPERORReduced),44 NCT03057977
Sotagliflozin in Patients
with Diabetes and Chronic
Kidney Disease (SCORED),45
NCT03315143
Sotagliflozin in Patients
with Diabetes and Recent
Worsening Heart Failure
(SOLOIST),46 NCT03521934
DAPA-CKD,42 NCT02065791

Dapagliflozin vs. placebo

1.5 years

4744 participants with HF
and an ejection fraction
≤40%

Empagliflozin vs. placebo

1.3 years

3730 participants with HF

Sotagliflozin vs. placebo

1.3 years

10,584 participants with
T2D and CKD at risk for
CVD

Sotagliflozin vs. placebo

9 months

1222 participants with
T2D and a recent HF
hospitalization

Dapagliflozin vs. placebo

2.4 years

T2D with DKD or
nondiabetic kidney
disease with eGFR 25–75
mL/min/1.73 m2 and

UACR 200–5000 mg/g

SGLT2i
Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE),31 NCT02065791
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME),38 NCT01131676
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS),39 NCT01032629

Primary: 14% reduction in composite death from CV causes, nonfatal MI, nonfatal stroke
Secondary: 27% reduction in albuminuria progression; 40% reduction in composite sustained 40% reduction in eGFR, need for renal replacement therapy, death from renal causes
Primary: 17% reduction in CV death or hospitalization for HF; no difference with respect to MACEs
Secondary: 24% reduction in composite renal events (>40% decrease in eGFR to <60 mL/min/1.73 m2, new ESKD, or death from renal or CV causes); 7% reduction in death from any cause
Primary: noninferiority for MACEs
Secondary: no difference in death from CV causes or hospitalization for HF; no difference in death from renal causes, renal replacement therapy, or doubling of serum Cr
26% reduction in composite worsening HF or CV death

Primary: 25% reduction in composite CV death or hospitalization for worsening HF
Secondary: slower eGFR decline, reduced renal outcomes
26% reduction in composite death from CV causes, HF hospitalizations/urgent visits; 16% reduction in death from CV causes, nonfatal MI, or nonfatal stroke
33% reduction in death from CV causes, hospitalization, and urgent visits for HF

Primary: 44% reduction in kidney composite endpoint (≥50% sustained decline in eGFR, ESKD, or kidney or CVD death)
Secondary: 29% reduction in CV mortality or hospitalization for CHF; 31% reduction in all-cause mortality

Summary of Selected Large Clinical Trials of Recently Established and Potential New Therapeutics in Diabetic Kidney Disease—cont’d

TABLE 33.2

Study	Treatment Arms	Duration	Patient Cohort	Outcome
EMPA-KIDNEY (NCT03594110)	Empagliflozin vs. placebo	Ongoing	DKD (T2D or T1D) or nondiabetic kidney disease with eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 with UACR ≥200 mg/g	Ongoing: Composite outcome of time to first occurrence of kidney disease progression (ESKD, sustained decline in eGFR to <10 mL/min/1.73 m^2), kidney death, or a sustained decline of ≥40% in eGFR from randomization), or CV death
	Liraglutide vs. placebo	3.8 years	9340 participants with T2D at high CV risk	Reduction in composite of death from CV causes, nonfatal MI, or nonfatal stroke
	Semaglutide vs. placebo	2 years	3297 participants with T2D	Primary: 26% reduction in composite of CV death, nonfatal MI, or nonfatal stroke Secondary: reduction in new or worsening kidney dysfunction
	Albiglutide vs. placebo	1.5 years	9463 participants with T2D	

and CVD

22% reduction in composite of CV death, MI,
or stroke

Dulaglutide vs. placebo

5.4 years

9901 participants with T2D
and CV risk factors

12% reduction in composite nonfatal MI,
nonfatal stroke, or death from CV causes

Semaglutide vs. placebo

Ongoing

Ongoing: Time to first occurrence of a
composite primary outcome event defined
as persistent eGFR decline of ≥50% from
trial start, reaching ESKD, death from
kidney disease, or death from CVD

Cotadutide (dual GLP1
and glucagon receptor
agonist) vs. placebo

Ongoing

T2D with eGFR ≥50 to <75
mL/min/1.73 m2 with
UACR >300 mg/g and
<5000 mg/g or eGFR ≥25
to <50 mL/min/1.73 m2
with UACR >100 mg/g to
<5000 mg/g
T2D with eGFR ≥20 to <90
mL/min/1.73 m2 with
UACR >50 mg/g

Ruboxistaurin mesylate
32 mg vs. placebo

2.7 years

707 T2D participants with
diabetic neuropathy

Patients treated with ruboxistaurin had lower
UACR and higher eGFR

3.7 years

10,061 adults with a history
of MI and systemic
inflammation (elevated
high-sensitivity CRP >2
mg/mL); 40% had T2D
and 46% of those with
CKD in the trial had T2D

15% reduction in 3-point MACE:

nonfatal MI, any nonfatal stroke, or CV
death; subsequent post hoc analyses
demonstrated that the risk of MACE was
reduced in people with CKD and in those
with albuminuria or diabetes

GLP-1 Receptor Agonists
Liraglutide and Cardiovascular
Outcomes in Type 2 Diabetes
(LEADER),48 NCT01179048
Semaglutide and
Cardiovascular Outcomes
in Patients with Type 2
Diabetes (SUSTAIN-6),49
NCT01720446
Albiglutide and Cardiovascular
Outcomes in Patients
with Type 2 Diabetes
and Cardiovascular
Disease (HARMONY),50
NCT02465515
Dulaglutide and Cardiovascular
Outcomes in Type 2 Diabetes
(REWIND),51 NCT01394952
Effect of Semaglutide Versus
Placebo on the Progression
of Renal Impairment in
Subjects With Type 2
Diabetes and Chronic
Kidney Disease (FLOW),
NCT03819153
A Phase IIb, Multicenter,
Randomised, Double-Blind,
Placebo-Controlled, and
Open-Label Comparator
Study of Cotadutide in
Participants Who Have
Chronic Kidney Disease With
Type 2 Diabetes Mellitus,
(NCT04515849)
PKCβ Inhibitors
Treatment of Peripheral
Neuropathy in Patients with
Diabetes,109 NCT00044421

Antiinflammatory Agents
Canakinumab AntiCanakinumab 300 mg vs.
Inflammatory Thrombosis
canakinumab 150 mg
Outcome Study (CANTOS),110
vs. placebo
NCT01327846

Ongoing: UACR, HbA1c, body weight

Continued

TABLE 33.2 Summary of Selected Large Clinical Trials of Recently Established and Potential New Therapeutics in Diabetic Kidney Disease—cont'd

Study	Treatment Arms	Duration	Patient Cohort	Outcome
A Study to Evaluate the Safety and Efficacy of CCX140-B in Subjects With Diabetic Nephropathy,[111] NCT01447147	CCX140-B 10 mg (CCR2 inhibitor) vs CCX140-B 5 mg vs. placebo	52 weeks	332 T2D patients with proteinuria, GFR ≥25 mL/min/1.73 m2	Albuminuria lowering
Effects of Selonsertib in Patients with Diabetic Kidney Disease,[112] NCT02177786	1:1:1:1 allocation to selonsertib (oral daily doses of 2, 6, or 18 mg) or placebo	48 weeks	333 adults with moderate to advanced DKD (eGFR of 15–60 mL/min/1.73 m2 at screening) and albuminuria, defined as a UACR ≥600 mg/g if stage 3a CKD, UACR ≥300 mg/g if stage 3b CKD, and UACR ≥150 mg/g if stage 4 CKD	Primary endpoint: no difference in eGFR at 48 weeks In post hoc analyses from 4 and 48 weeks, eGFR decline was reduced by 71% for the 18-mg group vs. placebo (difference 3.11 mL/min/1.73 m2 per year, P = .043) Effects on UACR did not differ between

selonsertib and placebo

90 days

1066 patients with
worsening HFrEF and CKD
and/or T2D

90 days

823 T2D patients with high
or very high albuminuria
on ACEs or ARBs
5734 T2D patients with
DKD (persistent high
albuminuria or very high
albuminuria)

Finerenone reduced a composite endpoint of
death from any cause, CV hospitalizations,
or emergency presentation for worsening
HF; reduced albuminuria
Reduced albuminuria

Mineralocorticoid Receptor Antagonists
Finerenone (multiple
Mineralocorticoid Receptor
doses) vs. eplerenone
Antagonist Tolerability
Study–Heart Failure (ARTSHF),113 NCT01807221
ARTS–Diabetic Nephropathy
Finerenone (multiple
(RTS-DN),114 NCT1874431
doses) vs. placebo

Primary: 18% reduction in time to first
occurrence of the composite of onset of
kidney failure, sustained decrease of eGFR
≥40% from baseline over at least 4 weeks,
and renal death
Secondary: 14% reduction in death from
CV causes, nonfatal MI, nonfatal stroke, or
hospitalization for CHF
Primary: 13% reduction in time to first
occurence of the composite of death from
CV causes, nonfatal MI, nonfatal stroke,
or hospitalization for CHD.Secondary
outcome: no significant difference in time
to kidney failure, sustained decrease of
eGFR ≥40% from baseline, or renal death.

Efficacy and Safety of
Finerenone in Subjects with
Type 2 Diabetes Mellitus
and Diabetic Kidney
Disease (FIDELIO-DKD),83
NCT02540993

Finerenone vs. placebo

2.6 years

Efficacy and Safety of
Finerenone in Subjects

with Type 2 Diabetes
Mellitus and a Clinical
Diagnosis of Diabetic Kidney
Disease (FIGARO-DKD),
NCT02540993

Finerenone (10 mg vs. 20
mg vs. placebo)

3.4 years

7437 T2D patients with
DKD (persistent high
albuminuria or very high
albuminuria)

2.2 years

2,648 patients with T2D,
eGFR 25–75 mL/min/1.73
m2 and ACR 300–500
mg/g on RAS blockers

Early termination (lower number of events),
35% relative risk reduction of doubling of
serum Cr or ESKD

2.25 years

8399 patients with HFrEF
with and without DM

Slower rate of eGFR decline with neprilysin
inhibition (−1.3 vs. −1.8 mL/min/1.73 m2 per
year; P < .0001); though greater increase in
UACR (1.20 mg/mmol [95% CI, 1.04–1.36
mg/mmol] vs. 0.90 mg/mmol [95% CI,
0.77–1.03 mg/mmol]); greater impact in
diabetes cohort

Endothelin Receptor Antagonists
Atrasentan 0.75 mg vs.
SONAR,115 NCT01858532
placebo

Neprilysin Inhibitors
Prospective Comparison
of ARNI with ACEI to
Determine Impact on Global
Mortality and Morbidity
in Heart Failure trial,116
(PARADIGM-HF)

Sacubitril/valsartan vs.
enalapril

Summary of Selected Large Clinical Trials of Recently Established and Potential New Therapeutics in Diabetic Kidney Disease—cont’d

TABLE 33.2

Study	Treatment Arms	Duration	Patient Cohort	Outcome
Efficacy and Safety of LCZ696 Compared with Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction trial,117 (PARAGON-HF)	Sacubitril/valsartan vs. valsartan	2.9 years	4822 with HFpEF with and without DM	Nonsignificant reduction in the primary outcome of composite total hospitalizations for CHF and death from CV causes (HR, 0.87; 95% CI, 0.75–1.01; P = .06); renal composite outcome (time to first occurrence of either ≥50% reduction in eGFR, ESKD, or death from renal causes [HR, 0.50; 95% CI, 0.33–0.77; P = .001])
United Kingdom Heart and Renal Protection-III118	Sacubitril/valsartan vs. irbesartan	12 months	414 participants (40% with a history of DM at baseline) with eGFR 20–60 mL/min/1.73 m2 and without CHF	Sacubitril/valsartan reduced blood pressure, NT-pro-BNP, and troponin I significantly more compared with irbesartan, but without affecting eGFR or UACR

ACE, Angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PKCβ, protein kinase Cβ; RAS, renin-angiotensin system; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

SGLT2i are associated with increased risk of euglycemic diabetic ketoacidosis and genital mycotic infections. Patients should be advised of these adverse effects and monitored closely for their development. Additionally, the SGLT2i class is part of the routine “sick day” medication list that should be held during periods of illness.

Incretin Mimetics: Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) promote glucosemediated insulin secretion by pancreatic β-cells in response to food entering the gut and suppress glucagon secretion. These receptor agonists are potent antihyperglycemic agents and stimulate weight loss by appetite suppression, both centrally and by affecting gastric motility. Guidelines of KDIGO recommend initiation of GLP-1 RA in T2D patients who have not achieved glycemic control despite metformin and SGLT2i, in large part because of these agents’ CV and kidney benefits. In RCTs, GLP-1 RA therapies reduced major adverse CV events in people with T2D at high risk for CVD (LEADER, SUSTAIN-6, HARMONY, REWIND; Table 33.2).48-51 A subset of these studies reported a reduction in albuminuria and eGFR decline with GLP-1 RA use (detailed further later) Adverse effects associated with GLP-1 RA use include gastrointestinal symptoms and, with subcutaneously administered formulations, injection site reactions. Glucagon-like peptide-1 receptor agonists should be avoided in people with a history of medullary thyroid cancer or pancreatitis.

Sulfonylureas

Sulfonylureas are a class of insulin secretagogues that stimulate pancreatic insulin secretion by closing potassium–adenosine triphosphate channels on β-cell plasma membranes. First-generation sulfonylureas are long acting and should be avoided in people with CKD given their almost exclusive renal excretion. Second-generation agents are short acting and primarily metabolized by the liver, with most metabolites (which hold antihyperglycemic properties) undergoing kidney clearance. Their use carries the risk for hypoglycemia, especially as eGFR declines. Sulfonylureas are highly protein bound but can be displaced into the circulation by other drugs such as salicylates or β-blockers, further contributing to hypoglycemia. Sulfonylureas are therefore discouraged in patients with severe CKD.

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor (PPAR) modulators that function by increasing insulin sensitivity. These agents do not cause hypoglycemia and come at a low cost. However, thiazolidinediones may cause weight gain and fluid retention through transcriptional upregulation of tubular amiloridesensitive sodium channels, which may be problematic in people with CKD at risk for heart failure. Higher rates of bone fractures also have been reported in patients treated with these agents.

Meglitinides

Meglitinides are primarily metabolized in the liver and act as insulin secretagogues similar to sulfonylureas. Because of the risk of hypoglycemia, these agents should be avoided with advanced CKD. Alternatively, formulations that are not primarily excreted by the kidneys, such as repaglinide, may be used.

Gliptins: Dipeptidyl Peptidase-4 Inhibitors

Gliptins inhibit the effect of dipeptidyl peptidase-4 (DPP-4), a cellular membrane protein expressed in a variety of tissues that rapidly degrades endogenous incretin hormones (e.g., GLP-1). Agents such as linagliptin are primarily metabolized by the liver and excreted in the bile, and thus they do not require dose adjustments in CKD. Gliptins are advantageous because they do not cause weight gain or hypoglycemia. Despite their similar mechanism of action to GLP-1 RA, DPP-4 inhibitors do not have equivalent CV or kidney benefits.

α-Glucosidase Inhibitors

α-Glucosidase is an intestinal enzyme that digests carbohydrates by hydrolyzing complex starches to oligosaccharides in the lumen of the small intestine, releasing glucose. Inhibition of this enzyme maintains the integrity of complex carbohydrates, thereby allowing less glucose absorption. Thus, α-glucosidase inhibitors should be taken at the start of meals. These agents may be maintained but require dose adjustment with advancing CKD. Advantages of these agents include their low cost and low rates of hypoglycemia.

Insulin

Endogenously secreted insulin undergoes first-pass metabolism in the liver, leaving approximately 50% available to enter the systemic circulation. The kidney removes 30% to 80% of systemic insulin (endogenous insulin that escapes first-pass metabolism, or exogenous insulin given subcutaneously or parenterally).35 Patients with severe CKD are prone to hypoglycemia due to reduced insulin clearance and decreased renal gluconeogenesis,52 and doses may need to be reduced as GFR declines.53

Types of insulin. Commonly used rapid-acting analogs (e.g., aspart, lispro) and long-acting analogs (e.g., glargine, detemir) have a metabolic profile that is largely unaffected by CKD. Currently no specific insulin regimen is recommended in the setting of CKD. For T1D, the basal bolus regimen of 3 daily injections of short-acting insulin with meals combined with 1 or 2 injections of long-acting insulin, as used in the Diabetes Control and Complications Trial (DCCT), is the standard treatment regimen. Pumps administering continuous subcutaneous infusions of short-acting insulins are also common, increasingly paired with real-time glucose monitoring. For T2D patients requiring insulin, the regimen usually starts on once- or twice-daily long- or intermediate-acting insulin. Mixed formulations (fixed percentages of short- to long-acting insulins) or the basal bolus regimen as in T1D may be necessary if glycemic control is not achieved.

MANAGEMENT OF HYPERTENSION

Blood Pressure Goals

Blood pressure (BP) targets in patients with diabetes have gradually declined over the years. The 2021 KDIGO clinical practice guideline for the management of BP in CKD recommends the lowest target of a systolic BP less than 120 mm Hg in patients with hypertension and CKD (GRADE 2B).54 This recommendation differs from CKD targets in other guidelines, including the 2017 ACC/AHA recommendation of less than 130/80 mm Hg, the ESC/ESH recommendation of less than 130 to 139 mm Hg systolic, the NICE target of 120 to 139 mm Hg systolic, the ADA target of less than 130/80 mm Hg (for patients with diabetes at high CV risk), and the Hypertension Canada target of less than 130/80 mm Hg.55-58

The lower BP target in CKD currently advocated for by the 2021 KDIGO BP guideline is largely based on a lack of heterogeneity in the CV and all-cause mortality outcomes of the Systolic Blood Pressure Intervention Trial (SPRINT) within the CKD subgroup.59 However, the SPRINT trial, which compared less than 120 mm Hg to less than 140 mm Hg, excluded participants with diabetes, and KDIGO does acknowledge that benefits of intensive BP lowering is less certain in patients with DKD. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial remains the preeminent trial comparing the less than 120 mm Hg to less than 140 mm Hg targets in an entirely diabetic population. This trial failed to show a difference in the primary CV outcome between groups, though the intensive target did significantly reduce the risk of stroke.60 KDIGO argues that ACCORD excluded participants with a creatinine greater than 1.5 mg/dL (>132 μmol/L) and does not offer adequate evidence against intensive BP reduction in this population. This is contrasted with the large number of participants with CKD in SPRINT, as well as the 42% of SPRINT participants with prediabetes and preserved CV/mortality benefits within this group.61 When considering a systolic target of less than 120 mm Hg for people with diabetes, it is important to acknowledge the lack of direct evidence supporting or refuting this recommendation. The current recommendations of intensive BP control, whether a systolic BP less than 120 mm Hg or less than 130 mm Hg, are based on

CV and mortality benefits as opposed to kidney protection. Intensive BP lowering in SPRINT, ACCORD, and the Secondary Prevention of Small Subcortical Strokes Trial (SPS3) was actually associated with higher overall rates of eGFR decline, and a meta-analysis of BP control trials including the African American Study of Kidney Disease and Hypertension (AASK) and Modification of Diet in Renal Disease (MDRD) demonstrated that more intensive BP control reduced kidney failure risk only in participants with baseline proteinuria.62,63

Newer studies of intensive BP lowering on CV and kidney outcomes in patients with DKD are warranted, particularly in light of newer therapies offering cardiorenal protection including SGLT2i, GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists (MRA).

Notwithstanding the recommendations of clinical practice guidelines, an individualized approach accounting for patients' unique clinical situation and preferences is explicitly recommended by KDIGO and ADA.54,64,65 Standardized BP measurement techniques and validated equipment for all methods is an additional recommendation.

Established techniques include ambulatory BP monitoring, home BP monitoring, and automated office BP measurements (preferable over auscultation).

Choice of Agents Including Renin-AngiotensinAldosterone System Blockade

Most clinical practice guidelines recommend the use of RAS inhibition with ACE inhibitors/ARBs in patients with DKD and moderately severely increased albuminuria.8,58 Evidence for kidney protection from RAS inhibitors in macroalbuminuria is derived from the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) trials.66,67 The use of ACE inhibitors in DKD with microalbuminuria was studied in the Micro-HOPE study demonstrating benefits in the composite CV outcome though without reductions in hard kidney outcomes.68 The kidney benefits of RAS inhibitors in DKD patients without albuminuria are less clear.

The HOPE, EUROPA, and PEACE studies do support the use of RAS inhibitors for CV protection in this population, however,68-70 but other antihypertensive agents may confer similar cardioprotective effects in this population. The BENEDICT and ROADMAP trials additionally demonstrated a RAS inhibitor–associated reduction in the progression to microalbuminuria in patients with T2D without DKD.71,72

RAS inhibitor side effects include hyperkalemia, hemodynamicmediated acute decline in kidney function, and ACE inhibitor–induced angioedema. Dual RAS inhibition with ACE inhibitors, ARB, or direct renin inhibitors is associated with increased harm from hyperkalemia and AKI without long-term CV or kidney benefits. Hyperkalemia, even if modest, may lead to premature and unnecessary discontinuation of RAS inhibitors. However, there are several approaches to mitigate these risks. In addition to dietary advice and use of diuretics, newer potassium binders such as patiromer and sodium zirconium cyclosilicate (SZC) safely reduce serum potassium levels. An ongoing trial is testing whether these agents confer CV and kidney benefits by controlling hyperkalemia to enable maximal RAS blockade in the treatment of heart failure and/or CKD (NCT03888066).

Patients with DKD usually will require more than one antihypertensive agent to achieve BP targets. Thiazide diuretics and dihydropyridine calcium channel blockers have been demonstrated to reduce CV events in large outcomes studies, which, however, were not dedicated CKD trials.73-75 In patients with diabetes requiring antihypertensive therapy in addition to RAS inhibition, Hypertension Canada suggests that a dihydropyridine calcium channel blocker is preferable to a thiazide/thiazide-like diuretic,58 based on favorable CV outcomes of the Avoiding Cardiovascular Events Through Combination Therapy

in Patients Living With Systolic Hypertension (ACCOMPLISH) trial with benazepril/amlodipine compared with benazepril/hydrochlorothiazide.74 The ACCOMPLISH trial was not a dedicated CKD trial and used a shorter-acting thiazide diuretic, which may have been inferior to longer-acting thiazides like indapamide or chlorthalidone. Indeed, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial compared combination therapy with perindopril and indapamide to usual care without thiazide-type diuretic in patients with T2D. The primary outcome—a combination of macrovascular and microvascular events that included progression of DKD—was significantly reduced in the active treatment arm. A significant reduction in "all kidney events" with active treatment was also observed. Considering that both treatment groups had high rates of RAS blockade, the observed benefits in CV and kidney outcomes were attributed to greater BP lowering and/or addition of a long-acting thiazide diuretic in the active treatment arm.75

ADDITIONAL APPROACHES TO SLOWING CKD PROGRESSION IN DIABETES

The significant residual risk of DKD progression despite the aforementioned therapeutic strategies has led to the emergence of additional pharmacotherapies.

SGLT2 Inhibitors

The CV and kidney protective effects of SGLT2i in patients with T2D were demonstrated in several CV outcome trials with post hoc analyses of kidney outcomes.76-78 Two dedicated kidney outcome trials have followed: CREDENCE, involving participants with T2D, eGFR of 30 to 90 mL/min/1.73 m^2, and ACR of 300 to 5000 mg/g; and DAPA-CKD, involving participants with and without diabetes, eGFR of 25 to 75 mL/min/1.73 m^2, and ACR of 200 to 5000 mg/g. Both studies demonstrated significant reductions in kidney outcomes with SGLT2 inhibition including ESKD, decline in eGFR, and death from kidney/CV causes.31,42 Results of DAPA-CKD were consistent among subgroups of participants with and without T2D, and SGLT2i have been incorporated into most diabetes and CKD guidelines including KDIGO.

suffered from hyperkalemia events.82,83 FIDELIO-DKD was a phase III trial of the nonsteroidal MRA finerenone, in addition to standard of care, in participants with T2D, most in CKD stage III and with a median urinary albumin-to-creatinine ratio (UACR) of 852 mg/g. Finerenone was safe and reduced rates of the primary composite of kidney failure, sustained 40% decline or greater in eGFR, or death from renal causes by 18% as well as the secondary composite CV outcome.84 The FIGARO-DKD trial demonstrated a 13% reduction in the same composite CV outcome with finerenone compared with placebo, establishing finerenone as another treatment option to improve clinical outcomes in DKD.84a

Implementation of Newer Agents to Slow DKD Progression

It is expected that SGLT2i, GLP-1 receptor agonists, and nonsteroidal MRAs increasingly will be used together in the setting of DKD on a background of single-agent RAS blockade. The 28-week, phase III, DURATION-8 trial demonstrated that dual therapy with dapagliflozin and exenatide had additive effects on lowering weight and blood pressure, though with a less than additive effect on HbA1c. Additive effects on weight loss were similarly demonstrated in the SUSTAIN-9 and AWARD-10 trials.85,86 The effect of combination therapy on heart and kidney outcomes in DKD is unknown. A propensity-matched cohort from the EXSCEL trial demonstrated that the addition of exenatide in patients on a background of SGLT2 inhibition resulted in modest improvements in major adverse cardiovascular events (MACE), all-cause mortality, and slower rates of kidney function decline compared with patients not on an SGLT2i.87 Only 4% to 11% of FIDELIO-DKD participants were on an SGLT2i over the course of the study, and CREDENCE did not enroll participants taking an MRA at baseline, so there is limited evidence for the combined use of these two agents.

Emerging Therapies in DKD

New agents continue to be developed to prevent patients with diabetes developing CKD and progressing to ESKD (see Table 33.2). Alongside these treatment avenues is the development of more sensitive biomarkers that may aid the decision of when to commence new therapies.

Glucagon-Like Peptide-1 Receptor Agonists

Cardiovascular Complications

Glucagon-like peptide-1 receptor agonists also exert significant CV benefits in T2D, though kidney benefits have been variable.79 A metaanalysis of CV outcome trials of available GLP-1 receptor agonists did not demonstrate a reduction in the risk of doubling in serum creatinine, though there was moderate heterogeneity in the included trials.79 In the REWIND trial comparing dulaglutide to placebo, there was an 11% reduction in the incidence of a sustained decline in eGFR of 30% or greater (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78–1.01), but further sensitivity analyses showed a 30% and 44% reduction in the incidence of a sustained decline of eGFR of 40% or greater (HR, 0.70; 95% CI, 0.57–0.85) and 50% or greater (HR, 0.56; 95% CI, 0.41–0.76), respectively.80 The ongoing FLOW trial (NCT03819153) involving semaglutide in participants with DKD assesses the composite outcome of persistent eGFR decline of 50% or greater, progression to ESKD, or death from kidney/CVD.

Diabetes is associated with increased risk for CV complications, including coronary artery disease (CAD) and heart failure. This risk is further compounded by the presence of CKD.88-90

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptors are widely expressed in kidney and cardiac tissue, and their activation by aldosterone leads to hemodynamic and nonhemodynamic effects culminating in inflammation, fibrosis, and progression of cardiac and kidney disease.81 However, clinical studies of MRA in DKD had not studied “hard” kidney outcomes and

Coronary Artery Disease

Although the risk of ischemic CV events is high in people with DKD, there is no established consensus about how best to detect subclinical CAD in this population. Chronic kidney disease increases CAD risk through mechanisms distinct from increased atherosclerotic disease burden. Additionally, people with CKD and CAD may present with atypical anginal symptoms. For these reasons, the usefulness of traditional CAD risk-prediction tools in people with CKD is limited. Patients with severe CKD and stable CAD experience no benefit with coronary revascularization compared with medical therapy based on the Management of Coronary Disease in Patients with Advanced Kidney Disease (ISCHEMIA-CKD) trial, which included 57% of patients with diabetes at baseline91 (see Chapter 85). In cases where revascularization may be indicated, patients with diabetes and severe CKD should undergo intervention irrespective of the radiocontrast agent risk in view of improved cardiac outcomes. Coronary artery bypass grafting (CABG) is superior to percutaneous coronary intervention (PCI) in patients with multivessel or complex CAD. Additionally, observational studies suggest that CABG reduces the risk from cardiac death more than PCI in DKD, including in patients on dialysis. Treatment with SGLT2i and/or GLP1-RA should be considered in patients with T2D, CKD, and increased CVD risk, as both of these agents have been demonstrated to reduce rates of major adverse cardiac events (a composite endpoint including myocardial infarction, stroke, and CV death). In patients with severe atherosclerotic CVD, GLP1-RA may be particularly useful.

Heart Failure

People with diabetes and CKD are at increased risk for developing heart failure and related mortality and hospitalization. Factors contributing to this increased risk include higher rates of CAD, hypertension, and impaired natriuresis.

In people with heart failure with reduced ejection fraction (HFrEF), treatment with β-blockers, RAS inhibitors, MRAs, and neprilysin inhibitors reduce CV risk (see Chapter 85). Though these agents do not have proven benefits for the treatment of heart failure with preserved ejection fraction (HFpEF), they are commonly used in this population as well. SGLT2i should be considered in subjects with increased CV risk or established HFrEF, as these agents reduce the risk of both heart failure hospitalization and heart failure progression (Table 33.2).31 38-40 43 44 Notably, these benefits were observed even in subjects without diabetes, suggesting glycemic control is not the primary underlying mechanism. GLP1-RA use has also been associated with reduced heart failure hospitalizations in a meta-analysis of seven RCTs, though to a much lesser degree compared with SGLT2i.

Antiplatelet Agents

Hyperglycemia has a procoagulant effect on platelet aggregation independent of insulin levels, and hyperinsulinemia itself carries an inhibitory effect on fibrinolysis and thus significantly increases the risk for thrombosis. Daily aspirin therapy is recommended for secondary CV prevention in people with diabetes and a history of atherosclerotic disease. Randomized controlled trials investigating the use of aspirin for primary CV prevention have yielded mixed results, demonstrating little to no benefit on CV outcomes yet an increased risk of bleeding.92-94 Furthermore, bleeding risk increases with advanced CKD due to uremic platelet dysfunction (see Chapter 87). As such, aspirin should be considered for primary prevention in people with diabetes and CKD only when risk of atherosclerotic CV events is high, and with careful consideration of bleeding risk. Use of dual antiplatelet agents is appropriate following acute coronary syndromes or revascularization procedures.

Dyslipidemia

Given the elevated risk for atherosclerotic events in DKD, it is generally recommended that hyperlipidemia be treated (Chapter 85). The KDIGO recommends that all adults aged 50 years or older with severe CKD receive treatment with a statin with or without ezetimibe, regardless of diabetes status. For adults with CKD who are between 18 to 49 years of age, statin treatment is recommended in the presence of diabetes, known coronary disease, or elevated CV risk. Patients should generally not be started on statins following dialysis initiation, but these agents may be continued in patients who had already been taking them prior to starting dialysis.

The effect of lowering low-density lipoprotein cholesterol (LDLC) was studied in the Study of Heart and Renal Protection (SHARP), which included patients with nondialysis CKD and no history of CVD, randomized to simvastatin and ezetimibe or placebo. A 17% reduction in adverse

CV outcomes was seen for every 33 mg/dL reduction

in LDL-C regardless of diabetes status, with no impact on mortality.95 However, in dialysis patients with diabetes, the SHARP, Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis (AURORA), and Atorvastatin in Patients With Type 2 Diabetes Mellitus Undergoing Hemodialysis (4D) trials did not show significant reductions in CV events or mortality despite LDL-C falling by up to 42%.96–98 Guidelines of KDIGO recommend continuation or cessation should be determined by the patients' condition and preference (see Chapter 85). Fibrates can reduce the risk for increased albuminuria and can replace statins for people with diabetes and eGFR less than 45 mL/min/1.73 m2 patients who are intolerant of statins.35 Dose reductions in statins are not normally required for advancing CKD.

Recently, proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors, when added to maximally tolerated statin therapy, have demonstrated significant reduction in LDL-C and improvement in CV outcomes in people with and without diabetes in the Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (FOURIER) and Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome (ODYSSEY OUTCOMES) trials.99,100

MICROVASCULAR COMPLICATIONS OF DIABETES

Diabetic Foot Disease

Patients with diabetes and advanced CKD are at increased risk for diabetic foot ulcers and their subsequent complications, including infection and amputation. Foot ulcers typically occur in the setting of peripheral neuropathy, which increases susceptibility to foot injuries, and peripheral artery disease, which impairs wound healing. Patients should undergo foot examinations at least yearly consisting of visual inspection for ulcerations or other deformities, and assessment of pedal pulses and peripheral sensation. Additionally, patients should be regularly screened for symptoms of peripheral artery disease (e.g., leg fatigue, claudication). Concerns of peripheral artery disease should prompt further evaluation, such as with ankle-brachial index testing or vascular imaging. Education on appropriate footwear and monitoring for signs of ulceration and early infection are fundamental to prevention.

Retinopathy

Initial testing for diabetic retinopathy should take place 5 years after T1D diagnosis and at the time of T2D diagnosis. Subsequent testing should be performed every 1 to 2 years, or more frequently if retinopathy is present.

Maintenance of adequate glycemic control reduces the risk of diabetic retinopathy and slows retinopathy progression.101 Therefore, glycemic control is an important therapeutic target even for patients with ESKD, for whom slowing CKD progression is no longer feasible. Ophthalmologic therapies for diabetic retinopathy include intravitreous antivascular endothelial growth factor injections and panretinal laser photocoagulation.

Neuropathy

Peripheral Neuropathy

Patients with diabetes should be evaluated for peripheral neuropathy at least annually. Patients should be assessed for symptoms of peripheral neuropathy (pain, numbness, or tingling of the extremities) and for signs of decreased temperature/pinprick and vibration sensation. The diagnosis of diabetic neuropathy should only be made after other potential etiologies of neuropathy are excluded.

Gabapentin is commonly used to treat neuropathic pain associated with diabetes, but dosing should be reduced as GFR declines. Dosing may require alternate days or administration after hemodialysis

sessions to avoid the known sedative and motor (myoclonus) effects of gabapentin accumulation that occur in individuals with reduced eGFR. Pregabalin is an alternative that is predominantly excreted by the kidneys and should be used cautiously with advancing CKD.

Gastroparesis

Gastroparesis occurs commonly in people with diabetes, can affect the absorption of oral medication, and can contribute to volume depletion due to poor oral intake. Pharmaceutical options for management of gastroparesis include metoclopramide, domperidone, and erythromycin. A surgically implanted gastric pacemaker may also alleviate symptoms in patients with severe symptoms. Optimizing the management of gastroparesis may be very challenging but should be considered before transplantation in view of the potential effects on immunosuppressant absorption.

Autonomic Neuropathy

Diabetic autonomic neuropathy may result in significant postural hypotension and orthostatic symptoms. As such, patients may require changes to their antihypertensive regimens in order to reduce hypotension risk. Additionally, autonomic neuropathy may contribute to hypotension during hemodialysis, necessitating the use of agents such as midodrine. Midodrine is contraindicated in patients with arrhythmias and previous cardiac events and, if used, should be done so with caution. Nonpharmaceutical approaches to managing postural hypotension include liberalizing dietary sodium and utilizing compressive leg or abdominal garments.

Erectile Dysfunction

Erectile dysfunction frequently occurs in DKD as a combination of vasculopathy and side effects of medications used to treat CAD and hypertension. Phosphodiesterase inhibitors may be used unless the patient is taking nitrates or has uncontrolled CAD.

COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Anemia

Anemia occurs commonly in DKD and acts as a risk multiplier for all-cause mortality and an independent risk factor for left ventricular hypertrophy (LVH), CVD, and congestive cardiac failure (Chapter 86). Compared with nondiabetics, diabetic patients have lower hemoglobin (Hb) levels at every CKD stage. One study found the prevalence of anemia to be 41% in diabetic versus 17% in nondiabetic CKD patients, occurring before kidney function begins to decline.102 Therefore, patients with diabetes and eGFR less than 60 mL/min/1.73 m2 should be tested for anemia.103 Patients with DKD have increased levels of proinflammatory cytokines from low-grade systemic inflammation, causing resistance to the effects of erythropoietin in various tissues of the body that impairs the efficient use of iron in the generation of new erythrocytes. Other factors causing resistance include autonomic neuropathy, RASi, and bone marrow microvascular injury.

The Trial to Reduce Cardiovascular Events With Aranesp Treatment (TREAT) assessed the use of erythropoiesis-stimulating agents in patients with T2D with GFR 20 to 60 mL/min/1.73 m2 and Hb 11 g/dL or less. Patients were randomized either to darbepoetin-alfa (targeting a Hb of 13 g/dL) or control with rescue darbepoetin treatment if Hb was less than 9 g/dL. The treatment group had fewer CV revascularization procedures but significantly increased risk for fatal and nonfatal nonhemorrhagic strokes.104 Of the TREAT cohort, 31% progressed to dialysis and death despite good BP, glycemic, and lipid control.

Long-term CV and kidney benefits of prolyl hydroxylase inhibitors (PHIs), which effectively increase Hb in DKD, have yet to be determined (see also Chapter 86).105 In an exploratory and pooled analysis, roxadustat led to fewer CV outcomes (a composite of myocardial infarction, stroke, or all-cause mortality) than epoetin alfa in patients new to dialysis (with and without diabetes) (HR, 0.70; 95% CI, 0.51–0.96).106 The rationale for the use of PHIs in DKD includes kidney hypoxia induced by DKD leading to HIF-1α activation. However, DKD may also be associated with instability of HIF-1 α with loss of downstream compensatory pathways to hypoxia and subsequent upregulation of pathogenic pathways.107 Prolyl hydroxylase inhibitors have been demonstrated in animal models to ameliorate deleterious metabolic and transcriptional changes associated with hypoxia in DKD.107

Mineral Bone Disease

Imbalance in mineral metabolism increases CV risk and is associated with bone disease in DKD. Targets for parathyroid hormone (PTH), calcium and phosphate levels, along with management should be aligned to those with non-DKD (Chapter 88).

Electrolytes and Fluid Retention

Salt restriction and diuretics are the mainstay treatment of fluid retention in DKD. Metabolic acidosis can be treated with bicarbonate supplementation. In patients with hyperkalemia, diet and RASi should be reviewed, and treatment with diuretics, sodium bicarbonate, gastrointestinal potassium binders, or dose reduction or discontinuation of RASi should be considered.

END-STAGE KIDNEY DISEASE

Decisions regarding dialysis modality should be guided by patient preference. There is no evidence to suggest superiority of one dialysis modality over another in people with diabetes and kidney failure. Mortality risk in this population is high and concomitant with the presence of multiple comorbidities.

Dialysis

Hemodialysis

Considerations for vascular access placement, hemodialysis initiation, and hemodialysis prescription in DKD are similar to those in patients without diabetes.

Peritoneal Dialysis

Most peritoneal dialysis solutions utilize dextrose as an osmotic agent. The dextrose content of peritoneal dialysis solutions may worsen hyperglycemia in people with diabetes. As a result, patients may need to adapt their hypoglycemic drug regimens. Commonly used peritoneal dialysate solutions contain between 1.5 to 4.25 g/dL glucose and may provide an additional 400 to 800 kcal/day. Non–glucose-containing solutions (e.g., icodextrin) avoid the risk for hyperglycemia and the potentially harmful effects of glucose degradation products while resulting in better ultrafiltration volume, BP control, and preservation of residual function (Chapter 102). Some metabolites of icodextrin also can act as a substrate for the glucose dehydrogenase present in blood glucose meters, resulting in potential overestimation of blood glucose levels.

Transplantation

Diabetic kidney disease remains the leading cause of ESKD among waitlisted patients. Kidney transplantation confers mortality benefit in these patients: the US Renal Data System data showed 5-year survival rates of 29% in patients with diabetes starting dialysis compared with rates of 75% and 85% in those undergoing deceased-donor

and living-donor kidney transplants, respectively.[108] When possible, preemptive kidney transplantation and living donor transplantation would be preferable to transplantation after starting dialysis and deceased donor transplantation, respectively. Considering the significant risk of remaining on dialysis and the benefit conferred by even marginal deceased donor kidney allograft, many patients with diabetes and ESKD should consider consenting for kidneys with a high kidney donor profile index (≥85%). For eligible patients with T1D, the ideal form of transplantation is simultaneous pancreas and kidney transplantation, or living-donor kidney transplant followed by deceaseddonor pancreas transplantation.[35]

SELF-ASSESSMENT QUESTIONS

1. A 56-year-old man with T2D, eGFR of 38 mL/min/1.73 m2, peripheral artery disease, and a history of myocardial infarction is referred for worsening proteinuria. His BP is 133/82 mm Hg, and his body mass index is 32 kg/m2. His HbA1c is 9.3% using canagliflozin and metformin. Which of the following changes to his antihyperglycemic regimen should you recommend?
A. Replace canagliflozin with empagliflozin.
B. Replace metformin with extended release exenatide.
C. Add liraglutide to current regimen.
D. Add linagliptin to current regimen.
E. Add pioglitazone to current regimen.
2. Which of the following factors favors a higher (more conservative) individualized HbA1c target?
A. History of recurrent severe hypoglycemia
B. Availability of continuous glucose monitoring
C. Absence of other diabetes microvascular complications
D. Higher eGFR
E. Relatively few comorbidities
3. Which of the following statements regarding BP control in diabetes is false?
A. There is evidence of a reduction in the risk of stroke with an intensive systolic BP target of less than 120 mm Hg versus less than 140 mm Hg in patients with diabetes.
B. Intensive BP lowering in the SPRINT trial was associated with lower rates of eGFR decline.
C. Automated office BP measurements are preferable to those made using the auscultation technique.
D. The 2021 KDIGO clinical practice guideline for the management of BP in CKD makes a grade 2B recommendation to target a systolic BP of less than 120 mm Hg in patients with hypertension and CKD.
E. The strongest evidence for kidney protection with RAS inhibition exists in patients with DKD and severely increased albuminuria.
4. Which of the following is true regarding newer therapies with cardiorenal protection in DKD?
A. The DAPA-CKD trial exclusively enrolled participants with T2D, eGFR of 30 to 90 mL/min/1.73 m2, and an albumin-tocreatinine ratio of 300 to 5000 mg/g, demonstrating the kidney benefits of dapagliflozin.
B. The CREDENCE trial demonstrated the kidney benefits of canagliflozin in participants with and without diabetes, eGFR of 25 to 75 mL/min/1.73 m2, and albumin-to-creatinine ratio of 200 to 5000 mg/g.
C. In a subgroup analysis within DAPA-CKD, the effects of dapagliflozin with respect to kidney protection were greater in participants with diabetes compared with those without.

D. The cardiovascular benefits of SGLT2i are largely related to reductions in heart failure hospitalizations, whereas there is stronger evidence of reductions in atherosclerotic cardiovascular disease with GLP-1 receptor agonists.

E. The kidney benefits of finerenone in the FIDELIO-DKD trial were demonstrated in a population with high rates of RAS and SGLT2 inhibition.

REFERENCES
1. Federation ID. International Diabetes Federation Diabetes Atlas. 7th ed. ; 2015. http://diabetesatlas.org/.
2. Whittier W.L., Korbet S.M.. Timing of complications in percutaneous renal biopsy. J Am Soc Nephrol. 2004;15(1):142–147.
3. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol. 2013;8(10):1718–1724.
4. Sanghavi SF, Roark T, Zelnick LR, et al. Histopathologic and clinical features in patients with diabetes and kidney disease. Kidney360. 2020;1(11):1217–1225.
5. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia. 2013;56(3):457–466.
6. de Boer MJ, Bilo HJ. Clinical decision making and cardiovascular risk factors: what about the Heart Team? Rev Clin Esp. 2014;214(4):200–201.
7. Haynes R, Staplin N, Emberson J, et al. Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the Study of Heart and Renal Protection (SHARP). Am J Kidney Dis. 2014;64(1):40–48.
8. Kidney Disease: Improving Global Outcomes Diabetes Work G. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1–S115.
9. Chatterjee S, Davies MJ, Heller S, Speight J, Snoek FJ, Khunti K. Diabetes structured self-management education programmes: a narrative review and current innovations. Lancet Diabetes Endocrinol. 2018;6(2):130–142.
10. Ruggenenti P, Perticucci E, Cravedi P, et al. Role of remission clinics in the longitudinal treatment of CKD. J Am Soc Nephrol. 2008;19(6):1213–1224.
11. Jeppsson JO, Kobold U, Barr J, et al. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med. 2002;40(1):78–89.
12. Lippi G, Targher G. Glycated hemoglobin (HbA1c): old dogmas, a new perspective? Clin Chem Lab Med. 2010;48(5):609–614.
13. Kilpatrick ES, Rigby AS, Atkin SL. Variability in the relationship between mean plasma glucose and HbA1c: implications for the assessment of glycemic control. Clin Chem. 2007;53(5):897–901.
14. Wu MS, Yu CC, Yang CW, et al. Poor pre-dialysis glycaemic control is a predictor of mortality in type II diabetic patients on maintenance haemodialysis. Nephrol Dial Transplant. 1997;12(10):2105–2110.
15. Morioka T, Emoto M, Tabata T, et al. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care. 2001;24(5):909–913.
16. Ricks J, Molnar MZ, Kovesdy CP, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. Diabetes. 2012;61(3):708–715.
17. Ramirez SP, McCullough KP, Thumma JR, et al. Hemoglobin A(1c) levels and mortality in the diabetic hemodialysis population: findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Diabetes Care. 2012;35(12):2527–2532.
18. Molnar MZ, Huang E, Hoshino J, et al. Association of pretransplant glycemic control with posttransplant outcomes in diabetic kidney transplant recipients. Diabetes Care. 2011;34(12):2536–2541.
19. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–1603.
20. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. J Am Med Assoc. 2001;286(4):421–426.
21. Viberti GC, Jarrett RJ, Mahmud U, Hill RD, Argyropoulos A, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulindependent diabetes mellitus. Lancet. 1982;319(8287):1430–1432.
22. Adler AI, Stevens RJ, Manley SE, et al. Development and progression

of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225–232.

23. Thomas MC, Macisaac RJ, Jerums G, et al. Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care. 2009;32(8):1497–1502.
24. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. J Am Med Assoc. 2016;316(6):602–610.
25. Zelnick LR, Weiss NS, Kestenbaum BR, et al. Diabetes and CKD in the United States population, 2009-2014. Clin J Am Soc Nephrol. 2017;12(12):1984–1990.
26. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jorgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function-even without albuminuria. Diabetes Care. 2019;42(10):1886–1894.
27. de Boer IH, Afkarian M, Rue TC, et al. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol. 2014;25(10):2342–2350.
28. Zoppini G, Targher G, Chonchol M, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol. 2012;7(3):401–408.
29. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. Adv Chronic Kidney Dis. 2016;23(1):19–28.
30. de Boer IH, Sun W, Cleary PA, et al. Longitudinal changes in estimated and measured GFR in type 1 diabetes. J Am Soc Nephrol. 2014;25(4):810–818.
31. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–2306.
32. Hundemer GL, Tangri N, Sood MM, et al. Performance of the kidney failure risk equation by disease etiology in advanced CKD. Clin J Am Soc Nephrol. 2020;15(10):1424–1432.
33. Cho A, Noh JW, Kim JK, et al. Prevalence and prognosis of hypoglycemia in patients receiving maintenance dialysis. Intern Med J. 2016;46(12):1380–1385.
34. Porrini E, Ruggenenti P, Mogensen CE, et al. Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2015;3(5):382–391.
35. Guideline Development Group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant. 2015;30(suppl 2):ii1–ii142.
36. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;4:CD002967.
37. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;1:CD002967.
38. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–2128.
39. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–657.
40. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–357.
41. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med. 2020.
42. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446.
43. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019.

44. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424.
45. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384(2):129–139.
46. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117–128.

47. Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Curr Diab Rep. 2016;16(10):92.
48. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377(9):839–848.
49. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–1844.
50. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519–1529.
51. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121–130.
52. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. Diabetologia. 1984;27(3):351–357.
53. Baldwin D, Zander J, Munoz C, et al. A randomized trial of two weightbased doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. Diabetes Care. 2012;35(10):1970–1974.
54. Kidney Disease: Improving Global Outcomes Blood Pressure Work G. KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3S):S1–S87.
55. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2022.
56. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;71(19):e127–e248.
57. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European Society of hypertension. J Hypertens. 2018;36(10):1953–2041.
58. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada’s 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and Children. Can J Cardiol. 2020;36(5):596–624.
59. Group SR, Wright Jr JT, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–2116.
60. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–2559.
61. Bress AP, King JB, Kreider KE, et al. Effect of intensive versus standard blood pressure treatment according to baseline prediabetes status: a post hoc analysis of a randomized trial. Diabetes Care. 2017.
62. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013;382(9891):507–515.
63. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185(11):949–957.
64. American Diabetes A. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(suppl

1):S111–S134.
65. de Boer IH, Bakris G, Cannon CP. Individualizing blood pressure targets for people with diabetes and hypertension: comparing the ADA and the ACC/AHA recommendations. JAMA. 2018;319(13):1319–1320.
66. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–860.

67. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–869.
68. Investigators HOPEHS. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet. 2000;355:253–259.
69. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised. double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782–788.
70. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-convertingenzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351(20):2058–2068.
71. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. J Am Soc Nephrol. 2006;17(4 suppl 2):S90–S97.
72. Haller H, Ito S, Izzo Jr JL, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907–917.
73. Officers A, Coordinators for the ACRGTA, lipid-lowering treatment to prevent heart attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and LipidLowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981–2997.
74. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–2428.
75. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–2572.
76. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol. 2018;6(9):691–704.
77. Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):610–621.
78. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7(8):606–617.
79. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation. 2019;139(17):2022–2031.
80. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019.
81. Belden Z, Deiuliis JA, Dobre M, Rajagopalan S. The role of the mineralocorticoid receptor in inflammation: focus on kidney and vasculature. Am J Nephrol. 2017;46(4):298–314.
82. Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the

progression of chronic kidney disease. Cochrane Database Syst Rev. 2020;10:CD007004.
83. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–2229.
84. Frias JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2016;4(12):1004–1016.

84a. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385:2252–2263.
85. Ludvik B, Frias JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2018;6(5):370–381.
86. Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(5):356–367.
87. Clegg LE, Penland RC, Bachina S, et al. Effects of exenatide and openlabel SGLT2 inhibitor treatment, given in parallel or sequentially, on mortality and cardiovascular and renal outcomes in type 2 diabetes: insights from the EXSCEL trial. Cardiovasc Diabetol. 2019;18(1):138.
88. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24(2):302–308.
89. Nathan D.M., Cleary P.A., Backlund J.Y., et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643–2653.
90. Gaede P., Vedel P., Larsen N., et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348(5):383–393.
91. Bangalore S, Maron DJ, O’Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. N Engl J Med. 2020;382(17):1608–1618.
92. Group ASC, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379(16):1529–1539.
93. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebocontrolled trial. Lancet. 2018;392(10152):1036–1046.
94. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509–1518.
95. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–2192.
96. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–1407.
97. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–2192.
98. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–248.
99. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–1722.
100. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–2107.

101. Aiello LP, Sun W, et al. Intensive diabetes therapy and ocular surgery in type 1 diabetes. N Engl J Med. 2015;372(18):1722–1733.
102. Al-Khoury S., Afzali B., Shah N., et al. Anaemia in diabetic patients

with chronic kidney disease–prevalence and predictors. Diabetologia. 2006;49(6):1183–1189.

103. Outcomes KDIG. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4).

104. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–2032.

105. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. Kidney Int Rep. 2021;6(3):624–635.

106. Provenzano R, Fishbane S, Szczech L, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. Kidney Int Rep. 2021;6(3):613–623.

107. Hasegawa S, Tanaka T, Saito T, et al. The oral hypoxia-inducible factor prolyl hydroxylase inhibitor enarodustat counteracts alterations in renal energy metabolism in the early stages of diabetic kidney disease. Kidney Int. 2020;97(5):934–950.

108. System URD. Annual Data Report. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2002.

109. Tuttle KR, McGill JB, Bastyr EJ, et al. Effect of ruboxistaurin on albuminuria and estimated GFR in people with diabetic peripheral neuropathy: results from a randomized trial. Am J Kidney Dis. 2015;65(4):634–636.

110. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–1131.

111. de Zeeuw D, Bekker P, Henkel E, et al. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. Lancet Diabetes Endocrinol. 2015;3(9):687–696.

112. Chertow GM, Pergola PE, Chen F, et al. Effects of selonsertib in patients with diabetic kidney disease. J Am Soc Nephrol. 2019;30(10):1980–1990.

113. Filippatos G, Anker SD, Bohm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J. 2016;37(27):2105–2114.

114. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015;314(9):884–894.

115. Heerspink HJL, Parving H-H., Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019.

116. Damman K, Gori M, Claggett B, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018;6(6):489–498.

117. McCausland FR, Lefkowitz MP, Claggett B, et al. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. Circulation. 2020;142(13):1236–1245.

118. Haynes R, Judge PK, Staplin N, et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. Circulation. 2018;138(15):1505–1514.

34

Normal Blood Pressure Control and the Evaluation of Hypertension

William J. Elliott

NORMAL BLOOD PRESSURE CONTROL

Systemic arterial blood pressure (BP) is the pressure of the blood within the arteries exerted against the arterial wall and is produced by the contraction of the left ventricle (producing blood flow) and the resistance of the arteries and arterioles. Systolic blood pressure (SBP), or maximum BP, occurs during left ventricular systole. Diastolic blood pressure (DBP), or minimum BP, occurs during ventricular diastole. The difference between SBP and DBP is the pulse pressure.[1] The mean arterial pressure (MAP) is calculated as the DBP plus one-third of the pulse pressure.

Blood flow (Q), as defined by the hydraulic analogy of Ohm's law, varies directly with the change in pressure (P), across a blood vessel, and varies inversely with the resistance (R), defined as Q = P/R. Rearrangement shows that pressure varies directly with blood flow and resistance: P = QR. Ohm's law suffices for an overall view of the circulation. However, the flow within a vessel is governed by the HagenPoiseuille equation:

(
)

$$Q = \Delta P \times \Pi r^4 / 8L \times (1/\eta)$$

where r is the radius of the pipe, L is its length, and η is the coefficient of viscosity. Thus, as the lumen of a vessel decreases, the pressure increases by the fourth power of the radius to maintain the same blood flow.

Normal BP is controlled by cardiac output and the total peripheral resistance and is dependent on the heart, the blood vessels, the extracellular volume, the kidneys, the nervous system, humoral factors, and cellular events at the membrane and within the cell (Fig. 34.1). Cardiac output is determined by the stroke volume in liters per minute (L/min) and the heart rate. In turn, stroke volume is dependent on intravascular volume (regulated by the kidneys) and myocardial contractility.

Myocardial contractility involves sympathetic and parasympathetic control of heart rate, intrinsic activity of the cardiac conduction system, complex membrane transport and cellular events requiring influx of calcium that lead to myocardial fiber shortening and relaxation, and effects of humoral substances (e.g., catecholamines) on increasing heart rate and myocardial fiber tension.

Total peripheral resistance is regulated by baroreflexes and sympathetic nervous system (SNS) activity, response to neurohumoral substances and endothelial factors, myogenic responses, and intercellular events mediated by receptors and mechanisms for signal transduction.[2]

Baroreflexes are derived from (1) high-pressure baroreceptors in the aortic arch and carotid sinus and (2) low-pressure cardiopulmonary baroreceptors in ventricles and atria. Aortic baroreceptor nerve fibers travel via the vagus nerve (cranial nerve X); carotid sinus fibers travel via the glossopharyngeal nerve (cranial nerve IX). These receptors respond to stretch (high pressure) or filling pressures (low pressure) and send tonic inhibitory signals to the brainstem. If BP and tonic inhibition increase, inhibition of sympathetic efferent outflow occurs, decreasing vascular resistance and heart rate. However, if BP decreases, less tonic inhibition occurs, and heart rate and peripheral vascular resistance (PVR) increase, thereby increasing BP.

The brainstem cardiovascular (CV) centers are localized in the dorsomedial medulla. Neural afferents from cranial nerves IX and X are integrated in the nucleus tractus solitarius (NTS). From here, vasoconstriction and increased heart rate are mediated through the caudal and rostral ventrolateral medulla by the SNS. Efferents from the NTS communicate with the nucleus ambiguus (vagal nucleus) to decrease heart rate via the vagus nerve. Also, the central neural control of kidney function modulates renal blood flow, glomerular filtration rate (GFR), excretion of sodium and water, and renin release. These factors in turn regulate intravascular volume, vascular resistance, and BP.[3] This complex physiology has taken on greater clinical relevance recently, given the mixed results of pivotal trials of percutaneous, catheter-based renal denervation.[4,5]

Inhibitory reflexes also originate in the kidney. Increases in urine flow rate increase renal pelvic pressure, which stretches the renal pelvic wall and leads to activation of mechanosensory nerves in the pelvic wall. Activation of these sensory nerves decreases renal sympathetic nerve activity and induces diuresis and natriuresis, an inhibitory renorenal reflex response. The responsiveness of the renal sensory nerves is modulated by dietary sodium. A high sodium intake enhances the responsiveness of the afferent renal mechanosensory nerves; conversely, renal denervation may increase urinary efflux and fractional excretion of sodium,[6] although not all recent studies agree.

Numerous vasoactive substances have effects on blood vessels, the heart, the kidneys, and the central nervous system (CNS) to regulate BP (Table 34.1). The renin-angiotensin-aldosterone system (RAAS) regulates volume and PVR (Fig. 34.2), particularly in the long term (hours to weeks; Fig. 34.3). Angiotensin II (Ang II) constricts vascular smooth muscle; stimulates aldosterone secretion; potentiates SNS activity; stimulates salt and water reabsorption in the proximal tubule; stimulates prostaglandin, nitric oxide (NO), and endothelin release; increases thirst; and stimulates vascular remodeling and inflammation. Aldosterone stimulates sodium channels in distal renal tubular

Some Factors Involved in the
Regulation of Blood Pressure
Central nervous system
Nucleus tractus
solitarius

Stress

Rostral ventrolateral
medulla
Cardiac
output

Arginine vasopressin
Arterial
baroreceptors

Atrial
natriuretic
peptide

Parasympathetic
efferents

Cardiopulmonary
baroreceptors

Sympathetic efferents
(NE)(α1)

Vascular
resistance
Na, K, Ca

Endotheliumderived factors
(Nitric oxide and endothelin)

Aldosterone ← Angiotensin II
(EPI)(β2)
Sympathetic
efferents
(NE)(β1)
Plasma renin
Angiotensin II
Preload
Prostaglandins
(NaCl and H2O)
Kinins

Renal efferents
Renal afferents

Renal regulation of
NaCl and H2O

Fig. 34.1 Some Factors Involved in Regulation of Blood Pressure. Dashed lines refer to feedback to the central nervous system from cardiovascular (green dash) or renal (purple dash) sites. EPI, Epinephrine; NE, norepinephrine.

epithelium, leading to sodium retention and potassium excretion.

Novel aldosterone antagonists have antiinflammatory and other beneficial effects in vascular cells, heart, and kidneys.7 Plasma concentrations of renin and aldosterone are both inversely related to salt intake and are influenced by many antihypertensive medications.

The second major effector system, working primarily over seconds to minutes (see Fig. 34.3), is the SNS. Sympathetic nerve endings release the vasoconstrictor (norepinephrine) that binds the α-adrenergic receptor (adrenoceptor) on vascular cells, renal cells, and other cells (e.g., adipocytes). Epinephrine increases heart rate, stroke volume, and SBP through α- and β-adrenoceptors. The hormone is released from the adrenal medulla. Increased sympathetic tone has long-term influences on CV regulation and may cause hypertension and contribute to chronic kidney disease (CKD).8 In the kidneys, sympathetic nerves mediate renin release. Furthermore, innervation of each individual nephron affects sodium reabsorption. In doing so, the SNS regulates both effective circulating fluid volume and PVR.

The kallikrein-kinin system counters the RAAS and produces vasodilator kinins, which stimulate prostaglandin and NO production (see Fig. 34.2). Prostaglandin E and prostacyclin block the vasoconstriction by Ang II and norepinephrine. Two endothelium-derived factors have opposite effects on the blood vessels: NO is a vasodilator, whereas the endothelins are vasoconstrictors. Natriuretic peptides, of the atrial, brain, or C-types, induce vasodilation and natriuresis and inhibit other vasoconstrictors (RAAS, SNS, endothelin). Chapter 37 discusses all the

drugs that affect the previously discussed physiologic systems that regulate BP.

Other physiologic systems that control BP can be used as investigative tools but not yet therapeutically in humans. Renalase is a flavin adenine dinucleotide–dependent amine oxidase that is secreted by the kidney, circulates in the blood, and modulates cardiac function and systemic BP by metabolizing catecholamines; there is debate about whether mutations in the gene coding for renalase are associated with hypertension.9 Heme oxygenase-1 is an intrarenal and systemic BP modulator that inhibits oxidants, resulting in decreased BP; in one study, individuals with an unfavorable gene promoter for this enzyme had a higher prevalence of hypertension and increased mortality.10 Endogenous digitalis-like factors, which inhibit cell surface Na^+,K^+ ATPase and include an ouabain-like factor and marinobufagenin, appear to regulate BP, CV, and renal function.11 Urotensin II is a locally expressed vasoconstrictive cyclic vasoactive peptide that stimulates proliferation of vascular smooth muscle cells and fibroblasts, inhibits insulin release, and modulates GFR. Nonetheless, high plasma urotensin II levels were associated with reduced CV complications and death in patients with CKD, stages 2 to 5.12 In obese persons, leptin may increase BP by activating the CNS through a melanocortin pathway.13 Although its clinical importance is still debated, higher serum uric acid levels have been associated with BP and CV outcomes in many (but not all) cohort studies, a mendelian randomization analysis, and meta-analysis of 15 clinical trials14; at least two hypouricemic drugs

Some Vasoactive Substances That Modulate Blood Pressure

TABLE 34.1
Group

Compound

Cellular Effects

Catecholamines

Norepinephrine, epinephrine, dopamine

Adrenergic receptors (α1, α2, β1, β2) causing protein phosphorylation and increased
intracellular calcium through G proteins linked to ion channels or second messengers (cyclic nucleotides, phosphoinositide hydrolysis)

RAS

Angiotensin II

Angiotensin receptors (AT1, AT2, AT4) cause increased intracellular calcium and protein phosphorylation through second messenger, phosphoinositide hydrolysis, and activated protein kinases
Angiotensin II stimulates aldosterone

Mineralocorticoids

Aldosterone

Genomic: binds to cytoplasmic mineralocorticoid receptor, translocates to nucleus,
modulates gene expression, and signal transduction and effectors (SgK, CHIF, K -Ras), which increases transport proteins (increasing ENaC number and open probability)Nongenomic: effects through separate membrane or cytosolic proteins

Kallikrein-kinin system

Bradykinin

Bradykinin receptors (B1, B2), B2-G protein coupling causes activation of phospholipase C, increased inositol phosphates, and intracellular calcium

Arachidonic acid
oxidation products

Prostaglandins: PGE, prostacyclin,
thromboxanes
Lipoxygenase enzyme products: leukotrienes,
hydroxyeicosatetraenoates

Nine prostaglandin receptors coupled to G proteins (e.g., PGI2 [receptor IP], PGE2
[receptors EP1, EP2]); PGF2α (receptor FP)

Endothelium-derived
factors

Endothelium-derived relaxing factor (nitric
oxide)
Endothelins (ET-1, ET-2, ET-3)

Increased levels of cyclic guanosine monophosphate cause activation of protein

kinasesG proteins activate phospholipase C and l-type calcium channels.
Class 2 G protein–coupled receptor

Natriuretic peptides

Atrial, brain, and C-type

Activation of three receptor types; further effects mediated by cGMP

Posterior pituitary
hormones

Arginine vasopressin

Vasopressin receptors (AVPR 1A; AVPR 1B) mediated by second messenger system, phosphatidyl inositol/calcium; AVPR2 effects via adenylate cyclase (cAMP)

Cyclic vasoactive
peptides

Urotensin II

Binds to G protein receptor GPR 14

Other substances

Acetylcholine, adenosine, insulin,
neuropeptide Y, serotonin, sex hormones
(estrogens, progesterone, androgens),
glucocorticoids, other mineralocorticoids,
substance P, vasopressin, renalase, heme
oxygenase 1, uric acid

Ang II, Angiotensin II; AVPR, arginine vasopressor receptor; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate;
ENaC, amiloride-sensitive epithelial sodium channel; PGE, prostaglandin E; RAS, renin-angiotensin system; UT II

Angiotensin and Kallikrein-Kinin Pathways
Angiotensinogen
Cathepsin G
t-PA

Renin
Angiotensin I
Chymase
CAGE

Plasma
kallikrein

Tissue
kallikrein

Bradykinin

Kallidin

ACE = Kininase II
ANG II

AT1 Receptor
- Vasoconstrictor
- ↑ Endothelin

- ↑ Aldosterone
- ↑ SNSA
- ↓ UNa V
- ↑ Cellular growth

HMW–Kininogens–LMW

AT2 Receptor
- Vasodilation
- ↓ Cellular growth

B2 Receptor
- Vasodilation
- ↑ PGs
- ↑ NO
- ↑ UNa V

B1 Receptor
Bronchoconstriction

Degraded fragment

Fig. 34.2 Interactions and functions of renin-angiotensin and kallikrein-kinin systems. ACE, Angiotensin-converting enzyme; ANG II, angiotensin II; AT1, AT2, angiotensin receptors; B1, B2, bradykinin receptors; CAGE, chymostatin-sensitive angiotensin II–generating enzyme; HMW, high molecular weight; LMW, low molecular weight; NO, nitric oxide; PGs, prostaglandins; SNSA, sympathetic nervous system activity; t-PA, tissue plasminogen activator; UNa V, urinary sodium excretion.

Temporal Sequence for Adjustment
of Blood Pressure Control

11
10
9
8
7
6
5
4
3
2
1
0

Acute change in pressure at this time

Maximum feedback gain at optimal pressure

∞

DEFINITION AND CLASSIFICATION OF HYPERTENSION

In the general population, casual or in-office BP follows an approximately normal distribution, with a shift to the left in the young and the opposite in older people or those with CKD. Thus, any definition of hypertension is arbitrary. Hypertension is often asymptomatic, with symptoms more commonly attributed to sequelae of hypertension or its treatment. Hypertension may be classified by its associated morbidity and mortality, as increases over arbitrary cut points, or by thresholds defining therapeutic benefit.

Blood Pressure Classification by Link to Future Morbidity and Mortality

0 15 30 1 2 4 8 16 32 1 2 4 8 161 2 4 8 16 ∞
Seconds
Minutes
Hours
Days

Time after sudden change in pressure
CNS ischemic response
Baroreceptors
Chemoreceptors
Stress relaxation

Renin-angiotensin–mediated vasoconstriction
Capillary fluid shift
Renal-blood volume pressure control
Aldosterone

Fig. 34.3 Temporal Sequence for Adjustment of Blood Pressure Control. Degree of activity, expressed as feedback gain, of several arterial blood pressure (BP) control systems at various times after a sudden change in arterial BP. Note the infinite gain of the kidney volume mechanism for BP control. CNS, Central nervous system. (From Hall JE. Role of the kidneys in long-term control of arterial pressure and in hypertension: the integrated system for arterial pressure regulation. In:

Hall J, Hall M. Guyton and Hall’s Textbook of Medical Physiology. 14th ed. Philadelphia: Elsevier; 2020:229–244.)

have lowered BP in pilot studies. Intracellular urate also may activate the renin-angiotensin system (RAS), induce intrarenal oxidative stress, block endothelial NO, and directly affect the vasculature.15 T cells also may be involved in primary hypertension, possibly via heat shock protein 70 and/or interleukin-17, and are present in kidneys and blood vessels where they release Ang II and oxidants.16 Chemoreceptors in the brain medulla and the carotid and aortic bodies respond to changes in carbon dioxide and oxygen tension, resulting in renal vasoconstriction and dilation of the CNS and coronary vasculature; these phenomena may be reversible after device-based therapy.17 The small guanosine triphosphatase, Rho, and its kinase stimulate vasoconstriction and may have a role in cerebral artery spasm, hypertension, heart failure, and other CV conditions; an inhibitor Rho kinase, netarsudil, was recently FDA-approved for ocular hypertension.18

The kidney is recognized as a source of hypertension, based on renal cross-transplantation experiments19 and the hypotensive effects of bilateral nephrectomy in patients with end-stage kidney disease (ESKD) and severe hypertension. Activation of CNS and kidney SNS pathways are important in long-term BP control, in part by delayed effects on the kidneys.20 Renal sympathetic denervation by radiofrequency ablation through the renal arteries has led to substantial reduction in BP in patients with resistant hypertension, but a large trial did not achieve significantly better BP control at 6 months, compared with sham-operated controls.21 22 This negative result more likely stemmed from technical issues in the conduct of the trial rather than indicating that the SNS does not contribute to the pathophysiology of hypertension.

The first approach defines hypertension by relating BP levels to the risk for morbidity and mortality. The association of SBP and DBP with CV and kidney complications is continuous over the entire BP range.23 Death from both heart disease and stroke increases progressively and linearly from BP as low as 115/75 mm Hg upward in all age groups from 40 to 89 years (Figs. 34.4 and 34.5). In observational studies an increase in SBP of 20 mm Hg or DBP of 10 mm Hg was associated with a doubling of mortality from heart disease or stroke. Several interventional trials have observed a J-shaped curve (suggesting that mortality increases below a threshold SBP), yet this phenomenon is also seen in the bottom decile in both individual and pooled observational studies of untreated subjects (see Figs. 34.4 and 34.5), indicating that those in the lowest decile have a higher risk, irrespective of treatment. Elevated SBP has been consistently identified by the Global Burden of Disease study to be the leading contributor to disability-adjusted life years worldwide. The investigators characterized an SBP between 110 and 115 mm Hg as the “theoretical minimum risk level” for BP. Although all national and international hypertension guidelines agree about the continuous relationship between risk and BP, as well as a recommendation for lifestyle modifications in people with BP 120/80 mm Hg or greater, the thresholds and categories have continued to evolve. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) introduced the term prehypertension for individuals with SBPs from 120 to 139 mm Hg or DBPs between 80 and 89 mm Hg (Table 34.2),24 which was retained by the American Society of Hypertension/ International Society of Hypertension 2013 guidelines and by the Expert Panel appointed to JNC 8.25 Somewhat different terms were used by the 2018 European Society of Hypertension/European Society of Cardiology guidelines (Table 34.3)26 and the 2020 International Society of Hypertension guidelines (Table 34.4).27 A completely different approach (independent of specific BP thresholds) was taken by the Writing Group of the American Society of Hypertension (WGASH), which proposed that hypertension is a complex CV disorder that included target organ damage, early disease biomarkers (including BP), and CV risk factors28 (Table 34.5).

Blood Pressure Classification by Population-Based Percentile

A second approach defined hypertension by the frequency distribution within a population. Until 2017, hypertension in American children was determined on a purely statistical basis: SBP or DBP at or above the 95th percentile for age, sex, and height, measured on at least three occasions.29 In this population, age, sex, body size, and race/ethnicity are all significant and strong predictors of BP. Using a frequency distribution method is less helpful for identifying a threshold for initiation of antihypertensive treatment but is common in epidemiologic studies. The crude prevalence of hypertension in adults (older than 20 years)

Diastolic Blood Pressure

256

Age at risk
80-89
years

128

70-79
years

64

60-69
years

32

50-59
years

16

40-49
years

8
4

A

IHD mortality
(floating absolute risk and 95% CI)

IHD mortality
(floating absolute risk and 95% CI)

Systolic Blood Pressure

256

Age at risk
80-89
years

128

70-79
years

64

60-69
years

32

50-59
years

16

40-49
years

8
4

2

2

1

1

120

140

160

407

70

180

Usual systolic blood
pressure (mm Hg)

B

80

90

100

110

Usual diastolic blood
pressure (mm Hg)

Fig. 34.4 Ischemic Heart Disease Mortality Rate in Each Decade of Age Versus Usual Blood Pressure at Start of That Decade. (A) Systolic blood pressure. (B) Diastolic blood pressure. Floating absolute risk is a relative risk score that adjusts for the absolute death rate within a particular age group. The size of the squares correlates inversely with the variance of the data collected for that data point. CI, Confidence interval; IHD, ischemic heart disease. (From Lewington S, Clarke R, Qizilbash N, et al. Prospective studies collaboration: age-specific relevance of usual blood pressure to vascular mortality—a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.)

in the United States, traditionally defined as BP of 140/90 mm Hg or greater or taking antihypertensive medication, has increased progressively from 11% in 1939 to 33.5% in 2013 to 2014, but has been relatively stable since the mid-1990s (31% ± 2%, after age adjustment).30

Blood Pressure Classification by Threshold of Therapeutic Benefit

The third concept for defining hypertension is derived from randomized controlled trials (RCTs) that compared two or more BP targets and showed significant reductions in morbidity and mortality. The Hypertension Optimal Treatment (HOT) study showed no significant outcome differences among 18,790 hypertensive subjects randomized to DBP targets of 80, 85, or 90 mm Hg or less, although a significant benefit was seen in diabetic patients with a diastolic target of less than 80 mm Hg.31 A post hoc analysis of the in-trial BPs determined that maximal prevention of major CV events was seen at a BP of 138.5/82.6 mm Hg. Of the relatively few outcome-based RCTs comparing traditional and lower BP targets, only the Systolic Blood Pressure Intervention Trial (SPRINT) showed significant reductions in both CV events and mortality when treating to a SBP target of less than 120 compared with the traditional less than 140 mm Hg.32 Some have argued that this benefit came at a huge (and largely unspecified) cost of more medications, more office visits, more adverse effects

(including emergency department visits), and greater than 30% worsening of renal function in those without CKD at baseline. Others have cast doubt about SPRINT’s generalizability, as less than 17% of adult Americans with hypertension would have been eligible to participate because of the large number of exclusion criteria (which included diabetes mellitus, prior stroke, polycystic kidney disease, or estimated GFR <20 mL/min/1.73 m2). A network meta-analysis then combined the SPRINT results with those of 41 other randomized clinical trials, using achieved in-trial SBPs in 144,220 subjects as the independent variable. For both cardiovascular events and all-cause mortality, the lowest risk was seen in subjects with SBPs between 120 and 124 mm Hg, significantly lower than those with SBPs between 130 and 134 mm Hg.33 Three other independent meta-analyses also concluded that major adverse cardiovascular events were significantly reduced in subjects treated to “lower SBPs” (typically <130 mm Hg) compared with “higher SBPs” (typically ≥140 mm Hg).

These data resulted in the 2017 ACC/AHA United States hypertension guideline.34 This guideline “redefined” hypertension as a usual office BP at or below 130/80 mm Hg, added the new diagnostic category of “elevated blood pressure,” reemphasized the value of out-of-office BP measurements, reinforced lifestyle modifications as appropriate for most people with higher than normal BPs, and revised some treatment targets for specific patient groups (see Table 34.6 for

Systolic Blood Pressure
256

256

Age at risk
80-89
years

128
64

60-69
years

32

50-59
years
16
8
4

50-59
years
16
8
4

1

1

160

180

Usual systolic blood
pressure (mm Hg)

A

60-69
years

32

2

140

70-79
years

64

2

120

Age at risk
80-89
years

128

70-79
years
Stroke mortality
(floating absolute risk and 95% CI)

Stroke mortality
(floating absolute risk and 95% CI)

Diastolic Blood Pressure

70

B

80

90

100

110

Usual diastolic blood
pressure (mm Hg)

Fig. 34.5 Stroke Mortality Rate in Each Decade of Age Versus Usual Blood Pressure (BP) at Start of That Decade. (A) Systolic BP. (B) Diastolic BP. Floating absolute risk is a relative risk score that adjusts for the absolute death rate within a particular age group. The size of the squares correlates inversely with the variance of the data collected for that data point. CI, Confidence interval. (From Lewington S, Clarke R, Qizilbash N, et al. Prospective studies collaboration: age-specific relevance of usual blood pressure to vascular mortality—a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.)

JNC 7 Classification of Blood
Pressure for Adults (2003)
TABLE 34.2
Classification

SBP (mm Hg)

Normal

<120

and

DBP (mm Hg)

Prehypertension

120–139

or

80–89

Stage 1 hypertension

140–159

or

90–99

Stage 2 hypertension

≥160

or

≥100

<80

DBP, Diastolic blood pressure; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure.

more details). The 2017 US hypertension guideline of the American College of Cardiology/American Heart Association (ACC/AHA) is controversial; some societies have declined to endorse or adopt it. About 3 months earlier, the American Academy of Pediatrics released its Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents29; the authors of that pediatric guideline were privy to an advance copy of the 2017 adult

guideline and arranged their recommendations to be consistent with it. These new definitions have increased the overall prevalence of hypertension in US adults to 46% but decreased the prevalence in children and adolescents to 3.5%. The ACC/AHA 2017 US hypertension guideline also recommended an office BP target below 130/80 mm Hg for individuals with a 10-year cardiovascular risk greater than 10%, but retained the traditional less than 140/90 mm Hg for most lower-risk individuals.

The most recent set of hypertension guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) did not formally redefine hypertension but recommended that only “standardized office BPs,” supplemented by out-of-office BP measurements, be used in clinical decision-making, and (based on “weak” evidence) that all patients with chronic kidney disease be treated to a systolic BP less than shiftenter120 mm Hg.35 The authors concluded that this target may be harmful if “standardized” BPs are not measured.

The concept of evaluating a person’s “total CV risk” had been prominent in several prior US guidelines on BP, dyslipidemia, and acute coronary syndrome. It was largely abandoned by JNC 7 but still plays a major role in other countries26 27 36 and was incorporated in the 2017 ACC/AHA US hypertension guideline.34 Age, sex, and ethnicity

European Society of Cardiology and European Society of Hypertension Classification Scheme and Diagnostic Thresholds for Hypertension (2018)

TABLE 34.3

CLASSIFICATION OF OFFICE BP

THRESHOLD BPS FOR DIAGNOSIS OF HYPERTENSION

Category

Systolic
(mm Hg)

Diastolic
(mm Hg)

Category

Systolic
(mm Hg)

Diastolic
(mm Hg)

Optimal

<120

and

<80

Office BP

≥140

and/or

≥90

Normal

120–129

and/or

80–84

Ambulatory BP

High normal

130–139

and/or

85–89

Daytime (or awake)

≥135

and/or

Grade 1 hypertension

140–159

and/or

90–99

Nighttime (or asleep)

≥120

and/or

≥85
≥70

Grade 2 hypertension

160–179

and/or

100–109

24-hour

≥130

and/or

≥80

Grade 3 hypertension

≥180

and/or

≥110

Home BP

≥135

and/or

≥85

Isolated systolic
hypertension

≥140

and/or

<90

Modified from Williams B, Mancia G, Spierling W, et al. for the Task Force for

the Management of Arterial Hypertension of the European Society
of Cardiology and the European Society of Hypertension. 2018 ESC/ESH guidelines
for the management of arterial hypertension. J Hypertens
2018;36:2284–2309.

International Society of Hypertension Classification Scheme and Diagnostic
Thresholds for Hypertension (2020)

TABLE 34.4

CLASSIFICATION OF OFFICE BP
Category

Systolic
(mm Hg)

THRESHOLD BPS FOR DIAGNOSIS OF HYPERTENSION
Diastolic
(mm Hg)

Category

Systolic
(mm Hg)

Diastolic
(mm Hg)

Normal BP

<130

and

<85

Office BP

≥140

and/or

≥90

High-normal BP

130–139

and/or

85–89

Office BP

≥140

and/or

≥90

Grade 1 hypertension

140–159

and/or

90–99

Ambulatory BP
Grade 2 hypertension

≥160

and/or

≥100

24-hour average

≥130

and/or

≥80

Daytime (or awake)

≥135

and/or

≥85

Nighttime (or asleep)

≥120

and/or

≥70

Home BP

≥135

and/or

≥85

BP, Blood pressure.
From Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension 2020;75;1334–1357.

TABLE 34.5

Hypertension

Working Group: American Society of Hypertension Definition and Classification of

Class

BP Elevation

Normal

Normal or rare

CV Diseasea

CV Risk Factors

Early Disease Markers Target Organ Disease

or

None

None or few

None

None
None

Hypertension
Stage 1

Occasional intermittent

or

Early

Several

Usually present

Stage 2

Sustained

or

Progressive

Many

Overtly present

Early signs present

Stage 3

Marked and sustained

or

Advanced

Many

Overtly present with
progression

Overtly present with or
without CV disease events

aCardiovascular

(CV) disease determined by constellation of risk factors, early disease markers,
and target organ disease.

BP, Blood pressure.

Modified from Giles TD, Materson BJ, Cohn JN, Kostis JB. Definition and classification of hypertension: an update. J Clin Hypertens (Greenwich). 2009;11:611–614. Correction J Clin Hypertens (Greenwich). 2010;12:13.

are important nonmodifiable risk factors, whereas low-density lipoprotein (LDL) cholesterol, smoking, control of diabetes, obesity, and left ventricular hypertrophy are potentially modifiable36 (Fig. 34.6). The cluster of risk factors that increase CV risk and are often associated with hypertension is termed the metabolic syndrome37 (Table 34.7).

CKD, as defined by decreased GFR or by increased urinary albumin excretion, is also recognized as an independent risk factor for ESKD, CV events, and death.35 JNC 7 included recommendations for serial follow-up evaluation of BP and CV risk factors based on initial BP measurement (Table 34.8).

ACC/AHA 2017 US Hypertension Guideline: Categories of Blood Pressure in Adults (mm Hg)
TABLE 34.6

Category	Systolic		Diastolic
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Individuals with systolic and diastolic blood pressures in two different categories should be assigned into the higher category. Blood pressures are based on an average of ≥2 careful readings obtained on ≥2 occasions, usually separated by a week or more.
ACC/AHA, American College of Cardiology/American Heart Association.
From Whelton PK, Carey RM, Aranow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018, 71:e13–e115.

Special Definitions
Prehypertension. Although no longer a feature of the ACC/AHA 2017 US hypertension guideline,[34] prehypertension was defined in JNC 7 as SBP of 120 to 139 and DBP of 80 to 89 mm Hg.[24] Prehypertension

was found in 28% of American adults in the US National Health and Nutrition Examination Survey (NHANES) 2005 to 2006.38 Prehypertension is associated with age, obesity, dyslipidemia, impaired fasting glucose levels, a higher risk for both CV and renal events, and progression to hypertension (which was significantly delayed by drug therapy in two RCTs). Lifestyle modifications (see Chapter 36) are recommended by essentially all guidelines for affected people until the BP meets or exceeds levels corresponding to hypertension.

“White coat” hypertension. “White coat” hypertension, defined as normal BP during usual daily activities yet elevated only in a clinical setting, has a prevalence of 20% to 25% in hypertensive persons and is most accurately diagnosed by ambulatory BP monitoring (with home BP measurements a distant second choice). Unfortunately, ambulatory BP monitoring is not widely available for routine clinical use in many countries (including the United States) despite having become the gold standard for diagnosis in research settings. The white coat (or “alerting”) phenomenon is less common when a nurse or technician measures the BP (compared with when taken by a physician), and is

Absolute Risk of Cardiovascular Disease by Systolic Blood Pressure
50
SBP = 110
SBP = 120
SBP = 130
SBP = 140
SBP = 150
SBP = 160
SBP = 170
SBP = 180

45
40

5-year CVD risk (%)

35

44%

33%

30
25

24%

20

18%

15

12%

10
6%
3%

5
璆1%
0

Reference
TC ꞃ 7 mmol/L

Smoker
HDL n 1 mmol/L
Male
Diabetes
>60 years

Fig. 34.6 Absolute Risk for Cardiovascular Disease During 5 Years in Patients by Systolic Blood Pressure at Specified Levels of Other Risk Factors. Reference category is a nondiabetic, nonsmoking woman age 50 years with total cholesterol (TC) level of 4 mmol/L (155 mg/dL) and high-density lipoprotein (HDL) level of 1.6 mmol/L (62 mg/dL). Risks are given for systolic blood pressure (SBP) levels of 110, 120, 130, 140, 150, 160, 170, and 180 mm Hg. In the other categories, additional risk factors are added consecutively; for example, the diabetes category is a diabetic 50-year-old male cigarette smoker with TC level of 7 mmol/L (270 mg/dL) and HDL level of 1 mmol/L (39 mg/dL). CVD, Cardiovascular disease. (Modified from Jackson R, Lawes CM, Bennett A, et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual’s absolute cardiovascular risk. Lancet. 2005;365:434–441.)

TABLE 34.7

Common Definitions for Metabolic Syndrome

Criterion

NCEP ATP III, 2005 Update (≥3 Criteria)

Abdominal obesity

International Diabetes Federation, 2005
(Obesity + 2 Other Criteria)

Waist circumference

Required for diagnosis

Men

>40 inches (>102 cm)

>94 cm

Women

>35 inches (>88 cm)

>80 cm

>150 mg/dL (>1.7 mmol/L)

>150 mg/dL (>1.7 mmol/L) or treatment

Men

<40 mg/dL (<1.03 mmol/L)

<40 mg/dL (<1.03 mmol/L) or treatment

Women

<50 mg/dL (<1.30 mmol/L)

<50 mg/dL (<1.30 mmol/L) or treatment

Hypertension

≥130/85 mm Hg or taking antihypertensive medication

≥130/85 mm Hg or taking antihypertensive medication

Impaired fasting glucose or diabetes

Glucose ≥100 mg/dL (≥5.6 mmol/L) or taking insulin or
hypoglycemic medication

Glucose ≥100 mg/dL (≥5.6 mmol/L) or taking insulin or
hypoglycemic medication

Hypertriglyceridemia

Low HDL

HDL, High-density lipoprotein; NCEP ATP III, National Cholesterol Education Program—Adult Treatment Panel III.
Modified from Jackson R, Lawes CM, Bennett A, et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual’s absolute cardiovascular risk. Lancet. 2005;365:434–441.

Recommendations of JNC 7
for Follow-up Based on Initial Blood Pressure
Measurements for Adults

TABLE 34.8

INITIAL BP (MM HG)a
Systolic

Diastolic

Follow-up Recommendation

<130

<85

Recheck in 1 year

130–139

85–89

Recheck in 1 year; provide information about lifestyle modification

140–159

90–99

Confirm within 2 months

160–179

100–109

Evaluate or refer to source of care within 1 month

≥180

≥110

Evaluate or refer to source of care immediately or within 1 week, depending on clinical situation

aIf

systolic and diastolic categories are different, follow recommendations for the shorter time for follow-up. The schedule for follow-up should be modified according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.
BP, Blood pressure; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
Modified from Chobanian AV, Bakris GL, Black HR, et al. Joint National

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206–1252.

rare when automated office BPs are taken with the patient alone in the examination room (as was recommended in the SPRINT trial32). Although the most recent meta-analysis of 27 observational studies suggested that people with white coat hypertension have an increased long-term risk for all-cause and CV mortality (mostly driven by data from a large Spanish registry, which have since been retracted),39 several prior studies (using rigorous diagnostic criteria concluded that CV risk in untreated persons was not significantly elevated compared with normotensive individuals (Fig. 34.7). If CV risk is indeed elevated in white coat hypertension, it may be more appropriately attributed to subtle target organ damage and biomarkers that are intermediate

between normotensive and sustained hypertensive persons.

Although many people with white coat hypertension will progress to sustained hypertension, most authorities recommend initial lifestyle modifications without drug therapy, ongoing risk assessment, and close follow-up.

Masked hypertension. Masked hypertension, defined as normal BP in the medical setting but elevated during ambulatory (or, perhaps less strictly, home) BP measurements, has a prevalence of 10% to 15% in the general population. Not surprisingly, such people often have target organ damage (which is often the only clue on initial evaluation) and a CV prognosis that is not much different than individuals with sustained hypertension40 (see Fig. 34.7).

Sustained hypertension. Sustained (sometimes persistent) hypertension is diagnosed when the BP is elevated both inside and outside the medical setting, including at home and during usual daily activities. Patients with sustained hypertension should receive antihypertensive drug therapy, which reduces their risk for CV and renal events, albeit not to the level of normotensives (see Fig. 34.7).

Pseudohypertension. Pseudohypertension is defined as a significantly higher BP measured by cuff compared with that measured by an intraarterial catheter. Typically, this condition occurs in older patients and is attributed to calcium deposition, atheromatosis, and/or medial hypertrophy of the brachial (and likely other) arteries. It is suggested by the presence of a “positive Osler maneuver,” in which the nonperfused radial or brachial artery is still palpable after inflating the cuff to greater than 20 mm Hg higher than the palpated SBP. Confirmation requires arterial catheterization documenting a BP 10 to 15 mm Hg lower compared with a cuff-measured BP.

Isolated systolic hypertension. Isolated systolic hypertension (SBP ≥140 mm Hg, DBP <90 mm Hg) is recognized by current hypertension guidelines in Europe26 but not in the United States. Its prevalence increases markedly with age, becoming by far the most common form of hypertension after the age of 60 years. It arises from vascular aging and large artery stiffening, both of which reduce their capacitance, accelerate pulse wave velocity, and widen the pulse pressure. Perhaps as a consequence of these processes, SBP continuously increases throughout life, whereas DBP usually decreases after the age of 50 years (Fig. 34.8).41 Although there was once great concern that lowering BP in patients with isolated systolic hypertension would push the DBP below the J-curve inflection point (and increase the risk for cardiac ischemia), all three RCTs (Systolic Hypertension in the Elderly

Cardiovascular Risk With Hypertension and Untreated Blood Pressure Patterns

Odds ratio (95% CI)

Events

Subjects

Sustained hypertension

4.34 (2.63–7.14)

959

7046

Masked hypertension

2.56 (2.00–3.33)

193

1667

White coat hypertension

1.56 (0.95–2.56)

224

3172

Referent

499

11,438

Category

Normotension

1.0

2.0

4.0

7.0

Summary odds ratio for incident cardiovascular events

Fig. 34.7 Results of separate recent meta-analyses of various types of cardiovascular risk associated with treated and controlled hypertension and four types of untreated blood pressure patterns, as classified by ambulatory or home blood pressure monitoring: normotension, white coat hypertension, masked hypertension, and sustained hypertension. Horizontal lines represent the bounds of the 95% confidence intervals (CI), squares are drawn in proportion to the number of events. The cross-hatched area corresponds to the 95% confidence limits of the risk of treated and controlled hypertension (272 events/1829 subjects), indexed to masked hypertension (222 events/997 subjects 40). The many sources of inhomogeneity in these data (e.g., types of cardiovascular events, treated vs. untreated subjects, baseline demographics) are ignored in these comparisons. (Modified from Cohen JB, Lotito MJ, Trivedi UK, Denker MG,

Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. Ann Intern Med. 2019;170:853-862; and Pierdomenico SD, Pierdomenico AM, Coccina F, et al. Prognostic value of masked uncontrolled hypertension. Hypertension. 2018;72:862–869.)

Changes in Systolic and Diastolic Blood Pressure With Age
Men

Women
150

Systolic
blood pressure

130

130

110

110

mm Hg

mm Hg

150

80

70

Systolic
blood pressure

Non-Hispanic Black
Non-Hispanic White
Hispanic American

80
Diastolic
blood pressure

70

Diastolic
blood pressure

0
0
18-29 30-39 40-49 50-59 60-69 70-79 $80
18-29 30-39 40-49 50-59 60-69 70-79 $80
Age (y)
Age (y)

Fig. 34.8 Changes in Systolic and Diastolic Blood Pressures With Age. Systolic blood pressure and diastolic blood pressure by age and race or ethnicity for men and women older than 18 years in the US population (NHANES III, 1988–1991). (From Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension. 1995;23:305–313.)

Program in the United States, Systolic Hypertension in Europe trial, and Systolic Hypertension in China trial) showed a similar, significant decrease in stroke and no increase in cardiac events, with active drug treatment compared with placebo. The significant benefits on stroke and mortality of antihypertensive drug therapy (beginning with a thiazidelike diuretic) have now been extended to relatively healthy octogenarians (most of whom had isolated systolic hypertension) in the Hypertension in the Very Elderly Trial.42 This RCT established a SBP target of less than 150 mm Hg for octogenarians, which was also recommended by JNC 8 for patients older than 60 years,25 but a dissenting minority of panel members later suggested that the more traditional SBP target of less than 140 mm Hg is reasonable, even if not directly supported by RCT evidence.43 This position was strengthened by the subgroup analysis of SPRINT subjects older than 75 years, who had a 34% reduction in the primary composite end point and a 33% reduction in mortality, if randomized to the SBP of less than 120 mm Hg.44 The 2021 KDIGO BP guidelines did not recommend a universal diastolic BP goal, primarily because of the lack of evidence in several important renal outcomes trials (e.g., Modification of Diet in Renal Disease, African American Study of Kidney Disease and Hypertension, both of which used mean arterial pressures, not systolic/diastolic BPs).35

Resistant hypertension. Resistant hypertension is defined as BP above treatment goal, despite optimal doses of three antihypertensive drugs, including a diuretic.45 Some clinical trials suggested that resistant hypertension may occur in 30% of hypertensive patients, but more population-based surveys put the US prevalence at 9% to 20%. Older age and obesity are strong risk factors; in several data sets from Southern European countries, white coat hypertension is found in up to 38% of individuals with resistant hypertension. Although nonadherence to prescribed antihypertensive drug therapy is the most common cause overall, suboptimal medication regimens and secondary hypertension (especially sleep apnea or hyperaldosteronism) are more frequently seen in referral centers.

Hypertensive emergencies and urgencies. A hypertensive emergency exists when elevated BP (usually BP >180/120 mm Hg) is associated with severe, ongoing target-organ damage (e.g., aortic dissection, hypertensive encephalopathy, cardiac ischemia, hematuria), which benefits from BP reduction within minutes to hours, typically using intravenous, short-acting antihypertensive agents in an intensive care unit (see Chapter 38). Examples include acute aortic dissection, acute decompensated heart failure, intracranial hemorrhage, eclampsia, and pheochromocytoma crisis.46 “Hypertensive urgencies” often have similar elevations in BP but no ongoing severe target organ damage, and they can be handled in the outpatient department with oral antihypertensive agents and quick follow-up efforts. Aggressive drug therapy and intensive monitoring in this situation has little benefit.47

Hypertension in children and adolescents. As discussed earlier, hypertension in youth was defined in the United States (until 2017) on a purely statistical basis: SBP or DBP at or above the 95th percentile for age, sex, and height, measured on at least three occasions. Although this made quality assurance for hypertension simple in large pediatric practices, the 2017 hypertension guidelines for children and adolescents have made this rubric more complex.29 Children have a higher risk for secondary hypertension than adults; most secondary hypertension in young children has a renal origin. Most adolescents with hypertension have primary hypertension; risk factors include a family history of hypertension and obesity, but renal causes of hypertension are more common in stage 2 hypertension (see Table 34.9).

Hypertension in pregnancy. Hypertension occurs in more than 5% of all pregnancies and in approximately 5% of women taking oral contraceptives.48 Definitions and implications of hypertension in pregnancy are discussed in Chapters 44 and 45

Secondary Hypertension: Acquired Causes

TABLE 34.9

Condition/ Disorder	Diseases/Comments
Kidney disorders	Kidney parenchymal disease, including acute and chronic glomerular diseases, chronic tubulointerstitial disease, PKD, diabetic nephropathy, and obstructive uropathy Renovascular disease: renal artery stenosis caused by atherosclerosis or fibromuscular dysplasia; arteritis; extrinsic compression of renal artery Other renal causes: renin-producing tumors, renal sodium retention (Liddle syndrome)
Endocrine disorders	Adrenocortical disorders: primary aldosteronism, congenital adrenal hyperplasia, Cushing syndrome Adrenomedullary tumors: pheochromocytoma (also extraadrenal chromaffin tumor) Thyroid disease: hyperthyroidism, hypothyroidism Hyperparathyroidism with hypercalcemia Acromegaly Carcinoid tumors
Exogenous substances and/or drugs	Oral contraceptives, sympathomimetics, glucocorticoids, mineralocorticoids, NSAIDs, calcineurin inhibitors, tyramine-containing foods and monoamine oxidase inhibitors, EPO, ergot alkaloids, amphetamines, herbal remedies, licorice (mimics primary aldosteronism), ethanol, cocaine and other illicit drugs, abrupt withdrawal of clonidine
Pregnancy	Preeclampsia and eclampsia
Coarctation of the aorta	Usually congenital, diminished pulses below the coarct, positive Hill’s sign
Neurologic disorders	Sleep apnea Increased intracranial pressure: brain tumors Affective disorders Spinal cord injury: quadriplegia, paraplegia, GuillainBarré syndrome Baroreflex dysregulation

Psychosocial factors

Hostility, time-urgency/impatience, depression, anxiety, occupational stress

Intravascular volume overload

Pedal or presacral edema, jugular venous distention, pulmonary rales

Systolic hypertension

Loss of elasticity of aorta and great vessels

Obesity

White adipose tissue that has endocrine function: leptins, adiponectin, cytokines, chemokines, Ang II, other adipokines

Hyperdynamic cardiac output: hyperthyroidism, aortic insufficiency, anemia, arteriovenous fistula, beriberi, Paget disease of bone

Ang II, Angiotensin II; EPO, erythropoietin; NSAID, nonsteroidal antiinflammatory drug; PKD, polycystic kidney disease.

Classification by Cause of Hypertension

In 90% to 95% of adults with hypertension, the cause is unknown, and therefore the diagnosis is primary (or essential) hypertension (see Chapter 35). Table 34.9 lists the more common causes of secondary hypertension in descending order of prevalence in large

Guidelines for Measurement of Blood Pressure (BP): Patient Factors, Equipment, and Technique

BOX 34.1

Patient Factors

- Caffeine should not be consumed for 1 hour before the BP measurement.
- Cigarettes should not be smoked for at least 15 minutes before the BP reading.
- The standard BP measurement should be made with the patient not talking and seated comfortably, back and arm supported, and legs uncrossed. The cuff must be at the level of the heart, and the arm should be bare.
- The urinary bladder should be empty.
- Initially, BP should also be checked in both arms in the supine position after 5 minutes of rest; thereafter the arm with the higher reading is used for both supine and standing readings (after 2 minutes), especially in patients who are diabetic, older than 65 years, or receiving antihypertensive therapy. If sequential BP readings are taken in the same position, at least 30 seconds should elapse between BP readings. In patients younger than 30 years, check BP in one leg initially.
- To establish a diagnosis of hypertension, obtain BP readings on two different occasions, at least 1 week apart.

Equipment

- The bell of the stethoscope is preferred. The length of the bladder with the cuff should encircle at least 80% of the arm.
- The width of the cuff should be equal to two-thirds of the distance from the antecubital space to the axilla and should be 40% of the arm circumference. The best cuff for most adults is the 15-cm-wide cuff with a bladder of 33 to 35 cm in length. The distal edge of the cuff should be 2.5 cm (1 inch) above the antecubital fossa. For leg BP, thigh cuff length should encircle 80% of the thigh, and width should be 40% of the thigh circumference. For leg BP, the patient should be prone and popliteal artery sounds detected by auscultation.
- For infants, ultrasound equipment may need to be used.

Technique

- The initial systolic BP should be checked by palpating the disappearance of the radial or brachial pulse before auscultation and the cuff then deflated.
- The second BP check requires cuff inflation 20 mm Hg above the palpable systolic level.
- Deflate the cuff at a rate of 2 to 4 mm Hg per second for heart rates of 60 to 120, respectively.
- Record the Korotkoff sound I (appearance of sound) as the systolic BP and record the Korotkoff sound V (silence, 2 mm Hg below the last sound) as the more reproducible diastolic BP. If the sounds do not disappear, record the muffled sound (phase IV) as the diastolic BP.
- The sounds may be augmented by having the patient raise the arm and open and close the hand 10 times before inflating the BP cuff.
- Do not stop between systolic and diastolic BP readings; deflate the cuff, wait at least 30 seconds, and then reinflate. On each occasion, record at least two (and preferably three) BP readings. If the BP readings vary by more than 5 mm Hg, take additional BP readings until two are within 5 mm Hg.
- In children, the same standards apply for cuff size; Korotkoff sound V should be used. If the child is uncooperative, the systolic BP may be determined by palpation.

Acceptable Bladder Dimensions for Various Arm Sizes.

TABLE 34.10

Usual Patient	Arm Circumference Range at Midpoint (cm)	Bladder Width (cm)	Bladder Length (cm)
Newborn	6	3	6
Infanta	6–15	5	15
Childa	16–21	8	21
Small adult	22–26	10	24
Adult	27–34	13	30
Large adult	35–44	16	38
Adult thigh	45–52	20	

[a]To approximate a bladder width to arm circumference ratio of 0.4 more closely in children, additional cuffs are available. There is some overlap in the recommended ranges for arm circumference to limit the number of cuffs. It is suggested that the larger cuff be used if it is available. Modified from Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals, part 1: blood pressure in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45:142-161.

EVALUATION OF HYPERTENSION

Blood Pressure Measurement

Arterial BP is traditionally measured in the brachial artery with the cuff-based sphygmomanometer by detecting sounds that are generated (auscultatory method) or by recording vascular pulsations (oscillometric method) after decompression of a compressed artery.49 Box 34.1 lists guidelines for traditional BP measurement. The most common error is using an inappropriately sized cuff, because cuffs that are too small routinely underestimate the BP. Table 34.10 provides acceptable bladder dimensions for varying arm sizes. Because of the low frequency of Korotkoff sounds, the bell of the stethoscope provides better detection than the diaphragm. Accurately taking BP is a teachable and testable skill, but many routine measurements are made with little effort to ensure their quality. As a result, many health care systems have transitioned to using automated oscillometric office BP measurements, which minimize the white coat effect, and after 5 minutes of quiet rest provide standardized triplicate measurements in a 5-minute period. Because elemental mercury (used in classic manometers and sphygmomanometers) has been eliminated from workplaces in most countries and aneroid (“dial”) manometers are fragile, oscillometric techniques have become increasing popular. This method directly measures MAP and then uses a proprietary algorithm to estimate SBP and DBPs. Many such semiautomatic (typically for home BP readings) and fully automatic oscillometric devices have been validated against the traditional mercury column,50 but they still require regular calibration, validation, and maintenance.

Variability of Blood Pressure

Office Versus Home Blood Pressure and Circadian Variation

series. Renal parenchymal disease is most common (especially in nephrology clinics, particularly in diabetics; see Chapters 31 and 33), followed by endocrine causes (Chapters 39 and 40), renovascular hypertension (Chapter 43), sleep apnea, coarctation of the aorta, drug-induced hypertension, and rare monogenetic causes (see Chapter 49). Hypertension occurring in dialysis patients is covered in Chapter 42, while neurogenic hypertension such as can occur with stroke is discussed in Chapter 41

BP varies considerably throughout the day and over time, even in the same individual. This intrinsic variation causes difficulty in identifying hypertensive individuals because there are many false negatives and even more false positives. Aside from measurement errors (which can be overcome by proper technique), intrinsic biologic variation can be addressed by taking at least three BP readings at a given visit. Recent US guidelines consider the lowest SBP and DBP at any given visit (even if not measured simultaneously) to be the BP for that visit.51 Confirming elevated

Increased Risk of Cardiovascular Mortality
Systolic Blood Pressure
130 mm Hg

140 mm Hg

Diastolic Blood Pressure
80 mm Hg

150 mm Hg

12

11.5

13.8

12
9.8

10

10
8

0.8

1.3 1.7

2.4
1.1

2.0

6

4.6

4.5

4.3

4

8

7.1

7.1

6

4

3.1

2.8
1.5

2

1.3

2.0

4.2

3.4

2.5

1.8

1.2

6.3

5.5

5.1

2.6

1.7

2.4

24 hour

Nighttime

Daytime

Office

Home

24 hour

Nighttime

Home

Daytime

Office

24 hour

Nighttime

24 hour

Nighttime

Daytime

Office

Home

24 hour

Nighttime

Home

Daytime

Office

24 hour

Nighttime

Daytime

Office

Home

Daytime

0

0

Office

2

100 mm Hg

14

Home

Risk of CV death (%)

14

90 mm Hg

Fig. 34.9 Risk for Cardiovascular Mortality in an Early Population-Based Italian Study. Risk for cardiovascular death (%) over 11 years, for a 10 mm Hg increase in office, home, and ambulatory blood pressure (BP) readings at various initial BP values. CV, Cardiovascular. (From Sega R, Fachetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation. 2005;111:1777–1783.)

readings at a second visit takes advantage of regression to the mean to better identify the true BP for a given individual. Another widely recommended option is to measure home BPs (see later discussion).

In addition to physical/mental activity, and emotional/environmental stress, BP is affected by circadian variation. About 80% of the population display a dipping pattern, with average nocturnal BP that is 10% to 20% lower than the daytime average; this difference diminishes with increasing age. The normal morning surge in BP and heart rate that begins about 30 minutes before awakening correlates with an increased risk for death, myocardial infarction, and stroke in the early morning hours. Individuals with a nondipping nocturnal BP pattern more commonly have CKD, target-organ damage, secondary hypertension, autonomic dysfunction, and/or an increased risk for CV events.

Home and Ambulatory Blood Pressure Monitoring

Most ambulatory BP monitors use oscillometry and record BPs for 24 hours, making measurements frequently during the daytime (e.g., every 15 minutes) and less so at night (e.g., every 30 minutes). Inaccurate readings can occur with inappropriately sized cuffs, cardiac dysrhythmias, vigorous activity, inability to sleep because of pain resulting from cuff insufflation, and many other conditions. Because ambulatory BP monitoring (1) can diagnose white coat, masked, and nocturnal hypertension; (2) correlates better with both target-organ damage and future CV events than either office or home BPs; and (3) has been found to be cost-saving in many countries, it has been recommended (as at least one of several options) by many policymaking authorities, including British, European,26 Canadian, and KDIGO Guidelines,35 and the US Task Force on Preventive Services52 before starting antihypertensive drug therapy. Multiple national and international expert panels have issued guidelines regarding indications, technique, reporting, and implications of the procedure.34 49 53

Because of the limited availability of, and scarce reimbursement for, ambulatory BP monitoring, home BP monitoring with semiautomated devices (typically duplicate measurements morning and evening for a week) has been recommended.26 34 49 53 Home BP readings, on average, are slightly higher than ambulatory BP readings (because the latter

Assessment of Patients for Hypertension
by Use of Clinic, Home, and
Ambulatory Monitoring
White coat hypertension
(Isolated clinic hypertension)
Persistently raised
clinic BP
Target organ damage?

Masked hypertension
(Isolated ambulatory
hypertension)
Persistently normal
clinic BP

Yes

Target organ damage?

High
High
No
Yes
Home BPs elevated?
24-hour ambulatory
Start
BP
treatment
No
24-hour ambulatory High
BP

Low
Continue to monitor
clinic and home
BP

Continue to monitor
clinic and ambulatory
BP

Fig. 34.10 Algorithm for diagnosis of hypertension using clinic, home,

and/or ambulatory monitoring of blood pressure (BP).

includes nocturnal BPs) and slightly lower than office BPs. Home BP readings should be obtained with a device that has been calibrated (usually in the practitioner's office), are subject to reporting bias (which can be minimized by telemonitoring systems), and their interpretation is not often reimbursed. In general, home BP readings correlate better with target-organ damage and CV outcomes than office BP measurements but less well than ambulatory BP results (Fig. 34.9).54 For many reasons, therefore, ambulatory BP monitoring is preferred over home BP recording in several settings49 (Fig. 34.10 and Box 34.2).

Indications for Ambulatory Blood Pressure (BP) Measurement

BOX 34.2

- White coat hypertension
- Evaluation of apparent drug resistance
- Hypotensive symptoms (especially during sleep, e.g., in obstructive sleep apnea)
- Autonomic dysfunction
- Episodic hypertension
- Evaluation of nocturnal decreases in BP as a prognostic factor for target organ damage (e.g., left ventricular hypertrophy, ischemic optic neuropathy)
- Evaluation of BP changes in patients with paroxysmal nocturnal dyspnea and/or nocturnal angina
- Carotid sinus syncope
- Pacemaker syndromes
- Safety of withdrawing antihypertensive medication
- Assessment of 24-hour BP control in patient receiving once-daily medication
- Borderline hypertension with target organ damage (evaluation for masked hypertension)
- Evaluation of antihypertensive drug therapy in clinical trials

Risk Assessment in Hypertension

The medical history, physical examination, and a limited laboratory evaluation (biochemistry panel, including estimated GFR, and fasting glucose and lipid panel, urinalysis and urinary albumin-to-creatinine ratio, complete blood count, electrocardiogram) provide useful information to assess the presence and extent of target-organ damage and estimate future CV and renal risk (see Chapter 35).[24-27,34] The ACC/AHA 2017 US hypertension guideline added serum thyroid-stimulating hormone to the list of recommended initial tests.[34]

Consideration of Primary Versus Secondary Hypertension

If the history, physical examination, or screening laboratory studies suggest secondary hypertension, additional studies may be warranted (Tables 34.11 and 34.12). If renal parenchymal disease is suspected, ultrasound may be useful to evaluate renal size and echogenicity and rule out obstructive uropathy; Doppler flow studies also can help stratify risk for renovascular hypertension (see Chapter 43). Because primary aldosteronism can now be controlled either with chronic aldosterone antagonists or (occasionally) after laparoscopic surgery, a ratio of plasma aldosterone to plasma renin activity ratio may be useful (see Chapter 39). Suggested evaluations for other forms of secondary hypertension are listed in Table 34.12

Acknowledgment

I thank the late William J. Lawton, MD, and Drs. DiBona, Kopp, and Luft for their contributions to this chapter in previous editions.

TABLE 34.11

Evaluation for Primary Versus Secondary Hypertension

Classification	Medical History	Physical Examination

Laboratory Studies

General information and evaluation of target organs

Duration and course of hypertension
Prior workup and treatment
Diet/lifestyle: salt intake, tobacco, caffeine

Evaluation of volume status, optic fundi, heart, lungs, peripheral vessels, and nervous system

Complete blood count, fasting glucose, lipid profile (includes HDL, LDL, cholesterol, triglyceride), uric acid
Consider echocardiogram

Primary (essential or idiopathic) or secondary (?)

Family history: Hypertension, cardiovascular and renal diseases
Symptoms of target organ disease (related to eyes, central nervous system, cardiorespiratory, and peripheral vasculature)

See Table 34.12 for signs suggestive of secondary hypertension

See Table 34.12 for additional laboratory studies to rule out secondary hypertension

HDL, High-density lipoprotein; LDL, low-density lipoprotein.

TABLE 34.12

Hypertension

History, Physical Examination, and Initial Laboratory Evaluation for Secondary

Target Organ/System Medical History

Physical Examination

Laboratory Studies

Tenderness in costovertebral angles; palpable kidneys, edema

BUN, serum creatinine; urinalysis, urine culture if indicated; first morning UACR

Epigastric bruit; other vascular bruits

Kidney ultrasound with duplex Doppler flow study; consider angiography or magnetic resonance angiography

Kidney
Kidney parenchymal

Renovascular
hypertension

History of kidney disease (including glomerulonephritis, nephrotic syndrome, calculi, urinary tract infection)
Symptoms include nocturia, frequency, dysuria, hesitancy, urgency, incomplete emptying, dribbling, hematuria, pyuria, flank pain

TABLE 34.12 History, Physical Examination, and Initial Laboratory Evaluation for Secondary
Hypertension—cont’d
Target Organ/System Medical History

Physical Examination

Laboratory Studies

Endocrine
Primary aldosteronism

Muscle weakness, cramps

Serum aldosterone/plasma renin
activity ratio

Cushing syndrome

Weight gain, muscle weakness, changes in
body habitus

Body habitus: Central obesity,
dorsocervical fat pad, abdominal
striae

Midnight salivary cortisol; consider
morning serum cortisol after
dexamethasone suppression

Pheochromocytoma

Headaches, vasomotor symptoms, (inappropriate
sweating, pallor), cardiac symptoms
(awareness, tachycardia, palpitations)

Paroxysmal or intermittent hypertension
(50% of patients)

24-hr urine for VMA, metanephrines,
and catecholamines or plasma
fractionated metanephrines

Carcinoid

Flushing

Hyperthyroidism

Weight loss, tachycardia, palpitations,
sweating, heat intolerance

Palpable thyroid

Ultrasensitive serum thyroidstimulating hormone level

Hypothyroidism

Weight gain, dry skin, cold intolerance, hair
loss

Palpable thyroid

Serum ultrasensitive thyroidstimulating hormone level

Hyperparathyroidism

Nausea, vomiting, bone pain, nephrolithiasis

Acromegaly

Change in size of head, hands, or feet (adult)

24-hour urine for
5-hydroxyindoleacetic acid

Serum calcium, intact parathyroid
hormone levels
Appearance

Serum insulin-like growth factor-1
level (see Box 40.1)

Onset or detection of hypertension in
childhood or adolescence

Simultaneous palpation of radial and
femoral arteries to detect pulse lag in
femoral arteries; leg blood pressure

Chest radiograph for heart size,
configuration of aorta, rib notching;
consider echocardiogram

Sleep apnea

Obesity; weight gain; daytime somnolence;
snoring, poor sleep habits (frequent
awakening, not rested on arising); earlymorning headache

Obesity, narrowed airway in
hypopharynx, redundant pharyngeal
tissue

Berlin questionnaire; consider formal
sleep study (polysomnography)

Increased intracranial
pressure

Headache, neurologic symptoms

Papilledema

Increased cerebrospinal fluid pressure

Increased jugular venous distention,
pulmonary crackles, presacral and
peripheral edema, hepatomegaly

Chest radiograph

Medication
Review of prescribed and over-the-counter

medications (especially oral contraceptives,
NSAIDs, sympathomimetic agents [cold
and allergy remedies], illicit or recreational
drugs, including alcohol, herbal remedies)
Coarctation of the Aorta

Neurologic Disorders

Affective disordersa
Spinal cord injurya
Psychosocial Factors
Family and support structure, occupation,
education, stressors
Volume Overload
Excess salt and water intake (may be
iatrogenic with excess parenteral fluid)
Isolated Systolic Hypertension
Pseudohypertension (positive Osler
maneuver), cardiac and vascular
examination (aortic insufficiency,
arteriovenous fistula)
aMedical

history, physical examination, and laboratory tests are beyond the scope of this discussion.
A more detailed discussion is provided in other relevant chapters. Pregnancy-associated hypertension is discussed in Chapters 44 and 45.
BUN, Blood urea nitrogen; NSAID, nonsteroidal antiinflammatory drug; UCAR, urine albumin-to-creatinine ratio; VMA, vanillylmandelic acid.

SELF-ASSESSMENT QUESTIONS

1. Short-term (within seconds to minutes) regulation of blood pressure in normal humans is most often attributed to which of the following physiologic systems?
A. Atrial natriuretic peptides
B. Endothelin
C. Kallikrein-kinin system
D. Renin-angiotensin-aldosterone system
E. Sympathetic nervous system

2. An asymptomatic, presumably healthy 67-year-old man visits the physician's office and has seated blood pressures of 140/96, 138/94, and 142/88 mm Hg, as measured personally and appropriately by the physician. According to guidelines promulgated by the Healthcare Effectiveness Data and Information Set (HEDIS) 2021 and the ACC/AHA 2017 US hypertension guideline, his blood pressure at this visit is most appropriately classified using which of the following terms?
A. Normal
B. Elevated
C. Stage 1 hypertension
D. Stage 2 hypertension
E. Isolated systolic hypertension

3. A 62-year-old White man visits the nephrologist because his routine tests last week showed that his estimated glomerular filtration rate was 59 mL/min/1.73 m2 and his first morning voided urine contained 28 mg (normal <30) of albumin/gram of creatinine. Past medical history includes “prehypertension” since 2015, but he takes no medications. Blood pressures are 136/84, 134/86, and 132/82 mm Hg when measured personally and appropriately by the nephrologist. His 10-year risk of a cardiovascular event is estimated at 9.2%. According to the ACC/AHA 2017 US hypertension guideline, the most appropriate recommendation for this patient is which of the following?
A. Recheck blood pressure in this office in 1 year.
B. Recheck blood pressure in this office in 1 year, and provide guidance about lifestyle modifications.
C. Repeat blood and urine tests in 3 months, and recheck blood pressure in this office soon thereafter.
D. Recheck blood pressure within 2 months.
E. Institute antihypertensive drug therapy today with an angiotensin converting-enzyme inhibitor or angiotensin II receptor blocker.

4. A 32-year-old woman is referred to the nephrologist because her ophthalmologist noted grade II hypertensive retinopathy last month, and her obstetrician/gynecologist noted 2+ proteinuria on dipstick (without blood or nitrite), despite normal office blood pressures last week. Past medical history is remarkable for preeclampsia 4 and 6 years ago, but both of her children were delivered without complications, and her blood pressure has since been normal. Office blood pressures are 128/84, 126/82, and 124/80, measured by a calibrated automated oscillometric device. In addition to the retinopathy, electrocardiogram shows voltage criteria for left ventricular hypertrophy, and a random urinalysis shows 3+ protein. According to recent surveys, her condition is most commonly seen in what proportion of which population?
A. Less than 1% of people older than 65 years
B. 5% to 10% of the hypertensive population
C. 10% to 15% of the general population
D. 20% to 25% of the hypertensive population
E. 29% to 32% of the general population

5. A 56-year-old non-Black man is referred to the nephrologist because his blood pressures in his primary care medical home have never been below 190/120 mm Hg, yet the rest of his evaluation is normal. A request for prior authorization for ambulatory blood pressure monitoring was denied by his insurance plan. His home blood pressures, measured with a validated semiautomatic oscillometric device, have a mean and standard deviation of 128 ± 4/78 ± 3 (122 measurements over 3 months). He has no family history of hypertension. Office blood pressures, taken with the same machine, were 194/122, 196/120, and 192/118 mm Hg. Physical examination and laboratory studies were unremarkable. The most appropriate recommendation for him is which of the following?

A. A renal biopsy is indicated to identify the cause of his hypertension.

B. He should have an iothalamate clearance measured to assure that the estimated glomerular filtration rate is accurate.

C. He should undergo renal ultrasound with Doppler flow studies, a 24-hour urine collection for vanillylmandelic acid and metanephrines, and a plasma aldosterone/renin activity ratio to rule out common causes of secondary hypertension.

D. He should start an angiotensin converting-enzyme inhibitor or an angiotensin II receptor blocker today and return to this office in 1 month for repeat blood pressure measurement by his home device.

E. He should continue to monitor his home blood pressures and call for another appointment when/if they meet or exceed 125/75 mm Hg.

REFERENCES

1. Hall JE. Role of the kidneys in long-term control of arterial pressure and in hypertension: the integrated system for arterial pressure regulation. In: Guyton and Hall’s Textbook of Medical Physiology. ; 2020:229–244.
2. Izzo Jr JL, Sica D, Black HR, eds. Hypertension Primer. 4th ed. Council on High Blood Pressure Research, American Heart Association; New York: Lippincott, Williams & Wilkins; 2008:1–113.
3. Sata Y, Head GA, Denton K, May ON, Schlaich MP. Role of the sympathetic nervous system and its modulation in renal hypertension. Front Med [Lausanne]. 2018;5:82.
4. Syed M, Osman M, Alhamoud H, et al. The State of Renal Sympathetic Denervation for the Management of Patients with Hypertension: A Systematic Review and Meta-Analysis. Catheter Cardiovasc Interv; 2020(Epub ahead of print).
5. Schmieder RE. Renal denervation: where do we stand and what is the relevance to the nephrologist?. Nephrol Dial Transplant. 2020 (Epub ahead of print).
6. Pöss J, Ewen S, Schmieder RE, et al. Effects of renal denervation on urinary sodium excretion in patients with resistant hypertension. Clin Res Cardiol. 2015;104:672–678.
7. Bakris G, Agarwal R, Anker SD, et al. For the fidelio-dkd Investigators. effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219–2229.
8. Hering L, Rahman M, Potthoff SA, Rump LC, Stegbauer. Role of β2-adrenoceptors in hypertension: focus on renal sympathetic neurotransmitter release, inflammation, and sodium homeostasis. Front Physiol. 2020;11:566871.
9. Lv Y-B., Wang Y, Ma W-G., et al. Association of the renalase SNPs 4s2296545 and rs2576178 with the risk of hypertension: a meta-analysis. PLoS One. 2016;11:e0158880.
10. Wenzel P, Rossmann H, Müller C, et al. Heme oxygenase-1 suppresses a proinflammatory phenotype in monocytes and determines endothelial functioning and arterial hypertension in mice and humans. Eur Heart J. 2015;36:3437–3446.
11. Buckalew V. Endogenous digitalis-like factors: an overview of the history. Front Endocrinol. 2015;6:49.
12. Ravani P, Tripepi G, Pecchini P, et al. Urotensin II is an inverse predictor of death and fatal cardiovascular events in chronic kidney disease. Kidney Int. 2008;73:95–101.
13. do Carmo JM, da Silva AA, Wang Z, et al. Obesity induced hypertension: brain signaling pathways. Curr Hypertens Rep. 2016;18:58.
14. Gill D, Cameron AC, Burgess S, et al. Urate, blood pressure and cardiovascular disease: evidence from Mendelian randomization and meta-analysis of clinical trials. Hypertension. 2021;77:383–392.
15. Sato Y, Feig DI, Stack AG, et al. The case for uric acid-lowering treatment in patients with hyperuricemia and chronic kidney disease. Nat Rev Nephrol. 2019;15:767–775.
16. Rai A, Narisawa M, Li P, et al. Adaptive immune disorders in hypertension and heart failure: focusing on T-cell subset activation and clinical implications. J Hypertens. 2020;38:1878–1889.
17. Lohmeier TE, Hall JE. Device-based neuromodulation for resistant hypertension therapy. Circ Res. 2019;124:1071–1093.
18. Seccia TM, Rigato M, Ravarotto V, Calò LA. Rock (RhoA/Rho kinase) in cardiovascular-renal pathophysiology: a review of new advancements. J Clin Med. 2020;9:1328.
19. Rettig R, Grisk O. The kidney as a determinant of genetic hypertension: evidence from renal transplantation studies. Hypertension. 2005;46:463–468.
20. Evans RG, Bie P. Role of the kidney in the pathogenesis of hypertension: time for a neo-Guytonian paradigm, or a paradigm shift? Am J Physiol Regul Integr Comp Physiol. 2016;310:R217–R229.
21. Mahfoud F, Mancia G, Schmieder R, et al. Renal denervation in high-risk patients with hypertension. J Am Coll Cardiol. 2020;75:2879–2888.
22. Bhatt DL, Kandzari DE, O’Neill WW, et al. A controlled trial of renal

denervation for resistant hypertension. N Engl J Med. 2014;370:1393–1401.

23. Lewington S, Clarke R, Qizilbash N, et al. Prospective studies collaboration: age-specific relevance of usual blood pressure to vascular mortality—a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.
24. Chobanian AV, Bakris GL, Black HR, et al. Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure; national heart, Lung, and blood Institute; national high blood pressure education Program coordinating committee: seventh report of the Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–1252.
25. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–520.
26. Williams B, Mancia G, Spierling W, et al. For the task force for the management of arterial hypertension of the European society of Cardiology and the European society of hypertension. 2018 ESC/ESH guidelines for the management of arterial hypertension. J Hypertens. 2018;36:2284–2309.
27. Unger T, Borghi C, Charchar F, et al. 2020 international society of hypertension global hypertension practice guidelines. Hypertension. 2020;75:1334–1357.
28. Giles TD, Materson BJ, Cohn JN, Kostis JB. Definition and classification of hypertension: an update. J Clin Hypertens. 2009;11:611–614. erratum: J Clin Hypertens (Greenwich). 2010;12:13.
29. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140. e20171904.
30. Muntner P, Hardy ST, Fine LJ, et al. Trends in blood pressure control among US adults with hypertension. JAMA. 2020;324:1190–1200. 19992000 to 2017-2018.
31. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive bloodpressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. Lancet. 1998;351:1755–1762.
32. Wright Jr JT, Williamson JD, Whelton PK, et al. For the SPRINT Research Group. a randomized trial of intensive vs. standard blood-pressure control. N Engl J Med. 2015;373:2103–2116.
33. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2:775–781.
34. Whelton PK, Carey RM, Aranow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association Task Force on clinical practice guidelines. Hypertension. 2018;71:e13–e115.
35. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. Kdigo 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99:S1–S87.
36. Jackson R, Lawes CM, Bennett A, et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual’s absolute cardiovascular risk. Lancet. 2005;365:434–441.
37. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2:231–237.
38. Ostchega Y, Yoon SS, Hughes J, Louis T. Hypertension awareness, treatment, and control—continued disparities in adults: United States, 2005-2006. NCHS Data Brief. 2008;(3):1–8.
39. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. Ann Intern Med. 2019;170:853–862.
40. Pierdomenico SD, Pierdomenico AM, Coccina F, et al. Prognostic value of

masked uncontrolled hypertension. Hypertension. 2018;72:862–869.
41. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the third national health and nutrition examination survey, 1988-1991. Hypertension. 1995;23:305–313.
42. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age and older. N Engl J Med. 2008;358:1887–1898.

43. Wright Jr JT, Fine LJ, Lackland DT, et al. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med. 2014;160:499–503.
44. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016;315:2673–2682.
45. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation and management. a scientific statement from the American Heart Association. Hypertension. 2018;72:e53–e90.
46. van den Born B-J.H., Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. Eur Heart J Cardiovasc Pharmacother. 2019;5:37–46.
47. Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgencies in the office setting. JAMA Intern Med. 2016;176:981–988.
48. American College of Obstetricians and Gynecologists. Task Force on hypertension in pregnancy. Hypertension in pregnancy: executive summary. a report of the American College of obstetricians and gynecologists task force on hypertension in pregnancy. Obstet Gynecol. 2013;122:1122–1131.

49. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension. 2019;73:e35–366.
50. dabl Educational Trust. Blood pressure monitors: Validations, papers and reviews. http://www.dableducational.org.
51. National Committee on Quality Assurance. HEDIS; 2021. http://www.ncqa.org/hedis/measures/controlling-high-blood-pressure/.
52. Siu AL, for the US Preventive Services Task Force. Screening for high blood pressure in adults: US preventive services task force recommendation statement. Ann Intern Med. 2015;163:778–786.
53. Parati G, Stergiou G, O’Brien E, et al. European Society of hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32:1359–1366.
54. Sega R, Fachetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the pressioni arteriose monitorate e loro associazioni (PAMELA) study. Circulation. 2005;111:1777–1783.

35

Primary Hypertension

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DEFINITION

Primary (essential) hypertension is defined by most international societies as an office-based blood pressure (BP) with systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher,1 but in 2017 it was defined by the American College of Cardiology/American Heart Association (ACC/AHA) as BP of 130/80 mm Hg or higher without an identifiable cause2 (Table 35.1). The ACC/AHA guidelines have a more stringent definition because of the recognition of a graded increase of cardiovascular (CV) events that exist even in those with systolic BP of 120 to 129 mm Hg and less than 80 mm Hg (which is now termed elevated BP). An argument against the ACC/AHA guidelines is that they will lead to a majority of adults being given the diagnosis of hypertension requiring therapy.

Blood pressure is normally variable and related to a natural circadian rhythm, with the most significant increase in BP in the morning (6–10 am). Blood pressure falls during sleep secondary to a decrease in sympathetic nervous system (SNS) tone and reduced activity of other neuroendocrine systems. There are also minute-to-minute variations in BP (Fig. 35.1). Transient elevations in BP, reaching 150 mm Hg systolic, occur in most normotensive individuals in any given day, especially during exercise.3 Thus, diagnosis of elevated BP and/or hypertension should involve multiple measurements (see Chapter 34).

When only the systolic BP (SBP) is elevated (SBP >140 and diastolic BP [DBP] <90 mm Hg), the term used is isolated systolic hypertension. “White coat” hypertension is an increase of more than 20 mm Hg in SBP noted only in the physician’s office and above that seen at home or in another setting. In contrast, masked hypertension is BP that is normal in the office but elevated by more than 20 mm Hg when measured by ambulatory BP measurement.

Other terms used to describe specific clinical presentations include hypertensive emergency, associated with acute end organ damage requiring immediate treatment, usually in a critical care setting, and hypertensive urgency, in which there is no acute organ damage and BP needs correction in hours or a few days (see Chapter 38). In hypertensive emergencies in which an acute decrease of kidney function occurs, the reduction of BP will halt, prevent, or reverse decreasing glomerular filtration rate (GFR). These terms have replaced “malignant hypertension” and “accelerated hypertension.” Resistant hypertension is defined as hypertension that remains greater than 140/90 mm Hg (or 130/80 by US guidelines) despite use of three maximally dosed antihypertensive medications of different classes, including a diuretic. Patients that require four or more medications are also considered to have resistant hypertension. The definition of resistant hypertension is arbitrary and aims to identify patients that may benefit from special diagnostic or therapeutic considerations. Pseudoresistant hypertension defines uncontrolled hypertension that appears resistant but is due to other causes, usually poor adherence to therapy or inappropriate measurement (e.g., using an inappropriately small blood pressure cuff).

EPIDEMIOLOGY

Hypertension affects nearly one-third of adults worldwide, with a higher prevalence in low- and medium-income countries (31.5%, 1.04 billion people) than in high-income countries (28.5%, 349 million people).4 The prevalence of hypertension rose significantly in the twentieth century from approximately 5% in the United States in the early 1900s (based on studies using 140/90 mm Hg as the cutoff), possibly because of the increasing longevity of the population and the rising prevalence of obesity (Fig. 35.2).

There are multiple risk factors for primary hypertension (Table 35.2). Older age is a strong risk factor, especially after the age of 65 years, such that by 80 years of age, 90% of individuals are hypertensive.[5] Interestingly, the age-related increase in prevalence of hypertension has not been uniformly observed in all populations (e.g., the Yanomamo Indians on their native hunter-gatherer diet). Hypertension is more common in men, although the prevalence in women is similar to and slightly exceeds that of men after age 55 years. Certain ethnic groups are at increased risk of hypertension, especially African Americans, Filipino Americans, Australian Tiwi, and the Maori of New Zealand.

Other risk factors for hypertension include family history, obesity, insulin resistance, hyperuricemia and/or gout, sleep disorders including sleep apnea, and persistent high-stress environments either at work or home. Certain physical features, such as elevated heart rate or an increased BP response to exercise, are also predictive, as is elevated hematocrit.

Genetic factors play a role in 20% to 30% of patients with primary hypertension, likely from the cumulative effect of multiple susceptibility genes. To date over 90 genetic polymorphisms have been identified that are associated with primary hypertension,[6] including polymorphisms linked with natriuretic peptide, vasoactive mediators (angiotensinogen, endothelial nitric oxide synthetase, prostacyclin synthase, β2-adrenoceptor, 20-HETE synthase [CYP4F2 gene], G protein β3), mediators of vascular smooth muscle tone (calcium-dependent potassium channel, KCNMA), immune signaling (e.g., heat shock proteins), and mediators controlling kidney sodium transport (α-adducin and 11β-hydroxysteroid dehydrogenase type 2, aldosterone synthase, “with no lysine” kinase [WNK] kinases). Although genetic polymorphisms involving sodium excretion are common in persons with primary hypertension,[7] more than 80% also have effects on the immune system.[6]

Hypertension is also more likely to occur if the mother has a history of hypertension, obesity, preeclampsia, or malnutrition. A history of intrauterine growth restriction or low birthweight also are risk factors for hypertension.

Categories of Blood Pressure

TABLE 35.1

in Adults
Category

DBP (mm
Hg)

SBP (mm Hg)

ACC/AHA Hypertension Guidelines (2017)
Normal
<120
and
Elevated
120–129
and
Hypertension
Stage 1
130–139
and
Stage 2
≥140
and

<80
<80
80–89
≥90

ACC/AHA, American College of Cardiology/American Heart Association;
DBP, diastolic blood pressure; SBP, systolic blood pressure.

BP (mm Hg)

Diurnal Variation in Blood Pressure

Sleep
12

14

16

18

20

22

24

02

04

06 08

Fig. 35.1 Blood Pressure (BP) Variability in a Normotensive Individual. In most individuals, systolic blood pressure reaches 150 mm Hg at least once daily. (From Bevan AT, Honour AJ, Stott FH. Direct arterial pressure recording in unrestricted man. Br Heart J. 1969;31[3]:387–388.)

Epidemic of Hypertension
Prevalence of Hypertension (%)

35
30
One in
3
adults

20
15
10

One in
20 adults

5
0
1900

Genetic

Physical

Diet/toxin

Metabolica
Other

Major Risk Factors for Primary

Family history
Polymorphisms (adducin, endothelial nitric oxide synthase, angiotensinogen, β2-adrenoceptor, human G protein β3 subunit)
Low birthweight, low nephron number, maternal hypertension, maternal preeclampsia, maternal malnutrition
Obesity, older age, African American, African Caribbean, some Bantu-speaking peoples in Africa, increased heart rate (>83 beats/min), increased emotional stress
Increased sodium intake, low potassium intake, low dairy products intake, heavy alcohol intake, high intake of added sugars, low level lead or cadmium intoxication
Elevated serum uric acid, insulin resistance, elevated hematocrit
Low socioeconomic status, urban versus rural residence

aLaboratory-based

parameters.

Dietary and environmental factors also contribute to the risk for hypertension. Obesity, with or without features of insulin resistance and metabolic syndrome, is a major risk factor for hypertension, and the increased incidence of obesity parallels the rise in hypertension in most countries. Epidemiologic and interventional studies have linked high salt and low potassium intake with persistent BP elevation (especially in African Americans), whereas increasing potassium intake lowers BP in both experimental and human studies. Intake of added sugars (e.g., sucrose, high-fructose corn syrup) predicts higher BP, and excessive alcohol consumption, physical inactivity, and chronic lowlevel exposure to lead and cadmium have all been associated with the development of hypertension.

10

Time of day (hours)

25

Hypertension

Congenital

European Society of Hypertension Guidelines (2018)

Optimal	<120	and/or	<80
Normal	120–129	and/or	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

160
140
120
100
80
60
40
20

TABLE 35.2

ETIOLOGY AND PATHOGENESIS

Primary hypertension is thought to be due to a defect in kidney sodium handling. Whereas increasing salt intake will only increase BP slightly (several mm Hg) in normal individuals, in subjects with salt-sensitive hypertension, the BP response is shifted rightward with a change in slope, leading to a greater relative increase in BP for the same load of salt (Fig. 35.3).8 In contrast, some hypertensive patients, especially those younger than 40 years, are considered to have salt-resistant hypertension, as the response to a salt load is similar to that in normal individuals but simply shifted rightward There is some evidence that individuals can begin with salt-resistant hypertension and evolve to being salt-sensitive.

The importance of salt in primary hypertension is supported by a direct association between dietary sodium content and the prevalence of hypertension in diverse populations, and intervention studies in which salt restriction has led to improvement in hypertension.9 Several hypotheses have been proposed to explain the kidney defect in sodium excretion in primary hypertension.

Genetic (Polygene) Hypothesis

1920

1940

1960
1980
2000
Year

Fig. 35.2 Epidemic of Hypertension. The prevalence of primary hypertension (defined as blood pressure >140/90 mm Hg) in the United States increased from 11% in 1939 to 31% in 2008, leveling to 29% of the population in 2012.

Lifton and colleagues determined that many monogenic forms of both hypertension and hypotension involve genes regulating kidney sodium transport (Chapter 49).7 Lifton has suggested that polymorphisms in genes that favor sodium reabsorption in the kidney, coupled with excessive salt intake (>10 g/day) that is pervasive in Western diets, may underlie the pathogenesis of primary hypertension.7 Likewise,

Physiologic Defect in Sodium
Excretion in Essential Hypertension

Increasing sodium intake

Normal

Saltresistant

Saltsensitive

Normal salt diet

Low salt diet

100

150
200
Blood pressure (mm Hg)

Fig. 35.3 Physiologic Defect in Sodium Handling in Primary Hypertension. Evidence suggests that increasing salt in the diet will only slightly increase blood pressure (BP) in subjects with normal BP or subjects with salt-resistant hypertension, whereas subjects with saltsensitive hypertension will show an exaggerated BP response. (Modified from Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med. 1972;52[5]:584–594.)

mutations that favor sodium excretion might provide protection from hypertension, such as polymorphisms involving the Na-K-2Cl cotransporter SLC12A1, the inward rectifier K+ channel KCNJ1 (carrier state for Bartter syndrome), and the Na-Cl cotransporter SLC12A3 (carrier state for Gitelman syndrome).

Nevertheless, the single-nucleotide polymorphism (SNP) variants identified by genome-wide association studies account for only 4% to 13% of the BP variability in studies of quantitative changes in BP,2 10 and studies that analyzed hypertension as a dichotomous trait found only two SNPs corresponding to hypertension: one associated with the uromodulin gene and the other located near the endothelial nitric oxide synthase gene.11

Congenital (Low Nephron Number) Hypothesis

Environmental stress during pregnancy may cause epigenetic changes that affect the fetus and translate into hypertension later in life (fetal programming). Infants with low birthweight (LBW) are at increased risk for hypertension in addition to diabetes and obesity.12 Mothers of LBW infants frequently have hypertension, obesity, preeclampsia, or malnutrition, and these maternal factors also carry an increased risk for hypertension in the infant. Brenner and colleagues13 proposed that this excess risk among LBW infants is driven by lower nephron number, which may predispose to the development of hypertension and the progressive loss of nephrons with aging. Indeed, maternal malnutrition in laboratory rats predisposes to small pups, low nephron number, and the future predisposition for hypertension. A study of nine white subjects with primary hypertension who died of accidental causes also found almost 50% fewer nephrons than in age- and sexmatched controls.14

Other studies, however, did not confirm a relationship between birthweight or low nephron number and hypertension. One study reported that LBW infants have a 25% risk for developing hypertension as an adult, but infants with high birthweight also carried a 20% risk.[15]

Thus, LBW and low nephron number likely reflect risk factors for development of hypertension rather than the underlying mechanism.

Role of the Immune System and Subtle Kidney Injury

Recently, a role of the immune system has been identified in primary hypertension.[16] The initiating mechanism is not fully understood but may be initiated by renal vasoconstriction that results from a borderline hyperactive SNS, endothelial dysfunction, or oxidative stress and that is precipitated by diet (high salt or high sugar), metabolic mechanisms (hyperuricemia), emotional stress, a borderline hyperactive SNS, or other mechanisms.[17]

The renal vasoconstriction causes ischemia that stimulates low grade T-cell and macrophage infiltration (Fig. 35.4). Low-grade T-cell and macrophage infiltration in the interstitium occurs in 90% or more of kidney biopsy samples from patients with primary hypertension.[18]

Historically, the inflammatory and microvascular changes were considered the consequence of hypertensive kidney damage, but newer studies suggest that persistent kidney inflammation may have a role in causing the hypertensive response, possibly by causing renal vasoconstriction and impairing the ability to excrete sodium.

The mechanism is thought to be mediated by activation of the innate immune system followed by stimulation of adaptive immunity in which the T cells become sensitized to neoantigens, leading to an autoimmune mediated hypertension (Fig. 35.4). To date, two autoantigens have been identified, including heat shock protein 70 (HSP70) and oxidized isoketal-containing proteins (i.e., proteins oxidatively modified by highly reactive γ-ketoaldehydes).[19,20] A role for HSP70 as a neoantigen is supported by experimental studies in which blocking T-cell sensitization to HSP70 can block hypertension, whereas sensitization of T cells to HSP70 in the kidney can induce a rise in BP. Clinical studies also have found evidence for both autoantibodies and T-cell sensitization to HSP70 in humans with primary hypertension.[19] Isoketal accumulation in dendritic cells may also act as an autoantigen as it can induce costimulatory CD80 and CD86 proteins. Isoketal-modified proteins have been demonstrated in circulating dendritic cells and monocytes of hypertensive patients, and scavengers of isoketals prevent or ameliorate hypertension in several models of hypertension.[20]

It is thought that the immune response to the autoantigens is orchestrated by T cells, B cells, and macrophages, with the CD8 T cells primarily driving the hypertensive response, whereas the regulatory T-cell populations counterregulate the response.[16,21,22] Blocking the inflammation with immunosuppressive therapy can both prevent or correct the development of hypertension in experimental models.[16]

Pilot studies also suggest that blocking the immune system, such as by mycophenolate mofetil (MMF), can lower BP in subjects with primary hypertension.[16]

How Does Sodium Retention Lead to Hypertension?

Although the classical view has been that salt loading causes acute volume expansion followed by vasoconstriction and pressure-induced sodium excretion (pressure-natriuresis), in recent years the role of transient hypertonicity as driving the hypertensive response has become dominant (Fig. 35.5).

For example, an acute salt load increases blood pressure immediately through its effects to raise sodium concentration and vasopressin levels.[23] Hypertonicity also stimulates SNS activity in the brain that has systemic and kidney hemodynamic effects that increase BP and sodium retention. Hypertonicity also activates the immune response, stimulating dendritic cell activation, the production of interleukin-17

(IL-17) from T helper cells, cytokine release from T and B cells, and inducing immune cell infiltration in the kidney.24 25 Overproduction of IL-17, in addition to its effects on autoimmunity, also stimulates the

Pathogenesis of Primary Hypertension
Stages

Events

Target organ damage

Initiating factors

Stress (hyperactive SNS), diet (high Na,
low K, high sugar), hyperuricemia, insulin
resistance, low nephron numbers,
genetic polymorphisms

Renal ischemia,
oxidative stress

Generation of DAMPs

Immune
reactivity

Sodium retention

Innate immune response
Neoantigen generation
Autoimmmune reactivity
(T cells, B cells, macrophages)

Stimulation of Na reabsorption
Impaired pressure natriuresis

Inflammation
Renal (impaired presure
natriuresis, intrarenal
Ang II, afferent SNS),
periarterial, CNS and
SNS stimulation
Nephrosclerosis
Arteriolar remodeling
LVH

Hypertension

Fig. 35.4 Pathogenesis of Primary Hypertension. Initiating factors induce renal ischemia and oxidative stress with the stimulation of innate immune reactivity, neoantigen formation, and autoimmune reactivity that drives inflammation in the kidney, in the adventitia in the arteries, and in the central nervous system that stimulates the sympathetic nervous system. Sodium retention results from increased reabsorption and impaired pressure natriuresis as a consequence of renal inflammation. Established hypertension drives target organ damage. Ang II, angiotensin II; CNS, central nervous system; DAMP, damage-associated molecular patterns; LVH, left ventricular hypertrophy; SNS, sympathetic nervous system.

Hemodynamic Pathophysiology of Hypertension
↑ Sodium reabsorption
↑ [Na] and ↑ osmolarity

↑ Intravascular volume
Cardiotonic
steroids (?)

↑ UNaV

↑ Cardiac output
Normal peripheral
vascular resistance

Il-17→ ↑NHE3, ENaC (+)
CNS →↑ SNS

↑ Lymphatics
(–) NO-mediated
vasodilation

↑ Peripheral vascular resistance
Normal cardiac output
↑ Blood pressure

Fig. 35.5 Hemodynamic Pathophysiology of Hypertension. Sodium retention induces increase in sodium concentration, hyperosmolarity, and rise in intravascular volume with an increase in cardiac output, possibly driven in part by the generation of cardiotonic steroids. This transient state is followed by sustained increment in peripheral vascular resistance and normalization of the cardiac output. These events result from the combined effects of immune (IL-17) stimulated increase in sodium reabsorption and stimulation of the sympathetic nervous system (SNS). These effects are counterbalanced by vascular endothelial growth factor type C–mediated increase in the lymphatic network and endothelial nitric oxide (NO) generation induced by intravascular dilation (see text). The increase in blood pressure tends to correct sodium retention by stimulating pressure natriuresis. CNS, Central nervous system; ENaC, endothelial sodium channel; NHE3, sodium-hydrogen exchanger 3; UNaV, urinary sodium excretion.

sodium-hydrogen exchanger 3 (NHE3) in the proximal tubule and in the sodium chloride cotransporter (NCC) and epithelial sodium channel (ENaC) in the distal and collecting ducts, respectively, favoring sodium retention.[26]

The hypertonicity and sodium retention also stimulates the release of cardiotonic steroids from the adrenal glands, such as ouabain and marinobufagenin, that partially block Na^+,K^+-ATPases, thereby stimulating natriuresis by downregulating kidney sodium transporters. However, they do this at the expense of raising blood pressure by increasing vasoconstriction and myocardial contractility by increasing cytosolic Ca^{2+} in vascular smooth muscle cells and cardiomyocytes.[27]

There are also countering mechanisms that block the hypertensive response. Sodium retention activates the tonicity enhancer binding protein (TONEBP) in macrophages that produce vascular endothelial growth factor type C that stimulates the development of a lymphatic network that attenuates the hemodynamic effects of sodium retention.[28] Sodium retention may not be sequestered in an osmotically independent compartment[29] as originally considered[28]; nevertheless, the role of macrophages is well demonstrated because macrophage depletion accentuates hypertension. Another mechanism that counters the salt-induced increase in blood pressure is the endothelial production of nitric oxide stimulated by intravascular volume expansion.[30]

Pathogenic Mechanisms Driving the Current Epidemic of Hypertension

The rise of hypertension in the last century is largely thought to be the consequence of the rise in obesity, and also the increase in life span that occurred during that time. Although obesity-associated

hypertension likely involves all three mechanisms previously discussed, it may also result from other related mechanisms, including
diet (salt and sugar), subtle kidney injury, coexistence of endothelial

A

B

C

Fig. 35.6 Grades of Hypertensive Retinopathy. (A) Mild hypertensive retinopathy with arteriolar narrowing and arteriovenous nicking. (B) Moderate hypertensive retinopathy with cotton-wool spots (nerve fiber layer infarcts) and arteriovenous nicking. (C) Papilledema, cotton-wool spots, macular yellow exudates (star formation pattern), and retinal hemorrhages in a patient with hypertensive emergency. (Courtesy J. Kinyoun, University of Washington.)

dysfunction and oxidative stress, activation of the SNS and intrarenal renin-angiotensin-aldosterone system (RAAS), and effects of hyperleptinemia and hyperinsulinemia.[31,32] Chronically elevated leptin levels, which are common in obese persons, can activate the SNS in the central nervous system (CNS) through proopiomelanocortin neurons that activate melanocortin-4 receptors.[32]

Other proposed mechanisms include hyperuricemia, possibly driven by intake of fructose-containing sugars and purine-rich foods.[17] Studies also have implicated a hyperactive SNS in early hypertension, particularly in young or borderline hypertensive patients.[33] Postulated mechanisms include a defect in baroreceptor sensitivity and an increase in SNS response to emotional or work-related stress. Activation of either the systemic or the local renin-angiotensin system (RAS) is also common in hypertension. Whereas plasma renin activity is elevated in 20% of patients, renin activity is either normal (50%) or low (30%) in the majority. However, normal renin activity may be inappropriately high in relation to the total body sodium.[34] Some hypertensive patients also have elevated plasma aldosterone, especially if the RAS is inhibited with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[35] This condition is known as aldosterone breakthrough and is often observed in persons who are obese or have hyperinsulinemia.

CLINICAL MANIFESTATIONS

Evaluation of a patient with hypertension requires careful history and physical examination, an evaluation of risk factors for hypertension, a search for potential secondary causes, and evaluation for end organ damage.

Blood pressure should be measured on at least three occasions to confirm persistent hypertension using the techniques described in Chapter 34. Home BP monitoring or 24-hour ambulatory BP monitoring is recommended to determine whether the hypertension is white coat hypertension or masked hypertension. White coat and masked hypertension can be associated with end organ disease, including left ventricular hypertrophy (LVH) and mildly increased albuminuria; diagnosis should be followed by assessment of CV risk factors and frequent reevaluation of BP.

The history should investigate the onset and duration of hypertension and the presence of a family history of hypertension or cardiokidney disease. The history should identify risk factors for hypertension (obesity, diabetes, physical activity, gout, alcohol, smoking, diet, emotional or work-related stress) and any hypertension-related morbidity

as well as consumption of over-the-counter and prescribed medications that may increase BP.

Hypertension is often asymptomatic, but even childhood-associated hypertension can be associated with impaired memory and mental performance, and hypertension remains a major risk factor for vascular dementia.

Hypertension, especially when severe (BP >160/100 mm Hg), also may be associated with headache, classically occipital and pulsatile. In hypertensive emergency, encephalopathy rarely occurs, sometimes with altered mental status and seizures. Rarely, patients may lose vision from papilledema. Hypertension, especially over 160/100 mm Hg, also places individuals at acute risk for myocardial infarction (MI), congestive heart failure (CHF) with pulmonary edema, aortic dissection, cerebrovascular accident (stroke), and kidney failure.

Physical examination includes BP measurement in both arms and cardiac examination. Attention should be focused on both the large vessels (by both palpation and listening for bruits) and the retina to evaluate the microvasculature (Fig. 35.6). Lab tests should include hematocrit, electrolytes, creatinine (and estimated GFR), calcium and phosphate (to look for primary hyperparathyroidism), fasting lipid profile (cholesterol and triglycerides), uric acid, and urinalysis. A chest radiograph and electrocardiogram should be performed to assess cardiac size and look for aortic dilation.

Additional tests include 24-hour urine sodium and potassium excretion. Urinary Na+ and K+ excretion correlates with intake if the patient is in steady state (desirable values are <100 mmol/L Na+ and >100 mmol/L K+ in 24 hours). A spot urine albumin-creatinine and an echocardiogram may uncover additional evidence of end organ damage, especially in diabetic patients and those with cardiac problems, respectively (Fig. 35.7).

PATHOLOGY

Primary hypertension is characterized by arteriolosclerosis of the preglomerular afferent arteriole and interlobular artery. Arteriolosclerosis, seen in 90% of patients, involves the replacement of smooth muscle cells of the media in the afferent arteriole with connective tissue, often with hyaline material (plasma proteins) in the subintima (hyalinosis)[18] (Fig. 35.8). Glomerular and tubular ischemia are common, with shrinkage of the glomerular tuft, tubular atrophy, and interstitial fibrosis. Occasionally, glomerulosclerosis and severe tubulointerstitial injury are seen. With hypertensive emergency, a proliferative arteriolopathy occurs, occasionally with fibrinoid necrosis. Concentric layers of connective tissue and cells may give an onion-skin appearance to

Hypertension can also cause vascular changes that can lead to aortic dissection, cerebral and aortic aneurysms, and stiffening of blood vessels from changes in collagen content that can result in higher pulse pressures.[39,40] Both elevated systolic BP and elevated pulse pressure confer increased risks for stroke, but high pulse pressure is additionally complicated as it may limit the magnitude with which systolic BP can be lowered.[41] Studies in people with diabetes suggested that diastolic BP should not be lowered below 60 mm Hg as CV risk will start to increase.[42] A post hoc analysis of the ONTARGET and TRANSCEND trials support the notion that DBP less than 70 mm Hg or greater than 80 mm Hg is associated with a higher risk in patients with an SBP of 120 to 140 mm Hg. These findings support European guidelines, which take DBP at optimal SBP control into consideration.[1]

Hypertension also increases the risk of coronary heart disease (Fig. 35.9), peripheral vascular disease, and carotid atherosclerosis with or without cerebral emboli. Hypertension is also associated with increased risk for vascular dementia.

Fig. 35.7 Echocardiogram Showing Concentric Left Ventricular Hypertrophy. Septal thickness (between arrows) and posterior wall thickness (between arrowheads) are increased (to 16 mm) in a patient with primary hypertension (normal is ≤11 mm). (Courtesy A. Pearlman, University of Washington.)

the intima, which may progress to a total obliteration of the lumen. In addition to vascular changes, immune cell infiltration in tubulointerstitial regions is present even at stages when the vascular changes are minimal or nonexistent.[18,36]

DIAGNOSIS

Diagnosis of primary hypertension requires the elimination of secondary causes. Suspicion of secondary causes of hypertension should be raised by finding new onset hypertension in very young or elderly patients (renovascular hypertension), drug-resistant hypertension, hypokalemia in the absence of being on diuretic therapy (primary aldosteronism from hyperplasia or tumors), or with impaired kidney function (kidney parenchymal disease).

Medications that increase BP include nonsteroidal antiinflammatory drugs, corticosteroids, sympathomimetics, and oral contraceptives, as well as excessive alcohol intake and cocaine use. Table 34.9 in Chapter 34 provides a list of secondary causes along with recommended evaluations.

NATURAL HISTORY

Although hypertension is often asymptomatic (referred to as the “silent killer”), it represents a major risk factor for CV mortality, especially related to pressure-related morbidities such as heart failure (HF), stroke, aortic aneurysms and dissection, chronic kidney disease (CKD), and vascular dementia. Hypertension is also a risk factor for coronary artery disease, although the association is less strong.

Increased Risk for Cardiovascular Disease

Hypertension is the most common cause of both stroke and HF associated with preserved ejection fraction (Fig. 35.9).[37] In essence, hypertension causes concentric LVH with supernormal systolic function. However, subendocardial inflammation and fibrosis also occur, resulting in a stiffer myocardium and impairing diastolic filling and eventually causing heart failure. Almost 80% to 90% of patients with heart failure have a history of hypertension.[38]

Increased Risk for Chronic Kidney Disease

Most patients with newly diagnosed primary hypertension have normal kidney function, stage 1 CKD (GFR ≥ 90 mL/min/1.73 m2), or stage 2 CKD (GFR 60–90 mL/min/1.73 m2) with or without mildly increased albuminuria (formerly termed microalbuminuria). Despite relatively preserved kidney function, kidney biopsy, if done, usually shows early arteriolosclerosis, hyalinosis, and interstitial inflammation (see Fig. 35.8).

Mildly increased albuminuria, which is a marker of vascular disease and CV risk, occurs in 15% to 30% of patients, whereas more severe albuminuria is uncommon and nephrotic-range proteinuria rare.43

Elevations in serum creatinine over time develop in 10% to 20% of patients with poorly controlled BP, and the risk is greater in diabetic patients, African Americans, the elderly, patients with gout or hyperuricemia, and those with higher SBP (>160 mm Hg).44 In 2% to 5% of those with poorly controlled SBP (>160 mm Hg), progression to kidney failure will occur over 10 to 15 years (Figs. 35.10 and 35.11).45 46

Despite the relative infrequency for primary hypertension to progress to kidney failure, hypertension is recorded as the second most common cause of treated kidney failure after diabetes in the United States and Europe.47 Furthermore, almost all patients with diabetes have hypertension when they start dialysis.

The incidence of kidney failure in African Americans with hypertension is twofold to sixfold greater than in Whites (Fig. 35.11).46 47

Kidney biopsies of African Americans with hypertension show more severe hypertensive injury, with more prominent vascular changes and increased frequency of segmental and global glomerulosclerosis. The increased frequency of glomerulosclerosis may be caused in part by a polymorphism in apolipoprotein L1 (APOL1), the product of which is expressed in the podocyte.48 The mechanism by which APOL1 polymorphisms increase the risk for progression of kidney disease is unclear but may relate to effects on the podocyte that include lysosomal swelling, mitochondrial dysfunction, and blockade of autophagy.49 49a

Although hypertension is a risk factor for CKD, as CKD progresses the prevalence and severity of hypertension also increases and requires more medications to achieve control.50 Multiple mechanisms likely account for this, including sodium retention, increased afferent sympathetic tone induced by kidney inflammation,51 activation of the intrarenal RAS,52 endothelial dysfunction,53 and the frequent occurrence of sleep apnea. These effects are associated with loss of nocturnal BP dipping, and BP may even increase at night, which is associated with an increase in CV complications and progression of CKD.54

C

B

A

Fig. 35.8 Kidney Pathology in Primary Hypertension. (A) A granular pitted kidney in a patient with chronic primary hypertension. (B) Arteriolosclerosis with subintimal hyalinosis. (C) Electron micrograph showing hyalinosis with the accumulation of insudative plasma proteins (arrows) in the subendothelium of an arteriole. (A, Courtesy Harvard Medical School. B–C, Courtesy C.E. Alpers, University of Washington.)

Relative Risk of Coronary Heart Disease

4.00

4.00

2.00

2.00

Relative risk

Relative risk

Relative Risk of Stroke

1.00
0.50
0.25

0.50
0.25
0.00

0.00
0

A

1.00

76

84
91
98
Diastolic blood pressure
(approximate mean usual value, mm Hg)

0

105

B

76

84
91
98
Diastolic blood pressure
(approximate mean usual value, mm Hg)

105

Fig. 35.9 Relative Risk for Stroke and Coronary Heart Disease Increases With Increased Diastolic Blood Pressure. (A) Cerebrovascular accident (stroke) data are from seven prospective observational studies and 843 events. (B) Coronary heart disease data are from nine studies and 4856 events. Size of squares is proportional to the number of events in each category; vertical lines indicate 95% confidence intervals. (Modified from Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334[1]:13–18.)

Effect of Race on Incidence of End-Stage
Kidney Disease in Hypertension

25

Percentage with ESKD

Age-adjusted relative risk

End-Stage Kidney Disease and Blood Pressure

20
15
10
5
0
Optimal
<120

Normal
HighStage 1 Stage 2 Stage 3 Stage 4
(not
Normal 140-159 160-179 180-209 >210
optimal) 130-139
120-129

Fig. 35.10 End-Stage Kidney Disease and Blood Pressure. Incidence of treated kidney failure related to baseline blood pressure in the MRFIT study. Blood pressure stages were based on definitions at that time. Mean follow-up was 16 years. (From Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension. 1995;25[4 Pt 1]:587–594.)

5
4

African American
White

3
2
1
0

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Time from commencing therapy
for hypertension to ESKD (years)

Fig. 35.11 Effect of Race on Incidence of Treated Kidney Failure Disease in Hypertensive Patients. The cumulative incidence of treated kidney failure (end-stage kidney disease (ESKD) in AfricanAmerican and White hypertensive veterans (Kaplan-Meier estimates). (From Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res. 2017;122:1–7.)

TABLE 35.3 Meta-analysis of Effect of Antihypertensive Agents on Cardiovascular Outcomes in Hypertensive Patients

Outcome	Number of Trials	Effects Model	RR (95% CI)	P Value for Heterogeneity
Coronary heart disease	24	Fixed	0.86 (0.80–0.93)	
		Random	0.87 (0.80–0.94)	
Stroke	23	Fixed	0.69 (0.64–0.74)	
		Random	0.68 (0.61–0.76)	
CHF	7	Fixed	0.54 (0.45–0.66)	
		Random	0.60 (0.49–0.74)	
Major CVD events	28	Fixed	0.78 (0.74–0.81)	
		Random	0.73 (0.62–0.87)	
CVD mortality	23	Fixed	0.84 (0.78–0.90)	
		Random		
Total mortality	25	Fixed		
		Random		

0.84 (0.78–0.90)
0.90 (0.85–0.95)
0.90 (0.85–0.95)

.55
.55
.004
.004
.66
.80
<.001
<.001
.10
.10
.58
.59

Analysis was based on 42 clinical trials that included 192,478 patients randomized to seven major treatment strategies, including placebo.
CHF, Congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.
From Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003;289:2534–2544.

Effect of BP Control on Cardiovascular Mortality

Blood pressure control has been consistently shown to reduce CV outcomes (especially stroke and heart failure) and vascular dementia (Table 35.3).55 56 The Systolic Blood Pressure Intervention Trial (SPRINT) found that lowering SBP to 120 to 130 mm Hg provided greater CV protection in nondiabetic subjects than a target BP of 140 mm Hg.57 However, intensive BP lowering treatment carried a higher risk of hypotension, syncope, and acute hemodynamically associated kidney injury, which resolved within a month in almost 90% of the cases without change in BP goal.58 However, the SPRINT study showed that the benefits of lowering BP outweigh the associated risks. In contrast, a similar study, known as the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD), did not demonstrate overall CV protection in diabetics in which SBP was targeted to 120 mm Hg compared with 140 mm Hg.14 Nevertheless, recent analyses suggest a CV risk reduction, with more intensive BP treatment with achieved BP closer to 125 mm Hg.59 60

Although lowering BP protects against progression of CKD, the target BP has been controversial. Intensive BP control in the SPRINT trial did not provide any additional protection for CKD progression, but the SPRINT trial did not enroll patients with more than 1 g proteinuria per day. However, the Modification of Diet in Renal Disease (MDRD) and the African American Study of Kidney Disease (AASKD) studies did enroll patients with significant albuminuria and found less kidney disease progression in this subgroup with intensive BP lowering.61 62 Despite the lack of benefit on kidney disease in patients without severe albuminuria (<300 mg/day), the benefit on CV protection suggests that lower BP targets should be sought in these patients. These findings have led to the general recommendation of a target BP of 130/80 mm Hg for all patients, including the elderly, those with diabetes, and those with CKD by the American College of Cardiology, the European Guidelines,1 and by the American Diabetes Association.63

A discussion of pharmacologic management of hypertension is provided in Chapter 37. Blood pressure control in patients with high CV risk and/or CKD usually requires at least two medications, of which one should be a RAAS blocker at maximally tolerated doses. In the AASKD study, use of an ACE inhibitor (ramipril) was more

Ramipril Is Superior to Amlodipine in
Reducing Renal Events in Hypertensive
African Americans with Renal Impairment
25
Cumulative incidence (%)

20
15

Amlodipine

10

Ramipril

5
0
0

No. at risk
Amlodipine
Ramipril

3

12

216
432

209
422

Months

24
191
391

36
131
278

Fig. 35.12 Ramipril is Superior to Amlodipine in Reducing Kidney Events in Hypertensive African Americans With Mild to Moderate Kidney Impairment. The angiotensin-converting enzyme inhibitor ramipril resulted in fewer kidney end points (proteinuria, decline in kidney function, treated kidney failure, death) compared with the dihydropyridine calcium channel blocker amlodipine, in the African American Study of Kidney Disease. (From Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285[21]:2719–2728.)

effective at slowing CKD progression than either amlodipine (Fig. 35.12) or metoprolol.64 Similar results were seen in the Irbesartan Diabetic Nephropathy Trial (IDNT) trial, where irbesartan was superior to amlodipine in slowing diabetic nephropathy progression.65

Furthermore, in the high-risk hypertensive population, there is also evidence from the ACCOMPLISH trial that better CV protection can be provided if the ACE inhibitor is combined with a calcium channel blocker rather than a thiazide diuretic.66

In people with CKD and hypertension, a diuretic is often required. Nevertheless, diuretics should be used only as needed. Some studies suggest that thiazide and thiazide-like diuretics are associated with worsening of kidney function in patients with hypertension. In the European Working Party on High Blood Pressure in the Elderly trial67 and in the Systolic Hypertension in the Elderly trial,68 serum creatinine increased significantly in patients treated with thiazide diuretics compared with placebo. Similarly, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the chlorthalidone-treated group showed statistically worse kidney function than either the amlodipine or the lisinopril group at both 2- and 4-year end points despite its better reduction of strokes and heart failure.69 This could likely be accounted for by volume depletion in many cases, but diuretics have been shown to induce mild kidney injury in various animal models, possibly because of hypokalemia, hyperuricemia, and stimulation of the RAAS.70

Acute BP lowering with any medication may cause a rise in serum creatinine of up to 30% in the first month of therapy, and treatment should be continued if there are no electrolyte abnormalities or hypotension.71 72 In numerous trials including SPRINT and ACCORD, kidney disease progression is slowed and CV risk (especially from heart failure) markedly reduced. Furthermore, RAAS blockade should not be stopped due to small, limited increases in creatinine, as a retrospective analysis found that the discontinuation of ACE inhibitor or ARB therapy for acute decreases in eGFR (<30 mL/min/1.73 m2) was not associated with increased risk of kidney failure but carried a 39% higher risk of mortality and 37% increase in major adverse CV events (MACE).73

SELF-ASSESSMENT QUESTIONS

1. Primary hypertension is characterized by all of the following except:
A. Primary hypertension is more common in older patients.
B. Salt sensitivity is less common in older patients.
C. Primary hypertension is associated with a reduction in kidney blood flow and usually mild reduction in GFR.
D. Primary hypertension is more common in individuals with low birthweight and low nephron number.
E. The presence of the APOL1 polymorphism is associated with more rapid progression of kidney disease in African Americans with hypertension.
2. The kidney pathology in patients with primary hypertension may consist of all of the following except:
A. arteriolosclerosis with arteriolar fibrosis or hyalinosis.

B. evidence of tubular ischemia change is commonly present.
C. glomerulosclerosis may be present, especially in African Americans.
D. kidney histologic studies can rarely appear normal.
E. transmural necrosis of medium-sized vessels can occasionally be observed.
3. Which of the following is not a dietary risk factor for primary hypertension?
A. Sodium
B. Potassium
C. Sugar
D. Alcohol
E. Coffee

REFERENCES

1. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104.
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;71(19):2199–2269.
3. Bevan AT, Honour AJ, Stott FH. Direct arterial pressure recording in unrestricted man. Br Heart J. 1969;31(3):387–388.
4. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16(4):223–237.
5. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the third national health and nutrition examination survey, 1988-1991. Hypertension. 1995;25(3):305–313.
6. Rodriguez-Iturbe B, Johnson RJ. Genetic polymorphisms in hypertension: are we missing the immune connection? Am J Hypertens. 2019;32(2):113–122.
7. Lifton RP. Genetic dissection of human blood pressure variation: common pathways from rare phenotypes. Harvey Lect. 2004;100:71–101.
8. Guyton AC, Coleman TG, Cowley Jr AV, Scheel KW, Manning Jr RD, Norman Jr RA. Arterial pressure regulation. overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med. 1972;52(5):584–594.
9. He FJ, Tan M, Ma Y, MacGregor GA. Salt reduction to prevent hypertension and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(6):632–647.
10. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478(7367):103–109.
11. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. Circ Res. 2015;116(6):937–959.
12. Kanda T, Murai-Takeda A, Kawabe H, Itoh H. Low birth weight trends: possible impacts on the prevalences of hypertension and chronic kidney disease. Hypertens Res. 2020;43(9):859–868.
13. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens. 1988;1(4 Pt 1):335–347.
14. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. N Engl J Med. 2003;348(2):101–108.
15. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. Hypertension. 2000;36(5):790–794.
16. Rodriguez-Iturbe B, Pons H, Johnson RJ. Role of the immune system in hypertension. Physiol Rev. 2017;97(3):1127–1164.
17. Sanchez-Lozada LG, Rodriguez-Iturbe B, Kelley EE, et al. Uric acid and hypertension: an update with recommendations. Am J Hypertens. 2020;33(7):583–594.
18. Sommers SC, Relman AS, Smithwick RH. Histologic studies of kidney biopsy specimens from patients with hypertension. Am J Pathol. 1958;34(4):685–715.
19. Pons H, Ferrebuz A, Quiroz Y, et al. Immune reactivity to heat shock protein 70 expressed in the kidney is cause of salt-sensitive hypertension. Am J Physiol Renal Physiol. 2013;304(3):F289–F299.
20. Kirabo A, Fontana V, de Faria AP, et al. DC isoketal-modified proteins activate t cells and promote hypertension. J Clin Invest. 2014;124(10):4642–4656.
21. Guzik TJ, Hoch NE, Brown KA, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med. 2007;204(10):2449–2460.
22. Chan CT, Sobey CG, Lieu M, et al. Obligatory role for B cells in the development of angiotensin II-dependent hypertension. Hypertension. 2015;66(5):1023–1033.

23. Kanbay M, Aslan G, Afsar B, et al. Acute effects of salt on blood pressure are mediated by serum osmolality. J Clin Hypertens. 2018;20(10):1447–1454.

24. Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature. 2013;496(7446):513–517.
25. Kleinewietfeld M, Manzel A, Titze J, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature. 2013;496(7446):518–522.
26. Norlander AE, Saleh MA, Kamat NV, et al. Interleukin-17A regulates renal sodium transporters and renal injury in angiotensin II-induced hypertension. Hypertension. 2016;68(1):167–174.
27. Bagrov AY, Shapiro JI, Fedorova OV. Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. Pharmacol Rev. 2009;61(1):9–38.
28. Titze J, Luft FC. Speculations on salt and the genesis of arterial hypertension. Kidney Int. 2017;91(6):1324–1335.
29. Rossitto G, Mary S, Chen JY, et al. Tissue sodium excess is not hypertonic and reflects extracellular volume expansion. Nat Commun. 2020;11(1):4222.
30. Morris Jr RC, Schmidlin O, Sebastian A, Tanaka M, Kurtz TW. Vasodysfunction that involves renal vasodysfunction, not abnormally increased renal retention of sodium, accounts for the initiation of saltinduced hypertension. Circulation. 2016;133(9):881–893.
31. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res. 2017;122:1–7.
32. Hall JE, da Silva AA, do Carmo JM, et al. Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. J Biol Chem. 2010;285(23):17271–17276.
33. Grassi G, Ram VS. Evidence for a critical role of the sympathetic nervous system in hypertension. J Am Soc Hypertens. 2016;10(5):457–466.
34. Brunner HR, Laragh JH, Baer L, et al. Essential hypertension: renin and aldosterone, heart attack and stroke. N Engl J Med. 1972;286(9):441–449.
35. Bomback AS, Rekhtman Y, Klemmer PJ, Canetta PA, Radhakrishnan J, Appel GB. Aldosterone breakthrough during aliskiren, valsartan, and combination (aliskiren + valsartan) therapy. J Am Soc Hypertens. 2012;6(5):338–345.
36. Hughson MD, Gobe GC, Hoy WE, Manning Jr RD, Douglas-Denton R, Bertram JF. Associations of glomerular number and birth weight with clinicopathological features of African Americans and whites. Am J Kidney Dis. 2008;52(1):18–28.
37. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet. 1990;335(8692):765–774.
38. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68(13):1476–1488.
39. Nagao K, Inada T, Tamura A, et al. Circulating markers of collagen types I, III, and IV in patients with dilated cardiomyopathy: relationships with myocardial collagen expression. ESC Heart Fail. 2018;5(6):1044–1051.
40. Hung CS, Chou CH, Liao CW, et al. Aldosterone induces tissue inhibitor of metalloproteinases-1 expression and further contributes to collagen accumulation: from clinical to bench studies. Hypertension. 2016;67(6):1309–1320.
41. Bohm M, Schumacher H, Teo KK, et al. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120-140 mmHg) and cardiovascular outcomes in high-risk patients: results from ontarget and transcend trials. Eur Heart J. 2018;39(33):3105–3114.
42. Gomadam P, Shah A, Qureshi W, et al. Blood pressure indices and cardiovascular disease mortality in persons with or without diabetes

mellitus. J Hypertens. 2018;36(1):85–92.
43. Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care. 2014;37(3):867–875.
44. Johnson RJ, Segal MS, Srinivas T, et al. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol. 2005;16(7):1909–1919.
45. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334(1):13–18.

References

46. Perry Jr HM, Miller JP, Fornoff JR, et al. Early predictors of 15-year endstage renal disease in hypertensive patients. Hypertension. 1995;25(4 Pt 1):587–594.
47. Sarafidis PA, Li S, Chen SC, et al. Hypertension awareness, treatment, and control in chronic kidney disease. Am J Med. 2008;121(4):332–340.
48. Lipkowitz MS, Freedman BI, Langefeld CD, et al. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. Kidney Int. 2013;83(1):114–120.
49. Kumar V, Singhal PC. APOL1 and kidney cell function. Am J Physiol Renal Physiol. 2019;317(2):F463–F477.
49a.Wu J, Raman A, Coffey NJ, et al. The key role of NLRP3 and STING in APOL1-associated podocytopathy. J Clin Invest. 2021;131(20):e136329.
50. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis. 2010;55(3):441–451.
51. Converse Jr RL, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327(27):1912–1918.
52. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. J Clin Invest. 1996;98(4):1063–1068.
53. Baylis C. Nitric oxide deficiency in chronic kidney disease. Am J Physiol Renal Physiol. 2008;294(1):F1–F9.
54. Mojon A, Ayala DE, Pineiro L, et al. Comparison of ambulatory blood pressure parameters of hypertensive patients with and without chronic kidney disease. Chronobiol Int. 2013;30(1–2):145–158.
55. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003;289(19):2534–2544.
56. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic hypertension in Europe (Syst-Eur) trial. Lancet. 1998;352(9137):1347–1351.
57. Wright Jr JT, Whelton PK, Reboussin DM. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2016;374(23):2294.
58. Malhotra R, Craven T, Ambrosius WT, et al. Effects of intensive blood pressure lowering on kidney tubule injury in CKD: a longitudinal subgroup Analysis in SPRINT. Am J Kidney Dis. 2019;73(1):21–30.
59. Buckley LF, Dixon DL, GFt W, Wijesinghe DS, Baker WL, Van Tassell BW. Effect of intensive blood pressure control in patients with type 2 diabetes mellitus over 9 years of follow-up: a subgroup analysis of highrisk accordion trial participants. Diabetes Obes Metab. 2018;20(6):1499–1502.
60. Collard D, Brouwer TF, Peters RJG, Vogt L, van den Born BH. Creatinine rise during blood pressure therapy and the risk of adverse

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clinical outcomes in patients with type 2 diabetes mellitus. Hypertension. 2018;72(6):1337–1344.
Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363(10):918–929.
Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med. 2005;142(5):342–351.
Association AD. Standards of medical care in diabetes-2021. Diabetes Care. 2021 (in press).
Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285(21):2719–2728.
Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–860.
Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–2428.
Fletcher A, Amery A, Birkenhager W, et al. Risks and benefits in the trial of the European working party on high blood pressure in the elderly. J Hypertens. 1991;9(3):225–230.
Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the systolic hypertension in the elderly program. SHEP Cooperative Research Group. Arch Intern Med. 1998;158(7):741–751.
Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981–2997.
Reungjui S, Hu H, Mu W, et al. Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. Kidney Int. 2007;72(12):1483–1492.
Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000;160(5):685–693.
Taler SJ, Agarwal R, Bakris GL, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis. 2013;62(2):201–213.
Qiao Y, Shin JI, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med. 2020;180(5):718–726.

36

Nonpharmacologic Prevention and Treatment of Hypertension

Brian Rayner, Karen E. Charlton, Wayne Derman, Erika Jones

Diets that include increased fat and refined carbohydrate intake combined with reduced physical activity have resulted in a pandemic of obesity, type 2 diabetes mellitus, and hypertension that is most pronounced in underserved and indigenous populations. Adoption of healthy lifestyles is critical in preventing and managing high blood pressure (BP). According to the American College of Cardiology/American Heart Association (ACC/AHA)1 and International Society of Hypertension (ISH) Global Practice Guidelines, lifestyle interventions lower BP,2 enhance efficacy of antihypertensive medication, and reduce overall cardiovascular (CV) risk.3 The lifestyle changes that are widely agreed to lower BP and CV risk are smoking cessation, weight reduction, moderation of alcohol intake, increased physical exercise, reduced salt intake, increased fruit and vegetable intake, and decreased total fat, trans fat, and sugar intake (Table 36.1). These interventions may lower BP to a similar extent compared with single-drug therapy. However, lifestyle changes should not delay the initiation of drug therapy in patients at higher CV risk.

PREVENTION

The importance of primary prevention has been underscored by the recognition that hypertension is common, treatment is lifelong, the control of BP in hypertensive individuals does not restore CV risk to normal, and the majority of hypertensive individuals do not reach goal BP readings. The most important individuals to target are those with elevated BP (120–129/80–89 mm Hg)4 or high BP (>130/90 mm Hg) as defined by the ACC/AHA guidelines.1 Those with elevated BP have increased prevalence of early vascular damage, increased risk for incident hypertension, and increased risk for CV events compared with those who have optimal BP levels (<120/80 mm Hg).5 The World Health Organization (WHO) Global Non-Communicable Disease (NCD) Alliance Action Plan advocates the following voluntary global targets for country member states: 10% reduction in harmful use of alcohol, 10% reduction in sedentary lifestyle, 30% reduction in mean population intake of salt, and 30% reduction in current tobacco use. Up to 80% of cardiovascular disease (CVD) can be prevented through lifestyle measures that include maintenance of healthy weight, adequate physical activity, a healthy diet, and avoidance of tobacco.6 These targets align with the Lancet’s Commission on Hypertension (2016) that identifies key actions to prevent elevated BP at both the population and individual level.7 A life-course approach is recommended, which focuses on early lifetime programming. Exposure to CV risk factors in early childhood has been shown to promote adverse vascular damage in early adulthood and increase the trajectory of vascular aging.8

WEIGHT LOSS

Obesity is epidemic throughout the world; for example, 65% of the adult population in the United States is either overweight,

with a body mass index (BMI) of 25.0 to 29.9 kg/m2, or obese, with a BMI at or above 30 kg/m2. Obese individuals have a threefold increase in the prevalence of hypertension. Possible mechanisms for obesity-induced hypertension include overactivity of the sympathetic nervous system (SNS), hyperinsulinemia (which may increase renal sodium reabsorption), increased leptin, hyperuricemia, activation of the renin-angiotensin system, and sleep apnea. Visceral obesity is a greater predictor of both hypertension and CV risk than other types of body fat distribution. Visceral obesity is defined by waist circumference greater than 88 cm (>35 in) in women and greater than 102 cm (>40 in) in men. These reference values were developed in White populations and may need to be modified for other ethnic groups.

In obese hypertensive patients or those with elevated BP, weight loss of as little as 4 to 5 kg (9–11 lb) is often associated with a significant reduction in BP. A meta-analysis has demonstrated that a weight reduction of 5.1 kg reduced systolic BP (SBP) by 4.4 mm Hg and diastolic BP (DBP) by 3.6 mm Hg.9 A rule of thumb is that for every kilogram lost, there is a reduction of 1 mm Hg in SBP and DBP. To minimize the risk for relapse and maintain sustainability of the weight loss program, the initial target should be 5% to 10% of current weight, or 1 to 2 BMI units.

Marked oscillations in weight (weight cycling or yo-yo dieting) should be avoided because this increases the risk for development of hypertension in obese, normotensive persons.10 A randomized trial of the effectiveness of four popular diets on sustained weight loss and CV disease risk reduction concluded that a variety of diets can similarly reduce weight and BP, but only a minority of individuals can maintain high dietary adherence for prolonged periods.11

Very-low-carbohydrate diets, such as the Atkins diet and others with a carbohydrate content below 20% of energy, are not recommended because they result in a greater increase in low-density lipoprotein cholesterol, despite resulting in a greater weight loss over the short term, compared with a traditional low-fat diet.12

The pan-European Diet, Obesity and Genes (DiOGenes) study found that BP reduction after weight loss is better maintained when the intake of protein is increased at the expense of carbohydrates, to around 23% to 28% energy from protein, compared with usual lower protein intakes of between 10% and 15% energy.13

Weight reduction should be accompanied by recommendations to increase physical activity unless it is contraindicated.

Bariatric surgery and pharmacologic interventions for weight loss may be useful to achieve weight loss in some patients, but always as an adjunct rather than a substitute for lifestyle modification.

Lifestyle Modifications for Prevention and Management of Hypertension

TABLE 36.1

COR

LOE

1

A

1

A

1

A

1

A

1

A

1

A

1

A

Recommendations for Nonpharmacologic Intervention

Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese

A heart-healthy diet, such as the DASH diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension

Sodium reduction is recommended for adults with elevated BP or hypertension

Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion

Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension

Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than two and one standard drinks[a] per day, respectively

Complete cessation of smoking

[a] In the United States, one standard drink contains roughly 14 g of pure alcohol, which is typically found in 360 mL (12 fl oz) of regular beer (usually about 5% alcohol), 150 mL (5 fl oz) of wine (usually about 12% alcohol), and 45 mL (1.5 fl oz) of distilled spirits (usually about 40% alcohol).

BP, Blood pressure; CKD, chronic kidney disease; COR, class (strength) of recommendation; DASH, Dietary Approaches to Stop Hypertension; LOE, level of evidence.

Modified from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-1324.

PHYSICAL ACTIVITY AND EXERCISE TRAINING

Physical and Sedentary Activity and Risk Mitigation for Hypertension

Physical inactivity may account for 5% to 13% of the risk for developing hypertension.[14] In addition, physical inactivity accounts for 5.5% to 25.1% of the population attributable risk for coronary heart disease. Regular physical activity and reduced sedentary activity lowers all-cause morbidity and mortality and provides the basis for public health recommendations. The 2020 WHO guidelines suggest that all adults should undertake, per week, 150 to 300 minutes of moderateintensity, or 75 to 150 minutes of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorousintensity aerobic physical activity. The guidelines recommend regular muscle-strengthening activity for all age groups. Additionally, reducing sedentary behaviors is recommended across all age groups and has an important preventive effect with respect to hypertension and gestational hypertension.[15]

A recent review reported that patients with high BP who participated in any level of physical activity had a lower risk (by 16%–67%) of CV mortality, whereas a greater than twofold increase in CV mortality risk was observed in sedentary individuals.[16]

Effects of Exercise Training in Reduction of Blood Pressure in Normotensive and Hypertensive Individuals

In a meta-analysis of studies involving more than 1500 patients, exercise training in normotensive individuals has been shown to reduce SBP and DBP by 3.0 ± 1 and 1.7 ± 1 mm Hg, respectively.[17] However, in hypertensive patients, the effect of exercise training is even more marked. In a meta-analysis involving 27 randomized controlled trials (RCTs) and 1480 patients, aerobic activity was shown to reduce BP on average by 10.8 ± 4.7 mm Hg in hypertensive patients.[18]

Historically, it was accepted that only aerobic (dynamic) exercise was effective in lowering BP in hypertensive individuals. Other forms of exercise training, including resistance exercise, isometric resistance training, and high-intensity interval training (HIIT), are also considered safe, and they are recommended as effective exercise modalities.[1,19] However, there is no consensus whether HIIT exercise is superior to low-intensity continuous aerobic training for lowering BP.[20,21] There also appears to be benefit from a wide range of different exercise modalities, including tai chi[22] (which lowered BP by 6.58/0.57 mm Hg in a meta-analysis), qigong,[23] strength training,[24] and yoga.[25] Regular exercise also prevents the development of left ventricular hypertrophy that is independent of BP in young patients with stage 1 hypertension.[26]

Some studies indicate that mild to moderate exercise intensity

(40%–70% of maximal age-predicted heart rate) is effective for lowering BP with little additional benefit associated with further increases in intensity.17 However, exercise of higher intensity (75% maximum) is associated with a more marked and prolonged reduction in postexercise BP compared with lower-intensity exercise (50% maximum).27 Other studies have indicated that HIIT also effectively reduces BP in hypertensive individuals. Thus, limitations in the literature remain regarding the effects of different intensity and duration of exercise on BP. Available studies are hampered by varying methodological quality, selective reporting of BP outcomes, and few participants with diagnosed hypertension.28

Monitoring of Blood Pressure During Exercise

A standardized approach to monitoring BP before and during exercise should be considered for hypertensive patients. If resting BP is poorly controlled, exercise training should be postponed (SBP >180 mm Hg or DBP> 110 mm Hg) until control is improved. Furthermore, if SBP rises to more than 250 mm Hg and/or DBP to more than 115 mm Hg during exercise, the training session should be terminated.29

Mechanisms of Blood Pressure–Lowering Effects of Exercise

The mechanism(s) involved with reducing BP in hypertensive individuals are multiple and complex. The reduction in BP immediately after exercise has been linked to a sympathetic inhibition and increased release of vasodilator substances. The mechanisms by which exercise lowers BP over the longer term are less well understood, but possibilities include reductions in systemic vascular resistance secondary to neurohumoral and structural adaptations. It has further been suggested that physical inactivity negatively affects brain areas associated with sympathetic outflow. SNS overdrive is thought to account for more than 50% of all cases of hypertension, and a lack of balance between parasympathetic and sympathetic modulation has been observed in hypertensive subjects.30 In a recent meta-analysis of 14 trials, exercise improved the arterial stiffness that is associated with hypertension, particularly aerobic exercise, isometric exercise (static muscle contraction), and a

Practical Guidelines for Exercise in Patients With Hypertension

BOX 36.1

Modified from Pescatello LS, MacDonald HV, Ash GI, et al., eds. Assessing the existing professional exercise recommendations for hypertension: a review and recommendations for future research priorities. Mayo Clinic Proceedings. Elsevier; 2015; and Leosco D, Parisi V, Femminella GD, et al. Effects of exercise training on cardiovascular adrenergic system. Front Physiol. 2013;4:348.

combination of the two.31 Long-term exercise training is also associated with weight loss and a reduction of serum uric acid levels, both of which could reduce BP.

Antihypertensive Medication and Guidelines for Exercise

Box 36.1 provides exercise guidelines for patients with hypertension.32 β-Blockers decrease exercise tolerance. β-Blockers and diuretics also may alter thermoregulation in hot environments and provoke hypoglycemia. Patients using these medications should be educated about exercising in the heat, proper clothing, adequate hydration, and methods to prevent hypoglycemia.33 However, β-blockers are not the first-line treatment for physically active hypertensive patients. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers may be better suited for patients who exercise frequently or athletes with hypertension. For patients undergoing supervised exercise training, the monitoring of postexercise BP may be helpful, so medications may be adjusted to avoid postexercise hypotension, especially with calcium channel blockers or in patients exercising in a hot environment.

DIET

Salt Intake

The prevalence of hypertension is directly related to dietary salt intake in all societies in which Na intake exceeds 50 to 100 mmol/day (3–6 g

Prevalence of hypertension (%)

50

Rarotonga

40
30

Finland
Renfrew (Scotland) Japan
north
USA
Naples

Belgium

20

USA
Japan south

Bantu

Pukapuka

USA USA
USA
Yanomamo Eskimo Marshall Islands
10
0

0
50
100
Papua New Guinea
highlands

150

200

250

300

350

400

450

Urinary sodium excretion (mmol/24 h)

Fig. 36.1 Relationship of Salt Intake to Prevalence of Hypertension in Different Populations. (Modified from MacGregor GA. Sodium is more important than calcium in essential hypertension. Hypertension. 1985;7[4]:628–640.)

Blood Pressure Changes With
Age and Salt Intake
Systolic blood pressure (mm Hg)

All apparently healthy individuals should undergo preexercise screening to determine health risk status. The American College of Sports Medicine (ACSM) recognizes that two or more of the following risk factors increase the risk associated with exercise, and individuals should undergo preexercise graded exercise testing. Risk factors include male sex (>45 years) or female sex (>55 years), serum cholesterol concentrations greater than 5.2 mmol/L, impaired glucose tolerance or diabetes mellitus, smoking, obesity (BMI ≥30), inactivity, and family history of cardiovascular disease.

Patients with uncontrolled hypertension should embark on exercise training only after evaluation and initiation of therapy. Furthermore, patients should not participate in an exercise training session if resting systolic blood pressure is above 200 mm Hg or diastolic blood pressure is above 115 mm Hg.

Many patients with hypertension are overweight and should therefore be encouraged to follow a program that combines both exercise training and restricted calorie intake.

- Type of exercise: this should be predominantly endurance physical activity, including walking, jogging, cycling, swimming, or dancing. This should be supplemented by resistance exercise that can be prescribed according to the ACSM or American Heart Association guidelines.

- Frequency of exercise: most or preferably every day, but at least 5 days a week.
- Intensity of exercise: moderate intensity at 40% to 60% of maximal oxygen consumption (VO2 peak).
- Duration of exercise: more than 30 minutes of continuous or accumulated moderate physical activity daily.

Salt Intake and Hypertension

160
155
150
145
140
135
130
125
120
115
110

Rarotonga
Pukapuka

20-29

30-39

40-49

50-59

60-69

≥70

Age (years)

Fig. 36.2 Blood Pressure Changes With Age and Salt Intake. The increase in systolic blood pressure (SBP) with age correlates with a higher salt intake in two Polynesian populations. In men of Rarotonga Island, where the sodium intake averages 130 mmol/day, SBP increases with age. In contrast, it remains constant in men of Pukapuka Island, where the sodium intake averages 50 to 70 mmol/day. (Modified from Prior I, Evans JG, Harvey H, Davidson F, Lindsey M. Sodium intake and blood pressure in two Polynesian populations. N Engl J Med. 1968;279[10]:515–520.)

salt or NaCl) (Fig. 36.1).34 In societies in which daily intake is below that range, hypertension is rare. Salt intake also plays an important role in age-related increase in BP (Fig. 36.2).35 However, not all individuals respond similarly to a high salt intake. “Salt sensitivity” describes a group of individuals who significantly decrease or increase their BP during periods of salt restriction or salt loading, respectively. Those at greatest risk of salt sensitivity include Black ethnicity, older age, obese, type 1 or 2 diabetes, treatment with calcineurin inhibitors, and chronic kidney disease (CKD).

Putative mechanisms for salt sensitivity are alterations in circulating levels of (or renal responses to) atrial natriuretic factor,

Effect on Blood Pressure of Reduced Sodium
Intake and the DASH Diet

Systolic blood pressure (mm Hg)

135
Control diet

130

–2.1

–5.9
–4.6
–5.0
DASH diet
–1.3

125

–2.2
–1.7

120
Intermediate

High

A

Low

Sodium intake

Diastolic blood pressure (mm Hg)

85
–1.1

Control diet
–2.9

80

–2.4
–2.5

DASH diet
–0.6

–1.0
–1.0

75
High

Intermediate

Low

B
Sodium intake

Fig. 36.3 Reduced Sodium Intake and Dietary Approaches to Stop Hypertension (DASH) Diet. Effect on systolic blood pressure (A) and diastolic blood pressure (B). (B, Modified from Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344[1]:3–10.)

kallikrein, prostaglandins, and nitric oxide (NO); increased levels of norepinephrine; abnormal suppression of both renin and aldosterone; genetic mechanisms; congenital reduction in nephron number; and acquired renal microvascular and tubular injury.

More recent studies show that sodium-dependent serum osmolarity may have a higher correlation with BP36 and the progression to hypertension.37

In a Cochrane systematic review of 34 trials, the effect of modest salt reduction on BP was studied. The pooled mean change in urinary sodium (Na) was −75 mmol/24 h (equivalent to reduction of 4.4 g of salt) resulting in a mean reduction in SBP of −4.18 mm Hg and DBP of −2.06 mm Hg, respectively. Meta-regression analysis showed that older age, Black ethnicity, hypertensive status, and overall change in 24-hour urinary Na were associated with a greater fall in BP.38

In the Dietary Approaches to Stop Hypertension (DASH) sodium trial, the additional benefits of salt restriction over and above the DASH diet were investigated (Fig. 36.3).39 Reduction of sodium intake from high intake (150 mmol/day, or 9 g salt) to either intermediate (100 mmol/day, or 6 g salt) or low (65 mmol/day, or 4 g salt) intake resulted in a stepwise reduction in BP, which was approximately twice as great in the control group than those following the DASH diet (see Fig. 36.3). In those following the DASH diet, the addition of salt restriction resulted in a relatively small additional decrease in BP (3.0 and 1.6 mm Hg for SBP and DBP, respectively). Thus, the greatest benefits of salt restriction are seen in those with the typical Westernized high-fat, low-nutrient diet.

Most hypertension guidelines and the WHO now recommend a reduction of salt intake to less than 5 g salt (90 mmol Na) per day.

The US Department of Agriculture and US Department of Health and Human Services Joint Dietary Guidelines for Americans call for stricter reduction in salt intake to no more than 65 mmol/day, or 4 g salt in African Americans, those older than 51 years, and patients with hypertension, diabetes mellitus, or CKD.[40]

In countries where population-based reduction in salt intake has occurred (Finland, United Kingdom, and Japan), there has been an accompanying fall in BP and CV mortality. A recent AHA Presidential Advisory review concluded that the evidence supporting the effectiveness of population-level salt reduction to prevent hypertension and reduce the incidence of CV disease and stroke remains robust and persuasive for policy development.[40]

In the United States, as in most high-income countries, a major challenge to salt reduction efforts is the widespread use of sodium in the food supply, with more than 75% of total sodium intake from packaged and restaurant foods.[41] One of the most cost-effective ways to lower salt intake in the general population is to reduce salt in processed foods, as shown in an experimental study in South Africa.[42] In Belgium, reduction in the salt content of bread between the mid-1960s and the early 1980s was accompanied by marked reductions in 24-hour urinary sodium excretion. However, a multipronged approach is recommended to achieve overall salt reduction, as outlined by the WHO SHAKE Technical Package for Salt Reduction,[43] that addresses five key areas for action:

✓•✓ Surveillance: measure and monitor salt use in populations.

✓•✓ Harness industry: promote the reformulation of foods and meals to contain less salt.

✓•✓ Adopt standards for labeling and marketing: implement standards for effective and accurate labeling and marketing of food.

✓•✓ Knowledge: educate and communicate to empower individuals to eat less salt.

✓•✓ Environment: support settings to promote healthy eating.

The United Kingdom was the first country to set voluntary sodium reduction targets for categories of foods through its Food Standards Agency (2009), closely followed by Australia, the United States, and Canada. South Africa was the first country to adopt mandatory regulation for maximum sodium levels across a wide range of processed food categories that are major contributors to salt intake in that population; namely, bread, margarine and spreads, savory snacks, processed meats, soup powders, and stock cubes.

Potassium Intake

One of the confounding factors of the relationship of salt and BP has been the inverse relationship between the intake of salt and that of potassium. Typically, diets with a high salt content are relatively deficient in potassium (and calcium); but in persons who consume little salt, the potassium (and calcium) intake is high.

In normotensive individuals with an average potassium intake above 1.95 g/day (50 mmol/day), potassium supplementation has no significant effect on BP. However, among hypertensive patients who are potassium deficient because of diuretic treatment or low potassium intake, potassium supplementation lowers BP (Fig. 36.4).[44] The DASH diet lowers BP and is high in potassium because of the high fruit and vegetable content and inclusion of low-fat dairy products (Table 36.2). However, the synergistic effect of the various food groups in the DASH diet makes it difficult to ascertain the contribution of the individual nutritional components.

The mechanisms by which a low-potassium diet may contribute to hypertension are poorly understood but may relate to stimulation of intrarenal angiotensin II (Ang II), oxidants, and endothelin;

inhibition of intrarenal NO and prostaglandins; and induction of renal ischemia.

Potassium Supplements
in Hypokalemic Hypertensives

Pretreatment
K+ supplements
3.6
± 0.1

3.0
± 0.1

109
±2
104
±2

Serum K+
Blood pressure
(mmol/L)
(mm Hg)

Fig. 36.4 Potassium Supplementation Lowers Blood Pressure in Hypokalemic Hypertensive Patients. Treatment with potassium chloride (60 mmol/day potassium for 6 weeks) resulted in an increase in serum potassium concentration and a decrease in mean arterial pressure in hypertensive patients taking thiazide diuretics. (Modified from Kaplan NM, Carnegie A, Raskin P, Heller JA, Simmons M. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. N Engl J Med. 1985;312[12]:746–749.)

A systematic review of clinical trials identified that a lower 24h urine Na/K ratio was associated with a significantly greater reduction in both systolic and diastolic BP. Dietary strategies to achieve an increase in potassium while at the same time lowering sodium would be beneficial in lowering BP.45 Overall, it appears to be beneficial to optimize potassium intake in hypertensive patients to minimize hypokalemia, being careful to avoid the risk for hyperkalemia, especially in those with reduced glomerular filtration rate. If kidney function is normal, optimal potassium intake is 80 to 120 mmol/day. For CVD prevention, the WHO recommends a potassium intake that will keep the urine Na/K ratio close to 1 (i.e., 70–80 mmol/day if Na guidelines are met).

Calcium, Vitamin D, and Dairy Food Intake

Cross-sectional population surveys of self-reported nutrient intake suggest an inverse relationship between calcium intake and BP. The relationship is more convincing at low levels of calcium consumption (<300–600 mg/day). There may be a threshold of 700 to 800 mg/day, above which any further reduction in BP is attenuated. A meta-analysis of randomized calcium supplementation trials (mostly with 1 or 1.5 g calcium daily) demonstrated reductions in SBP (−0.9 to −1.7 mm Hg) that are of little clinical importance.46 Although calcium in milk may contribute to BP lowering, dairy products may lower BP by other mechanisms. Biologically active peptides formed during the milk fermentation process, such as the casein-derived tripeptides isoleucineproline-proline and valine-proline-proline, have ACE-inhibiting properties. Vitamin D, which is often added to milk, also may help reduce BP by reducing renin expression, but in a randomized controlled clinical trial, vitamin D had no effect on BP compared with placebo.47 At present, the AHA does not recognize dairy consumption as a dietary approach to the prevention and management of hypertension. Nevertheless, low-fat dairy products are recommended as an integral part of the DASH diet.

TABLE 36.2

Dietary Approaches to Stop Hypertension (DASH) Diet a

Food Group

Daily Servings

Serving Sizes

Examples and Notes

Contribution to the
DASH Diet Pattern

Grains and grain
products

7–8

Whole-wheat bread, muffin, pita bread,
bagel, cereals, oatmeal

Major sources of calories and
fiber

Vegetables

4–5

1 slice bread
½ cup dry cereal
½ cup cooked rice, pasta, or cereal
1 cup raw, leafy vegetables
½ cup cooked vegetables
6 oz vegetable juice

Rich sources of potassium,
magnesium, and fiber

Fruits

4–5

Low-fat or nonfat
dairy foods

2–3

Meats, poultry, and
fish

≤2

Nuts, seeds, and
legumes

4–5/wk

Tomatoes, potatoes, carrots, peas,
squash, broccoli, turnip greens, kale,
spinach, artichokes, green beans,

sweet potatoes
Apricots, bananas, dates, oranges,
orange juice, grapefruit, grapefruit
juice, mangoes, melons, peaches,
pineapples, prunes, raisins,
strawberries, tangerines
Skim or low-fat (2%) milk, skim or lowfat buttermilk, nonfat or low-fat yogurt,
nonfat or low-fat cheeses
Select only lean meats; trim away
visible fats; broil, roast, or boil instead
of frying; remove skin from poultry
Almonds, mixed nuts, peanuts, walnuts,
sunflower seeds, kidney beans, lentils,
split peas

1 medium fruit
½ cup dried fruit
6 oz fruit juice
½ cup fresh, frozen, or canned
fruit
8 oz milk
1 cup yogurt
1.5 oz cheese
3 oz cooked meats, poultry, or fish

1.5 oz or ½ cup nuts
½ oz or 2 tbsp seeds
½ cup cooked legumes

Important sources of potassium,
magnesium, and fiber

Major sources of calcium and
protein
Rich sources of protein and
magnesium
Rich sources of calories,
magnesium, potassium,
protein, and fiber

[a]The

DASH eating plan shown is based on 2000 kcal/day. Depending on energy needs, the number of daily servings in a food group may vary from those listed.

Magnesium Intake, Other Micronutrients, and Bioactive Food Components

A weak inverse relationship has been reported between dietary intake of magnesium and BP, and in a meta-analysis of 34 RCTs, magnesium supplementation with a median dose of 368 mg/day was associated with a 2 mm Hg and 1.78 mm Hg reduction in SBP and DBP, respectively.[48]

In contrast, the inverse association between fruit and vegetable intake and BP and other CV risk factors is well established.

Epidemiologic evidence suggests that polyphenol compounds found in fruit may partially explain the cardioprotective properties of fruits. Intervention trials have shown that fruits containing relatively high concentrations of flavonols, anthocyanins, and procyanidins, such as pomegranate, purple grapes, and berries, were effective at reducing CVD risk factors. Regular consumption of flavonol-rich foods, cocoa products, tea, and red wine may reduce BP. Folate, B vitamins, and l-arginine supplementation49 50 may also lower BP and decrease overall CV risk. Foods that have a high content of inorganic nitrate (NO3), such as beetroot, are considered to be a potential complementary treatment for hypertension.51-53 Inorganic NO3 supplementation may compensate NO-disrupted pathways in hypertension and increase NO bioavailability, an important physiologic mediator in regulating BP.54 The latest ISH guidelines for lifestyle modification include advice for moderate intake of beetroot juice, pomegranate juice, and cocoa.2

Dietary Sugars and Fats

Added sweeteners, such as table sugar and high-fructose corn syrup, have been linked with the epidemics of obesity, hypertension, metabolic syndrome, diabetes, and CV disease.55 Experimental studies suggest that fructose may increase the risk for obesity and diabetes because of its unique ability to reduce intracellular adenosine triphosphate levels and generate uric acid.56 One study has reported that reducing soft drink intake by one drink per day is associated with a decrease of 1.8 mm Hg SBP.57

Interestingly, whole fruits appear to be beneficial despite containing fructose, possibly as a result of the high content of protective nutrients such as vitamin C, antioxidants, flavanols, potassium, and fiber. Possibly because of this, a systematic review and meta-analysis of three prospective cohort studies in 37,375 men and 185,855 women reported no association of fructose consumption with the incidence of hypertension.58 However, although there was no excess risk associated with average levels of fructose consumption, a positive association was identified between the incidence of hypertension and high intake of fructose.

Supplementation with omega-3 fatty acids reduces the risk for myocardial infarction (MI) and sudden cardiac death, but their effect on BP is small. In a meta-analysis, omega-3 supplementation significantly reduced DBP by a mean of 1.8 mm Hg but had no effect on SBP, fibrinogen level, or heart rate.59 About 10 portions of oily fish per week or 9 or 10 fish oil capsules per day are required (equivalent to ~3 g/day long-chain n-3 fatty acids), but this is not tolerated by most because of belching and fishy taste. Concerns about the cholesterol content, as well as dioxin and polychlorinated biphenyl content (environmental pollutants that have carcinogenic potential and, being fat soluble, can accumulate in the body) of some fish oil supplements also raise questions about the safety of very large doses. As a guideline for overall health, individuals with hypertension should aim to consume about 2 to 3 portions (200–400 g) of oily fish (e.g., herring, kippers, mackerel, pilchards, sardines, salmon, trout, fresh tuna, swordfish) per week.

Dietary Approaches to Lower Blood Pressure

Although individual nutrients and components of foods can have an effect on BP, it is necessary to consider these within the context of a total dietary approach because of potential synergistic effects.[60] A meta-analysis of 41 studies of plant-based diets showed that these diets lowered the SBP and DBP, irrespective of sex and BMI, by 4.29 mm Hg and 2.79 mm Hg, respectively.[61] These dietary patterns included the DASH diet, the Mediterranean diet, and the Nordic diet, and the key factor is that they all emphasize plant-based foods, rich in fruits, vegetables, whole grains, legumes, nuts, seeds, dairy, and fish and low in processed foods and red meat. Both the DASH diet and the Mediterranean diet have been shown to decrease the decline in renal function, progression to dialysis, and mortality.[62]

SMOKING

Cigarette smoking is a major risk factor for CV disease, but its specific role in the development of hypertension is not well elucidated and not routinely included in recommendations for prevention and treatment of hypertension. The relationship with hypertension may be confounded by changes in weight during and after the cessation of smoking. In a large epidemiologic study of middle-aged and older men from the United States, smoking was associated with a modest but important risk for development of hypertension.[63] Furthermore, BP is elevated immediately after using nicotine-containing products.[64] In addition, smoking increases the risk for CKD progression, as well as morbidity and mortality from multiple causes, so all smokers should be advised to stop.

ALCOHOL

There is a linear relationship between alcohol consumption, BP levels, and prevalence of hypertension. In Japan, alcohol intake above 300 g/wk (about three drinks daily) was associated with significantly greater increases of BP during a 7-year period, and baseline BP was higher in drinkers consuming 200 g/wk.[65] Heavy drinking is associated with increased risk for stroke, increase in BP after alcohol withdrawal, and attenuation of antihypertensive efficacy. Paradoxically, alcohol has a J-shaped relationship with coronary heart disease, with moderate consumption (one to two drinks daily) having the lowest risk. In a large epidemiologic study, modest alcohol consumption was protective against first MI.[66] Alcohol may increase BP through activation of the SNS, whereas its protective effects include increasing high-density lipoprotein cholesterol, lowering fibrinogen, and inhibiting platelet activation. The ACC/AHA guidelines recommend that in adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than two and one standard drinks per day, respectively (Table 36.1).[1] One standard drink is equivalent to 360 mL (12 fl oz) beer, 150 mL (5 fl oz) wine, or 45 mL (1.5 fl oz) 80-proof spirit.

CAFFEINE

Caffeine is the most widely used psychoactive substance worldwide. Caffeine stimulates the CV system through the blockade of vascular adenosine receptors. In a meta-analysis of RCTs of coffee ingestion, there was no effect on BP or risk for hypertension, although the quality of the evidence was low.[67] The ISH global guidelines recommend moderate consumption of tea or coffee, but pharmacologic ingestion of caffeine and the use of “smart drinks” supplemented with caffeine should be avoided.[2]

PSYCHOLOGICAL STRESS

Chronic psychological stress is a contributor to the development and maintenance of hypertension. Men exposed to job strain had a 10.7 mm Hg and 15.4 mm Hg higher work and home ambulatory SBP than did controls, respectively.68 The INTERHEART study showed that psychosocial stress was associated with a twofold increase in the risk for the first MI.66 Although stress reduction techniques may be beneficial for other reasons, there are few long-term data on efficacy in reducing BP. However, there is rising evidence that stress reduction may assist in blood BP control,25 and it is recommended in the most recent ISH global hypertension guidelines.2

ADOPTING LIFESTYLE MODIFICATIONS

Maintaining adherence to lifestyle changes has always been challenging. The Prevention of Myocardial Infarction Early Remodeling (PREMIER) trial evaluated the effects of implementing JNC 7 lifestyle recommendations and the DASH diet in adults with prehypertension or untreated stage 1 hypertension.69 At 6 months, there was little additional benefit in adding the DASH diet to JNC recommendations, but both these intervention groups had greater BP reductions compared with a general advice-only group. Importantly, participants purchased their own foods instead of being provided with foods as in the DASH and DASH low-salt diet studies. In the DASH low-salt diet study in which all foods were provided, salt reduction alone resulted in a BP-lowering effect of −6.7/−3.5 mm Hg.39 A meta-analysis of 34 salt restriction trials in which participants mostly prepared their own low-salt meals reported an effect size of only −4.18/−2.06 mm Hg.38 Thus, even highly motivated individuals usually cannot meet DASH dietary goals unless their meals are provided.

The TOHP II study demonstrated the problems of sustainability of dietary intervention and the need for regular counseling.70 The effect of adding salt restriction to weight loss appeared to offer no further decrease in BP, but this was explained by poor compliance to salt reduction. Higher attendance at counseling sessions was associated with a greater reduction in urinary sodium, and the targets were met only in those participants who attended more than 80% of counseling sessions. In summary, the sustainability of long-term lifestyle interventions remains problematic, but it appears that regular and long-term counseling can improve adherence to both medication and lifestyle changes.71

SELF-ASSESSMENT QUESTIONS

1. In regard to exercise and hypertension, select the incorrect answer:

A. Physical inactivity may account for 5% to 13% of the risk for developing hypertension.

B. Regular physical activity and reduced sedentary activity lowers all-cause morbidity and mortality.

C. The 2020 World Health Organization guidelines suggest that all adults should undertake 150 to 300 minutes of moderateintensity physical activity or 75 to 150 minutes of vigorousintensity physical activity.

D. The guidelines do not recommend regular muscle-strengthening activity for all age groups.

2. For every kilogram reduction in weight, it is estimated that the systolic blood pressure will be reduced by:
A. 0.5 mm Hg.
B. 1 mm Hg.
C. 2 mm Hg.
D. 3 mm Hg.

3. Which of the following patients should not be targeted for stricter sodium reduction, according to the US Department of Agriculture and the US Department of Health and Human Services?
A. African Americans
B. Patients with chronic kidney disease

C. Hypertensive individuals
D. People younger than 40 years

4. In regard to alcohol consumption, which of the following statements is incorrect?
A. There is a linear relationship between alcohol consumption, blood pressure levels, and prevalence of hypertension.
B. Abstinence from alcohol may reduce the risk of myocardial infarction.
C. Reduction of alcohol consumption to 1 to 2 standard drinks is recommended.
D. Heavy drinking is associated with increased risk for stroke.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018;71(6):1269–1324.
2. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of hypertension global hypertension practice guidelines. J Hypertens. 2020;38(6):982–1004.
3. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens. 2014;16(1):14–26.
4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953–2041.
5. Vasan RS, Larson MG, Leip EP, Evans JC, O’Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001;345(18):1291–1297.
6. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000;343(1):16–22.
7. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the lancet commission on hypertension. Lancet. 2016;388(10060):2665–2712.
8. Pälve KS, Pahkala K, Magnussen CG, Koivistoinen T, Juonala M, Kähönen M, et al. Association of physical activity in childhood and early adulthood with carotid artery elasticity 21 years later: the cardiovascular risk in young finns study. J Am Heart Assoc. 2014;3(2):e000594.
9. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003;42(5):878–884.
10. Schulz M, Liese A, Boeing H, Cunningham J, Moore C, Kroke A. Associations of short-term weight changes and weight cycling with incidence of essential hypertension in the EPIC-potsdam study. J Hum Hypertens. 2005;19(1):61–67.
11. Atallah R, Filion KB, Wakil SM, Genest J, Joseph L, Poirier P, et al. Long-term effects of 4 popular diets on weight loss and cardiovascular risk factors: a systematic review of randomized controlled trials. Circ Cardiovasc Qual Outcomes. 2014;7(6):815–827.
12. Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of lowcarbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr. 2016;115(3):466–479.
13. Engberink M, Geleijnse J, Bakker S, Larsen TM, Handjieva-Darlesnka T, Kafatos A, et al. Effect of a high-protein diet on maintenance of blood pressure levels achieved after initial weight loss: the diogenes randomized study. J Hum Hypertens. 2015;29(1):58–63.
14. Geleijnse JM, Kok FJ, Grobbee DE. Impact of dietary and lifestyle factors on the prevalence of hypertension in western populations. Eur J Publ Health. 2004;14(3):235–239.
15. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451–1462.
16. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical

activity on mortality in patients with high blood pressure: a systematic review. J Hypertens. 2012;30(7):1277–1288.

17. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc. 2001;33(suppl 6):S484–S492; discussion S93.
18. Börjesson M, Onerup A, Lundqvist S, Dahlöf B. Physical activity and exercise lower blood pressure in individuals with hypertension: narrative review of 27 RCTs. Br J Sports Med. 2016;50(6):356–361.
19. Sharman JE, Smart NA, Coombes JS, Stowasser M. Exercise and sport science Australia position stand update on exercise and hypertension. J Hum Hypertens. 2019:1–7.
20. Ciolac EG. High-intensity interval training and hypertension: maximizing the benefits of exercise? Am J Cardiovasc Dis. 2012;2(2):102.
21. Nielson CM, Lockhart BD, Hager RL, George JD, Eggett DL, Steffen PR, et al. The effect of CardioWaves interval training on resting blood pressure, resting heart rate, and mind-body wellness. Int J Exerc Sci. 2016;9(1):89.
22. Guan Y, Hao Y, Guan Y, Wang H. Effects of Tai Chi on essential hypertension and related risk factors: a meta-analysis of randomized controlled trials. J Rehabil Med. 2020;52(5):jrm00057.
23. Chen D. Effect of health qigong mawangdui daoyinshu on blood pressure of individuals with essential hypertension. JAGS. 2016;64(7):1513–1515.
24. Cowell OR, Mistry N, Deighton K, Matu J, Griffiths A, Minihane AM, et al. Effects of a mediterranean diet on blood pressure: a systematic review and meta-analysis of randomized controlled trials and observational studies. J Hypertens. 2020.
25. Tolbanos Roche L, Miro Barrachina MT, Ibanez Fernandez I, Betancort M. Yoga and self-regulation in management of essential arterial hypertension and associated emotional symptomatology: a randomized controlled trial. Complement Ther Clin Pract. 2017;29:153–161.
26. Palatini P, Visentin P, Dorigatti F, Guarnieri C, Santonastaso M, Cozzio S, et al. Regular physical activity prevents development of left ventricular hypertrophy in hypertension. Eur Heart J. 2009;30(2):225–232.
27. Quinn T. Twenty-four hour, ambulatory blood pressure responses following acute exercise: impact of exercise intensity. J Hum Hypertens. 2000;14(9):547–553.
28. Pescatello LS, MacDonald HV, Ash GI, Lamberti LM, Farquhar WB, Arena R, et al., eds. Assessing the existing professional exercise recommendations for hypertension: a review and recommendations for future research priorities. Mayo Clin Proc; Elsevier; 2015.
29. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
30. Leosco D, Parisi V, Femminella GD, Formisano R, Petraglia L, Allocca E, et al. Effects of exercise training on cardiovascular adrenergic system. Front Physiol. 2013;4:348.
31. Lopes S, Afreixo V, Teixeira M, Garcia C, Leitao C, Gouveia M, et al. Exercise training reduces arterial stiffness in adults with hypertension: a systematic review and meta-analysis. J Hypertens. 2020.
32. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. Exercise and hypertension. Med Sci Sports Exerc. 2004;36(3):533–553.
33. Pollock ML, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, et al. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription an advisory from the committee on exercise, rehabilitation, and prevention, council on clinical cardiology, American Heart Association. Circulation. 2000;101(7):828–833.
34. MacGregor GA. Sodium is more important than calcium in essential hypertension. Hypertension. 1985;7(4):628–640.
35. Prior I, Evans JG, Harvey H, Davidson F, Lindsey M. Sodium intake and blood pressure in two polynesian populations. N Engl J Med. 1968;279(10):515–520.
36. Kanbay M, Aslan G, Afsar B, Dagel T, Siriopol D, Kuwabara M, et al.

Acute effects of salt on blood pressure are mediated by serum osmolality. J Clin Hypertens (Greenwich). 2018;20(10):1447–1454.
37. Kuwabara M, Kanbay M, Niwa K, Ae R, Andres-Hernando A, RoncalJimenez CA, et al. Hyperosmolarity and increased serum sodium concentration are risks for developing hypertension regardless of salt intake: a five-year cohort study in Japan. Nutrients. 2020;12(5).

References

38. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013:346.

39. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344(1):3–10.

40. Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. Circulation. 2012;126(24):2880–2889.

41. Mattes R, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr. 1991;10(4):383–393.

42. Charlton KE, Steyn K, Levitt NS, Peer N, Jonathan D, Gogela T, et al. A food-based dietary strategy lowers blood pressure in a low socio-economic setting: a randomized study in South Africa–Corrigendum. Publ Health Nutr. 2009;12(2):284.

43. World Health Organization (WHO). Global Strategy on Diet, Physical Activity, and Health. WHO, 2004.

44. Kaplan NM, Carnegie A, Raskin P, Heller JA, Simmons M. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. N Engl J Med. 1985;312(12):746–749.

45. Ndanuko R, Ibrahim R, Hapsari R, Neale E, Raubenheimer D, Charlton KE. Association between urinary sodium to potassium ratio and blood pressure in adults: a systematic review and meta analysis. Adv Nutr. 2021;12(5):1751-1767.

46. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. Am J Hypertens. 1999;12(1):84–92.

47. Pilz S, Gaksch M, Kienreich K, Grübler M, Verheyen N, FahrleitnerPammer A, et al. Effects of vitamin D on blood pressure and cardiovascular risk factors: a randomized controlled trial. Hypertension. 2015;65(6):1195–1201.

48. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, et al. Effects of magnesium supplementation on blood pressure: a meta-analysis of randomized double-blind placebo-controlled trials. Hypertension. 2016;68(2):324–333.

49. Menzel D, Haller H, Wilhelm M, Robenek H. L-Arginine and B vitamins improve endothelial function in subjects with mild to moderate blood pressure elevation. Eur J Nutr. 2018;57(2):557–568.

50. Baszczuk A, Thielemann A, Musialik K, Kopczynski J, Bielawska L, Dzumak A, et al. The impact of supplementation with folic acid on homocysteine concentration and selected lipoprotein Parameters in patients with primary hypertension. J Nutr Sci Vitaminol (Tokyo). 2017;63(2):96–103.

51. Gilchrist M, Winyard PG, Aizawa K, Anning C, Shore A, Benjamin N. Effect of dietary nitrate on blood pressure, endothelial function, and insulin sensitivity in type 2 diabetes. Free Radic Biol Med. 2013;60:89–97.

52. Kapil V, Khambata RS, Robertson A, Caulfield MJ, Ahluwalia A. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study. Hypertension. 2015;65(2):320–327.

53. Bahadoran Z, Mirmiran P, Kabir A, Azizi F, Ghasemi A. The nitrateindependent blood pressure-lowering effect of beetroot juice: a systematic review and meta-analysis. Adv Nutr. 2017;8(6):830–838.

54. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 2008;7(2):156–167.

55. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med. 2014;174(4):516–524.
56. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, Shafiu M, Sundaram S, Le M, et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes. 2013;62(10):3307–3315.
57. Chen L, Caballero B, Mitchell DC, Loria C, Lin P-H, Champagne CM, et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among US adults. Circulation. 2010;121(22):2398.
58. Jayalath VH, Sievenpiper JL, de Souza RJ, Ha V, Mirrahimi A, Santaren ID, et al. Total fructose intake and risk of hypertension: a systematic review and meta-analysis of prospective cohorts. J Am Coll Nutr. 2014;33(4):328–339.
59. Hartweg J, Farmer A, Perera R, Holman R, Neil H. Meta-analysis of the effects of N-3 polyunsaturated fatty acids on lipoproteins and other emerging lipid cardiovascular risk markers in patients with type 2 diabetes. Diabetologia. 2007;80(8):1593–602.
60. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Dietary patterns and blood pressure in adults: a systematic review and metaanalysis of randomized controlled trials. Adv Nutr. 2016;7(1):76–89.
61. Gibbs J, Gaskin E, Ji C, Miller MA, Cappuccio FP. The effect of plantbased dietary patterns on blood pressure: a systematic review and metaanalysis of controlled intervention trials. J Hypertens. 2021;39(1):23–37.
62. Yazdi F, Morreale P, Reisin E. First course DASH, second course mediterranean: comparing renal outcomes for two “heart-healthy” diets. Curr Hypertens Rep. 2020;22(8):54.
63. Halperin RO, Michael Gaziano J, Sesso HD. Smoking and the risk of incident hypertension in middle-aged and older men. Am J Hypertens. 2008;21(2):148–152.
64. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: the sapienza university of rome-vascular assessment of proatherosclerotic effects of smoking (SUR-VAPES) 2 randomized trial. J Am Heart Assoc. 2019;8(6):e010455.
65. Yoshita K, Miura K, Morikawa Y, Ishizaki M, Kido T, Naruse Y, et al. Relationship of alcohol consumption to 7-year blood pressure change in Japanese men. J Hypertens. 2005;23(8):1485–1490.
66. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the interheart study): case-control study. The Lancet. 2004;364(9438):937–952.
67. Steffen M, Kuhle C, Hensrud D, Erwin PJ, Murad MH. The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. J Hypertens. 2012;30(12):2245–2254.
68. Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. Psychosom Med. 1998;60(6):697–706.
69. Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the premier clinical trial. JAMA. 2003;289(16):2083–2093.
70. Kumanyika SK, Cook NR, Cutler JA, Belden L, Brewer A, Cohen JD, et al. Sodium reduction for hypertension prevention in overweight adults: further results from the Trials of Hypertension Prevention Phase II. J Hum Hypertens. 2005;19(1):33–45.
71. Perl S, Niederl E, Kos C, Mrak P, Ederer H, Rakovac I, et al. Randomized evaluation of the effectiveness of a structured educational program for patients with essential hypertension. Am J Hypertens. 2016;29(7):866–872.

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Pharmacologic Treatment of Hypertension

Bryan Williams

High blood pressure (BP) is a major preventable cause of premature death globally.1-3 Accordingly, the treatment of hypertension is one of the most cost-effective interventions in modern medicine.4,5 This chapter relies heavily on the 2017 US American Heart Association/American College of Cardiology (AHA/ACC)6 and the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) hypertension guidelines,7 referred here as the US and European guidelines, respectively. Both guidelines record the importance of lifestyle interventions prior to and in conjunction with pharmacologic treatment of hypertension, noting that they can delay the development of hypertension and can potentiate the efficacy of BP-lowering therapies (see Chapter 36). Nevertheless, most patients with confirmed hypertension will require lifelong drug treatment, invariably with more than one drug (Table 37.1). International hypertension guidelines have recently converged to prioritize simplicity and pragmatism, although some nuances and differences remain.8 This chapter summarizes these recommendations for treatment of hypertension.

DEFINING WHO SHOULD RECEIVE PHARMACOLOGIC TREATMENT FOR HYPERTENSION

BP follows a normal distribution within populations; thus hypertension is arbitrarily defined by diagnostic thresholds that are subject to change as new evidence from clinical trials emerges. Hypertension is best defined as that level of blood pressure at which treatment to lower blood pressure results in significant clinical benefit. The BP at which treatment results in “significant clinical benefit” for any individual will depend on their absolute cardiovascular (CV) risk.1-5 This varies because some people are more vulnerable than others to end organ damage at a given BP. Moreover, some patients (e.g., the frail elderly) will be less tolerant of more aggressive BP lowering than others. Consequently, complex differential BP thresholds and targets emerged in previous guidelines, grouping patients into categories defining their threshold BP for therapeutic intervention and optimal BP goals. In some cases, specific drug classes were also given “compelling indications” and “compelling contraindications” for specific groups of patients. Although useful in tailoring therapy, these recommendations were often misinterpreted as indicating that the specific drug was more important than the achieved BP, which is not the case. As guidelines have evolved, the BP threshold for intervention with drug therapy and the recommended treatment targets have been simplified, and the drug treatment algorithms are more pragmatic and focused on logical combinations of therapy. Key principles underpinning current guidance are that (1) most people need more than one drug to achieve currently recommended BP targets, and (2) the magnitude of BP reduction and the achievement of BP control are the most important drivers of benefit.4,5

Blood Pressure Thresholds for Intervention (Office Blood Pressure)

There is unequivocal evidence that drug treatment of a seated “office” BP of 160/100 mm Hg or higher (grade 2 hypertension) reduces the risk for stroke, myocardial infarction (MI), heart failure, and mortality.4-7 Treating pressures of 140/90 mm Hg or higher, especially in higher-risk patients, is similarly beneficial.4-7 Consequently, most international guidelines define hypertension as an office BP of 140/90 mm Hg or higher.9 The exception is the 2017 US hypertension guideline,6 which defined stage 1 hypertension as a BP of 130/80 mm Hg or higher. Note that the US hypertension guidelines refers to “stages” of hypertension, whereas other guidelines refer to “grades” of hypertension. The US guideline recommends lifestyle advice for such patients and drug treatment to lower BP to less than 130/80 mm Hg if there is coexisting cardiovascular disease (CVD) or an estimated 10-year risk for CVD greater than 10%.[6] This was a major change, especially setting the diagnostic threshold for “hypertension” at 130/80 mm Hg or higher, resulting in as many as 50% more people being diagnosed as “hypertensive,” with the majority, especially older patients, recommended for drug treatment. Other international guidelines have retained a diagnostic threshold for hypertension of 140/90 mm Hg for adults.[9] The European guidance in 2018 remained more cautious about the initiation of drug therapy in patients aged 80 years or older, recommending a treatment threshold of 160/100 mm Hg for previously untreated patients.[7] However, a 140/90 mm Hg threshold is now more widely adopted, especially for the fit and active elderly in this age group. Table 37.2 contrasts the US guidance and the 2018 European (ESC/ESH) guidelines, which are representative of most other international guidelines. All guidelines identify a category of patients with “high normal BP” (often referred to as borderline hypertension or prehypertension), which highlights people at high risk for progression to hypertension and in whom lifestyle changes can be beneficial.

Blood Pressure Thresholds for Intervention (Ambulatory and Home Blood Pressure Monitoring)

International guidelines favor the use of out-of-office BP measurement to confirm the diagnosis of hypertension, better identify masked hypertension or “white coat” hypertension, and monitor BP control. When the office BP is elevated, the elevation in BP should ideally be confirmed by ambulatory blood pressure monitoring (ABPM) or home BP monitoring.[6,7,10,11] This is not necessary when BP is markedly elevated in patients requiring urgent treatment (i.e., in the presence of hypertension-mediated clinical complications or organ damage). ABPM or home BP is also recommended to confirm the quality of BP control, especially in higher-risk patients. Moreover, the US guidelines cite evidence suggesting that home BP monitoring may better engage patients in their treatment and lead to better BP control. The shift toward increased awareness and use of home BP has accelerated during the COVID-19 pandemic as patients became more isolated from their routine clinic visits, and this is likely to be a continuing trend. Diagnostic thresholds for hypertension vary according to the method of measurement. When ABPM and home BP monitoring are used to classify hypertension, the diagnostic thresholds are lower than office BP because they represent the average of a greater number of

Development of Therapeutic Strategies for Hypertension

TABLE 37.1

Year	Therapy
Nondrug	
1920s	Strict low-sodium diet
1929	Lumbar sympathectomy
1944	Kempner rice diet
Drug	
1930s	Veratrum alkaloids
1940s	Thiocyanates
1948	Reserpine, phenoxybenzamine
1950	Ganglion blockers
1951	Monoamine oxidase inhibitors
1958	Thiazide diuretics (chlorothiazide)
1960s	Central α2-receptor agonists, non-DHP CCBs, β-blockers
1970s	ACE inhibitors, α1-receptor blockers
1980s	

DHP CCBs

1990s

ARBs

2000s

Renin inhibitors, ARNIs

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; DHP CCB, dihydropyridine calcium channel blocker.

measurements under different conditions. Table 37.3 summarizes the diagnostic thresholds for hypertension according to different methods of measurement (see Chapter 34).

BLOOD PRESSURE TREATMENT GOALS

There is no single BP treatment goal that will be optimal, achievable, and well tolerated by all. The ideal BP treatment goal is likely to be patient specific. Guidelines should therefore be conservative and pragmatic, curbing the zeal of specialists to advocate ever-lower BP goals, and should only make recommendations supported by solid evidence.

Until recently, there was international consensus that two BP goals were appropriate: less than 140/90 mm Hg for those with “uncomplicated hypertension” and a lower goal of less than 130/80 mm Hg for those at higher risk (i.e., patients with diabetes, established CVD or cerebrovascular disease, or chronic kidney disease [CKD]). The SPRINT trial challenged this consensus when it showed that more intensive BP lowering (targeting an office systolic BP <120 mm Hg) was more effective at reducing major CV events and mortality than the current, less intensive systolic BP goal of less than 140 mm Hg.[12] The SPRINT results are supported by a more recent and similar study in older patients from China.[13] Importantly, BP was measured in SPRINT using a very specific methodology: an automated device after 5 minutes of seated rest in a quiet room (either attended or unattended) followed by three oscillometric measurements. This approach to BP measurement undoubtedly results in lower BP readings compared with usual office BP measurements in clinical practice. Indeed, a recent study comparing routine BP measurement using routine electronic health record data from patients also participating in the SPRINT study showed that routine clinic readings were significantly higher than the SPRINT BP recordings, such that the lower attained systolic BP in the SPRINT cohort (121 mm Hg) was equivalent to 128 mm Hg in contemporaneously routinely measured clinic BP. Furthermore, a mean systolic BP of 135 mm Hg in the less intensively SPRINT cohort group was equivalent to 139 mm Hg using routine clinic BP.[14] These findings concur with the view that the office

Blood Pressure Classification and Definition of Hypertension According to International Guidelines

TABLE 37.2
BP Category

Systolic (mm Hg)

Diastolic (mm Hg)

BP Threshold (mm Hg)
Age <80 yr: 140/90

Age ≥80 yr: 160/90

ESC/ESH Classification of Hypertension (2018)
Optimal

<120

and

<80

Normal

120–129

and/or

80–84

High-normal

130–139

and/or

85–89

Grade 1 hypertension

140–159

and/or

90–99

Grade 2 hypertension

160–179

and/or

100–109

Grade 3 hypertension

≥180

and/or

≥110

Isolated systolic hypertension

≥140

and

<90

US Classification of Hypertension (2017)
Normal

<120

and

<80

Elevated

120–129

and

<80

Hypertension
Stage 1

130–139

or

80–89

Stage 2

≥140

or

≥90

130/80 if existing CV disease or
10-yr CVD risk >10%
140/90 in all others

BP, Blood pressure; CVD, cardiovascular disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Hypertension grades or stages replace the older terminology of mild, moderate, and severe.

TABLE 37.3 Diagnostic Thresholds for Hypertension According to Different Methods of BP Measurement

Measurement	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Office or Clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

Clinic	120/80
HBPM	120/80
Daytime ABPM	120/80
Nighttime ABPM	100/65
24-Hour ABPM	115/75

130/80

130/80

130/80

110/65

125/75

140/90

135/85

135/85

120/70

130/80

160/100

145/90

145/90

140/85

145/90

24-Hour, daytime and nighttime refer to ambulatory blood pressure (BP) averages over these periods. Home refers to an average of at least 4 days of seated readings at home, usually two readings, twice per day (i.e., an average of ~16 readings). The top panel shows BP thresholds according to the European 2018 Guidelines. The bottom panel shows the corresponding values of systolic BP and diastolic BP for clinic, HBPM, daytime, nighttime, and 24-hour ABPM measurements according to the US 2017 Guidelines.
ABPM, Ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring.
From Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104. Erratum Eur Heart J. 2019;40(5):475; and Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127–e248. Erratum J Am Coll Cardiol. 2018;71(19):2275–2279.

SBP should be treated to less than 140 mm Hg and ideally less than 130 mm Hg, if tolerated. This is consistent with the US guidance, which recommends a BP target of less than 130/80 mm Hg in all treated patients, irrespective of age or comorbidities.6
The ESC-ESH 2018 guidance recommended a target range, noting that the first objective should be to treat all patients to an office BP of less than 140/90 mm Hg and that the optimal systolic BP goal would for most treated patients be from less than 140 mm Hg down to 120 mm Hg, also noting that attempting to lower systolic BP below 120 mm Hg in all patients might be beneficial in some but may be hazardous to others.7 The guidance stated that the aim should be to reduce systolic BP to 130 mm Hg if possible, and lower if tolerated (which the guidance noted was likely to be more likely in patients <65 years). Thus, in reality, there is little difference between the US and European guidance for most patients with respect to BP treatment targets, except

that the European guidance is more nuanced with respect to the likelihood of achieving the lower end of the BP target range in older and especially frailer patients. The diastolic target in all guidelines is less than 80 mm Hg, although in most patients, this will be less difficult to achieve than the systolic targets. The simple takeaway from all of this is to aim to reduce systolic BP to less than 140/90 mm Hg in all patients, aiming for less than 130/80 mm Hg, and ideally lower if tolerated. Tables 37.4 and 37.5 summarize the treatment targets from the US and European guidelines, respectively.

GUIDE TO SELECTION OF ANTIHYPERTENSIVE AGENTS

Key Principles from Clinical Trials

Some important guiding principles with regard to treatment strategies for hypertension are as follows:

1. Effective BP lowering is overwhelmingly important to reduce risk of major CV events and death in people with hypertension. Thus, the first priority in treatment is to control BP.
2. Early studies focused on diastolic BP as the treatment target, but systolic BP is invariably more difficult to control and more closely linked to CV outcomes; thus it should now be the primary but not the sole focus of treatment.
3. Most patients will require more than one drug (i.e., combination therapy) as part of their treatment strategy, especially with the lower BP targets advocated in the most recent guidance.
4. The response to any class of BP-lowering medication is heterogeneous, with important effects of age and ethnicity, but this heterogeneity is diminished by combination therapy.
5. Some trials have suggested that certain comorbidities (e.g., diabetes) or target organ damage (e.g., left ventricular hypertrophy [LVH], CKD) provide compelling indications for inclusion of specific classes of drug therapy in the treatment regimen, usually renin-angiotensin system (RAS) blockade, but this consideration has become less relevant now that recommended combinations typically include RAS blockade.
6. On average, lowering of BP by 20/10 mm Hg in hypertensive patients will reduce the risk for major CV events by half.
7. The reduction in stroke risk and heart failure appears to follow the predicted reduction in risk based on the epidemiologic association between these morbidities and BP.
8. The observed benefits of BP lowering on coronary events are lower than expected based on epidemiologic predictions, which is best addressed by attention to concomitant risk factors, especially statin therapy.
9. The risk reduction associated with BP lowering is continuous across a wide range of BP, with the benefit from treatment greatest in those with the highest absolute CVD risk. This provides the rationale for advocating the use of complementary strategies to reduce CVD risk (e.g., statins for those with established vascular disease, with target organ damage, or at high calculated CVD risk [i.e., ≥10% during 10 years], and antiplatelet therapy for secondary prevention).

Summary of BP Thresholds and Treatment Goals (Office BP) Recommended by the US 2017 Hypertension in Adults Treatment Guidelines

TABLE 37.4

Clinical Condition(s)	Threshold (mm Hg)	Goal (mm Hg)
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years; noninstitutionalized, ambulatory, community-living adults)	≥130 systolic	<130 systolic
Specific Comorbidities		
Diabetes mellitus	≥130/80	<130/80
CKD	≥130/80	<130/80
CKD after kidney transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80

Secondary stroke prevention

≥140/80

<130/80

Secondary stroke prevention (lacunar)

≥130/80

<130/80

Peripheral arterial disease

≥130/80

<130/80

ASCVD, Atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease.

Summary of BP Thresholds and Treatment Goals (Office BP) Recommended by the European 2018 Hypertension in Adults Treatment Guidelines

TABLE 37.5
Age Group
(Years)

OFFICE SBP TREATMENT TARGET RANGES (mm Hg)

Office DBP Treatment
Target Range (mm Hg)

Hypertension

+ Diabetes

+ CKD

+ CAD

+ Strokea/TIA

18–65

Target to 130 (or
lower if tolerated
but not <120)

Target to 130 (or
lower if tolerated
but not <120)

Target to <140–
130 (or lower if
tolerated)

Target to 130 (or
lower if tolerated
but not <120)

Target to 130 (or
lower if tolerated
but not <120)

70–79

65–79b

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

70–79

≥80b

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

Target to 130–139
(or lower if
tolerated)

70–79

Office DBP
treatment
target range
(mm Hg)

70–79

70–79

70–79

70–79

70–79

aRefers

to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.
decisions and blood pressure targets may need to be modified in older patients who are frail and independent.
BP, Blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischemic attack.

bTreatment

Selection of Drug Therapy

Modern guidelines recommend that routine drug treatment of hypertension should be based on 5 major classes of drugs; angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and β-blockers, with the latter predominantly reserved for specific indications.6 7 9 Recent guidelines also advocate wider use of combinations of BP-lowering drugs, even as initial therapy, to achieve optimal BP control. Thus, the previous lists of compelling indications for individual drug classes for patients with specific comorbidities are less relevant than they were previously. The focus

now is on which combinations of drugs are appropriate for each clinical scenario. Nevertheless, it is important to understand the properties and mechanisms of action of individual drug classes that form the basis of treatment for hypertension, as well as their relative risks and benefits (Table 37.6 and Fig. 37.1) and contraindications for the use of specific classes of BP-lowering therapy in specific clinical situations (Table 37.7) and common adverse effects (Table 37.8). These lists are not comprehensive and are subject to change as new evidence emerges, and up-to-date prescribing information should always be consulted. Fig. 37.2 shows the major sites of action of major antihypertensive drug therapies.

TABLE 37.6

Relative Risk and Benefit of Antihypertensive Drug Classes

Outcome	Thiazide Diuretics	Calcium Channel Blockers	β-Blockers	ACEis/ARBs[a]
Unstable angina	0.89	0.88	0.98	0.97
Myocardial infarction	0.78	0.79	0.85	0.81
Diabetes	0.98	0.80	1.13	0.72
Stroke	0.69	0.65	0.85	0.73
Heart failure	0.53	0.73		

0.76

0.64

Death

0.91

0.88

0.93

0.90

aACE

inhibitors and ARBs were grouped as a single class for the purposes of this analysis.
Effectiveness of drugs: 1.0 = no benefit/harm, <1.0 = benefit, and >1.0 = potential harmful effect (from a meta-analysis of major blood pressure–lowering trials conducted for the United Kingdom).
ACEis, Angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
Modified from National Institute for Health and Clinical Excellence [NICE] Hypertension Guideline Development Group, 2006. https://www.nice.org.uk/guidance/cg127

Effects of Reduction in Systolic BP Stratified by Class of Antihypertensive

Studies	Intervention		Control		RR (95% CI)
	Events	Participants	Events	Participants	
10	5379	31652	9766	50805	1.03 (1.00–1.06)
8	3647	27140	3779	29331	0.98 (0.93–1.02)

Major cardiovascular events
ACE inhibitor
ARB
β-blocker

9

2863

25989

2520

27231

1.17 (1.11–1.24)

21

7857

63693

12808

82904

0.97 (0.94–0.99)

Diuretic
11
All-cause mortality

5830

38353

6782

42410

0.97 (0.94–1.00)

ACE inhibitor

14

3321

33104

5865

52263

1.01 (0.97–1.05)

ARB

11

2546

29282

2638

31404

0.99 (0.94–1.04)

β-blocker

12

2805

40953

2688

42170

1.06 (1.01–1.12)

CCB

26

5602

76672

8428

95932

0.97 (0.94–1.00)

Diuretic

12

3425

41625

3806

45707

1.02 (0.97–1.06)

CCB

0.5
1
2
Class superior Class inferior
to pooled comparators to pooled comparators
Fig. 37.1 Effects of Reductions in Systolic Blood Pressure (BP) Stratified by Class of BP-Lowering Drug.
ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker;
CI, confidence interval; RR, relative risk. (From Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet.
2016;387[10022]:957–967.)

Thiazide and Thiazide-like Diuretics

The class of diuretics includes the traditional thiazide diuretics such as hydrochlorothiazide and bendroflumethiazide, as well as thiazide-like diuretics such as chlorthalidone and indapamide. The latter are termed thiazide-like because, like the thiazides, they act primarily by inhibiting the Na+-Cl cotransporter in the distal tubule, promoting sodium excretion, which is integral to their antihypertensive effect. However, the thiazide-like diuretics have different structure than the thiazides and differing actions on other aspects of kidney tubular function, such as carbonic anhydrase inhibition in the proximal tubule. Thiazide and thiazide-like diuretics remain an important therapeutic option for the treatment of hypertension. The early changes in salt and water balance they induce are usually accompanied by counteractivation of several vasoconstrictor mechanisms, including the RAS, which may transiently raise peripheral vascular resistance (PVR) and attenuate BP lowering. Subsequently, a gradual reduction in PVR and a new steady state of reduced total body sodium and BP are established, usually after about 2 months of treatment.

The sustained actions of these diuretics on the kidney make them preferable to loop diuretics for the control of BP. Although loop diuretics are more potent promoters of acute sodium and water loss, their shorter duration of action can result in compensatory sodium retention during the latter part of the dosing interval, thereby reducing their BP-lowering efficacy. Loop diuretics have no place in the routine management of primary hypertension in patients with well-preserved glomerular filtration rate (GFR). However, thiazide and thiazide-like diuretics lose efficacy in patients with GFR less than 30 mL/min/1.73 m2. In such patients, loop diuretics are often required for effective BP lowering, especially when there is clinical evidence of sodium and water retention.

The main adverse effects of thiazide and thiazide-like diuretics are metabolic: hypokalemia, hyponatremia (less frequently),

Contraindications to Specific
BP-Lowering Therapies

TABLE 37.7
Pharmacologic
Therapy
Thiazide diuretics

β-Blockers

CONTRAINDICATIONS
Compelling
Gout

AV block (grade 2 or 3)

Calcium antagonists
(dihydropyridines)
Calcium antagonists
(verapamil,
diltiazem)

AV block (grade 2 or 3)
Heart failure
β-Blocker therapy

ACE inhibitors

Pregnancy
Angioneurotic edema
Hyperkalemia
Bilateral renal artery
stenosis

ARBs

Pregnancy
Hyperkalemia
Bilateral renal artery
stenosis

Diuretics
(antialdosterone)

Hyperkalemia

Direct renin
inhibitors

Pregnancy
Hyperkalemia
Bilateral renal artery
stenosis

Common Side Effects
Associated With Various Classes of
Antihypertensive Drugs

TABLE 37.8

Possible

Class

Metabolic syndrome
Glucose intolerance
Pregnancy

ACE inhibitors

Cough, hyperkalemia

ARBs

Much less frequent hyperkalemia compared with ACE inhibitors

Peripheral artery disease
Metabolic syndrome
Glucose intolerance
Athletes, physically active patients
COPD
Asthma (use cardioselective β-blocker)

CCBs

Tachyarrhythmias
Heart failure

DHP CCBs

Side Effects

Pedal edema, headache

Non-DHP CCBs

Constipation (verapamil), headache (diltiazem)

Diuretics

Frequent urination, hyperglycemia, hyperlipidemia, hyperuricemia, sexual dysfunction

Central α-agonists

Sedation, dry mouth, rebound hypertension, sexual dysfunction

α-Blockers

Pedal edema, orthostatic hypotension, dizziness

β-Blockers

Fatigue, bronchospasm, hyperglycemia, sexual dysfunction

Potassium channel openers

Hypertrichosis (minoxidil); lupus-like reactions,
pedal edema (hydralazine)

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; DHP, dihydropyridine.

Principal Site of Action of Major Classes
of Blood Pressure–Lowering Drugs
Decreased central sympathetic outflow
Centrally acting α2-agonist (e.g., clonidine)
Imidazoline receptor agonists (e.g., moxonidine)
Centrally acting—α-methyldopa

CKD stages 4 and 5a

aUse

only low doses and with extreme caution with respect to potassium levels in patients with advanced CKD.
ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

impaired glucose tolerance, and small increments in blood levels of low-density lipoprotein (LDL) cholesterol and triglycerides. These diuretics also elevate serum uric acid levels and should be avoided in patients predisposed to gout, as well as in those receiving lithium because of a high risk for lithium toxicity. Lithium reabsorption is similar to sodium in the proximal tubule, and thus distal sodium loss caused by thiazide and thiazide-like diuretics can promote proximal reabsorption of sodium and lithium, potentially leading to lithium toxicity. An incidental advantage of thiazide and thiazide-like diuretics may be reduced risk of osteoporosis, especially in women, as a result of calcium retention.
There has been a recent trend to reduce the recommended dose of these diuretics to minimize these metabolic effects. The dose response for BP to thiazide and thiazide-like diuretics is flat (unlike the adverse effect profile); however, some patients respond well to higher doses, which they tolerate. Moreover, when thiazide or thiazide-like diuretics

Decreased cardiac output β-blockers, diuretics
Increased vagal tone ACE inhibitors, ARBs, DRIs
Decreased heart rate β-blockers, non-DHP CCBs
Vasorelaxation
ACE inhibitors, ARBs, DRIs, CCBs, α-blockers
Thiazide-type diuretics
Direct vasodilators (e.g., hydralazine, minoxidil)
NEP-inhibitor

Natriuresis—all diuretics, CCBs, NEP inhibitor,
SGLT2 inhibitors
Renin inhibition—DRIs

Fig. 37.2 Principal Site of Action of Major Classes of Blood Pressure–Lowering Drugs. ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DRI, direct renin inhibitor; NEP, neprilysin; non-DHP CCB, nondihydropyridine calcium channel blocker; SGLT2, sodium-glucose cotransporter-2.

are combined with drugs that block the RAS, such as ACE inhibitors or ARBs, the dose response is steeper and higher doses (e.g., hydrochlorothiazide 25–50 mg or chlorthalidone 25 mg) may be especially effective in patients with more resistant hypertension. Guidelines favor the use of thiazide-like diuretics, such as chlorthalidone and indapamide, because they are longer acting than traditional thiazides, such as hydrochlorothiazide, and because there are limited outcome data with the latter when used at low doses.

Potassium-Retaining Diuretics

lethargy, muscle aches with exercise, impaired concentration and memory, aggravation of depression and psoriasis, erectile dysfunction, vivid dreams, and exacerbation of symptoms of peripheral vascular disease and Raynaud syndrome. Nonselective β-blockers are contraindicated in asthma patients and can cause impaired glucose tolerance and worsening of dyslipidemia, notably reduced high-density lipoprotein (HDL) cholesterol and raised triglyceride levels. β-Blockers increase the likelihood of new-onset diabetes, particularly in combination with thiazide-type diuretics.[20,21] Moreover, meta-analyses have consistently suggested that β-blocker–based treatment of hypertension reduces the risk of CV events (especially the risk of stroke) to a lesser extent than treatment with other major drug classes[4,22,23] (Fig. 37.1). As a consequence, US and European guidelines both state that β-blockers are not preferred as initial therapy for routine treatment of hypertension and should be used only when there is a compelling indication other than BP control (e.g., in patients with angina, chronic heart failure, or for heart rate control, as well as hypertension).[6,7]

Another exception is in younger women in whom β-blockers are often effective at lowering BP and are safer than ACE inhibitors or ARBs in women anticipating pregnancy. The good BP-lowering efficacy in younger people most likely reflects higher renin levels, and the BP-lowering action of β-blockers, at least in part, relates to suppression of renin release.

This class of agents includes spironolactone, eplerenone, and amiloride. Finerenone is a recently approved nonsteroidal mineralocorticoid receptor antagonist that has shown benefits in reducing the progression of diabetic kidney disease[15] and CV morbidity and mortality in patients with diabetes.[16] However, there is less data available on the use of finerenone for the treatment of hypertension.

Spironolactone is an aldosterone receptor antagonist that acts in the distal tubule and collecting ducts, decreasing the reabsorption of sodium and water and decreasing the excretion of potassium. The main action of spironolactone is to decrease tubular expression of epithelial sodium channels (ENaC) and kidney outer medullary potassium channels, and thus it has a relatively slow onset and offset of action. Because its main site of action is on sodium and water handling in distal tubule and collecting ducts, spironolactone as monotherapy is a relatively weak diuretic. Nevertheless, it is effective as a BPlowering agent although rarely used as initial therapy for hypertension.

Spironolactone has the advantage over thiazide-like diuretics in that it does not cause hypokalemia or hyperuricemia and it does not impair glucose tolerance. However, spironolactone has antiandrogen activity by binding to the androgen receptor and preventing it from interacting with dihydrotestosterone. Consequently, it can cause nipple tenderness and gynecomastia in some male patients (~6%) that is dose dependent and can limit its use. Another concern with potassium-sparing diuretics is the risk for hyperkalemia in people with substantially reduced GFR (see later discussion).

Eplerenone is more selective for the aldosterone receptor than spironolactone and consequently avoids its antiandrogen effects. There is very limited experience with the use of eplerenone for the routine management of hypertension. Empirically, milligram per milligram, eplerenone is less potent than spironolactone and less effective at lowering BP.

Amiloride is an antagonist of ENaC in the distal convoluted tubules and collecting ducts, decreasing sodium and water reabsorption and impairing potassium excretion. Previously, amiloride was a popular treatment of primary hypertension, when, like spironolactone, it was often used in combination with thiazide-like diuretics. Amiloride is now less frequently used even though it shares the advantage of spironolactone over thiazide-like diuretics of not causing hypokalemia, hyperuricemia, or impaired glucose tolerance. Amiloride is the treatment of choice in patients with Liddle syndrome.

The decline in popularity of potassium-sparing diuretics for the initial treatment of primary hypertension may reflect the increasing use of ACE inhibitors and ARBs for the management of hypertension and the increased risk for hyperkalemia when these are combined with spironolactone or amiloride, especially in patients with kidney impairment.

Spironolactone and amiloride are increasingly used as additional diuretic therapy in multidrug strategies for the treatment of resistant hypertension, when these drugs can be very effective (see “Resistant Hypertension” section).17-19

Newer Generation of β-Blockers: β1 Adrenoceptor Blockade Plus Vasodilation

β-Adrenoceptor Blockers

Calcium Channel Blockers

β-Blockers reduce BP and CV events in patients with hypertension.

Most β-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output by their negative chronotropic and inotropic effects. As with diuretics, short-term hemodynamic responses can be offset by counteractivation of vasoconstrictor mechanisms, which may limit initial BP lowering. Longerterm reduction in arterial pressure occurs because PVR is restored to pretreatment levels. Partial blockade of renin release from the kidney may contribute to the later hemodynamic response.

β-Blockers differ in their duration of action, selectivity for β1 receptors, lipophilicity, and partial agonist activity. Side effects include

Concerns regarding β-blockers predominantly reflect studies conducted with unselective or, more commonly, β1-cardioselective adrenoceptor blockers, especially atenolol. The newer generation of β-blockers retains β1-cardioselective adrenoceptor blockade but also has a vasodilator action, either through (1) associated α-adrenoceptor blocking activity (e.g., carvedilol or labetalol) or (2) nebivolol, via associated β3-adrenoceptor agonist activity, which dilates via nitric oxide–mediated mechanisms and also mediates favorable effects on glucose and lipid metabolism, offsetting the unfavorable metabolic effects of nonselective or selective β1-adrenoceptor blockade.

Labetalol has a rapid onset of action, making it a useful intravenous medication for the treatment of hypertensive emergencies.

Labetalol is also safe in pregnancy and in patients with coronary disease because it does not increase heart rate. Labetalol should not be used without prior adequate α-blockade in patients with hyperadrenergic states, such as pheochromocytoma, because unopposed, inadequately blocked α-adrenergic activity can increase BP if β-blockade is not complete.

Carvedilol and nebivolol have been shown to improve outcomes in randomized controlled trials (RCTs) in heart failure.24 Despite this, these agents have not been emphasized in most guidelines because of the lack of clinical outcome data from RCTs demonstrating that they improve outcomes when used to treat hypertension.

CCBs reduce BP,4,5 are effective antianginal agents, and have no adverse effects on glucose tolerance or lipid parameters. CCBs are especially effective at smoothing BP variability, which is an independent risk factor for stroke. Systematic reviews have shown CCBs (particularly amlodipine) to be the most cost-effective treatment option for hypertension, mainly because they are the most effective agent at preventing stroke.4,5,23 BP response to CCBs is largely determined by the magnitude of BP elevation, more so than with other drugs. Thus, patients with higher baseline BP experience greater BP lowering with CCBs than those with only modest elevations of BP. This property also may explain the smoothing effect of CCBs on BP variability.

There are two main groups of CCBs: the dihydropyridines (e.g., amlodipine, nifedipine) and the nondihydropyridines (e.g., diltiazem, verapamil). The dihydropyridine (DHP) CCBs act mainly by inducing relaxation of arterial smooth muscle by blocking l-type calcium channels, thereby inducing a fall in PVR and arterial pressure. Nondihydropyridine (non-DHP) CCBs block calcium channels in cardiac muscle and reduce cardiac output. Verapamil has an additional antiarrhythmic action through its effects on the atrioventricular node.

DHP and non-DHP CCBs have occasionally been combined, but no robust data are available on the BP-lowering efficacy or clinical outcomes of this approach, and it is not a recommended combination therapy in international guidelines.

Earlier formulations of some DHP CCBs, such as capsular nifedipine, had a rapid onset and a short duration of action, with unpredictable effects on BP. These responses were often accompanied by reflex sympathetic stimulation and tachycardia. These shorter-acting oral preparations of CCBs have no place in the routine management of hypertension. Longer-acting formulations of DHP CCBs produce more sustained and predictable responses.

Side effects of DHP CCBs include dose-dependent peripheral edema, which is caused by transudation of fluid from the vascular compartments into the dependent tissues as a result of precapillary arteriolar dilation. This edema does not respond to diuretic therapy but is alleviated by limb elevation or coadministration of an ACE inhibitor or ARB (because of their effects on venous capacitance). Gum hypertrophy can occur with DHP CCBs but is rarely seen with non-DHP CCBs. Non-DHP CCBs cause less peripheral edema but are negatively inotropic and negatively chronotropic and should therefore be avoided in patients with compromised left ventricular function and in combination with β-blockers. Verapamil use is commonly accompanied by constipation.

Renin-Angiotensin System Blockers

Inhibition of RAS is predictably effective at lowering BP by inhibiting the various central and peripheral pressor effects of angiotensin II (Ang II). Blockade of RAS also may lower BP by other mechanisms involving improvements in endothelial function, vagal tone, and baroreceptor function and through inhibition of the kidney tubular reabsorption of sodium. In addition, RAS inhibition has been popularized by clinical trial evidence showing reduced morbidity and mortality in patients with heart failure, delayed progression of kidney disease, and reduced CV events in those at high CV risk.[6,7,9] Two major classes of drugs directly target the RAS, ACE inhibitors, and ARBs. Direct renin inhibitors were also developed for this purpose but have declined in use and are not recommended for routine treatment of hypertension in international guidelines because of a lack of evidence that they improve CV outcomes.

Angiotensin-converting enzyme inhibitors. ACE inhibitors block the conversion of Ang I to Ang II by inhibiting ACE. The resulting reduction in levels of Ang II leads to vasodilation and a fall in BP. Ang II has many additional actions that are potentially harmful to the CV system and has been implicated in the pathogenesis of structural changes in the heart, blood vessels, and kidneys in hypertension. Sharp falls in BP after the introduction of ACE inhibitors may occur when the RAS is activated (e.g., in patients who are dehydrated, in heart failure, or have accelerated hypertension). This is rarely a problem when therapy is initiated in uncomplicated hypertensive patients.

Side effects of ACE inhibitors include the development of a persistent dry cough in about 20% of users. This is more common in women and in people from East Asia and the Pacific Rim. The cough disappears only after discontinuation of the drug. Another rare but important complication is angioedema, which occurs in about 1% and is much more common in the Black population (~4%). ACE inhibitors should be avoided in women of childbearing potential because of the danger of fetal malformation, especially from exposure in the first trimester, when women may be unaware they are pregnant. ACE inhibitors should not be used in patients with significant bilateral renal artery disease because they may precipitate deterioration in kidney function and kidney failure. Careful monitoring of kidney function and serum potassium concentration is also required in patients with more advanced kidney impairment of any cause, because of the risk for hyperkalemia.

Angiotensin receptor blockers. ARBs are highly selective inhibitors of the Ang II type 1 receptor (AT1). As with ACE inhibitors, ARBs inhibit the actions of Ang II on the CV system and kidney. ARBs reduce BP as effectively as ACE inhibitors and generally have a longer duration of action. ACE inhibitors and ARBs appear to be equally effective in reducing albuminuria and preserving GFR24 and have similar efficacy for preventing major CV events in patients with established CVD.4,25 Because of their selectivity and specificity for the AT1 receptor, the ARBs are well tolerated, with a placebo-like adverse effect profile. Cough and angioedema are much less likely to occur with ARBs than with ACE inhibitors, and most guidelines recommend switching patients to an ARB when an ACE-induced cough occurs. Cautions and contraindications are similar to those outlined for ACE inhibitors.

α-Adrenergic Blockers

The original members of the α-adrenergic blocking class (e.g., prazosin) were short-acting drugs that blocked the activation of α1adrenoceptors in the vasculature, leading to vasodilation. Initially, the recommended dosage was too high, and postural hypotension and syncope were frequent. The use of lower doses and the development of longer-acting agents (e.g., doxazosin) have largely overcome this problem. Blockade of sphincteric receptors improves symptoms in men with benign prostatic hypertrophy but can worsen stress incontinence in women. Uniquely among antihypertensive drugs, the α1antagonists produce modest favorable changes in plasma lipids, with a reduction in total and LDL cholesterol and triglyceride levels and an increase in HDL cholesterol. α1-Antagonists are not recommended for routine treatment of hypertension and are largely reserved for their specific indications (e.g., prostatic outflow obstruction) or as “add-on” treatment for resistant hypertension when alternative treatments are not tolerated.

Centrally Acting Sympatholytic Drugs

Some of the earliest drugs developed to treat hypertension targeted the activation of the sympathetic nervous system (SNS) at various levels, including the CV regulatory nuclei in the brainstem, the peripheral autonomic ganglia, and the postganglionic sympathetic neuron. Few of these agents are used today because side effects are common. Methyldopa reduces sympathetic outflow from the brainstem and frequently causes sedation, impaired psychomotor performance, dry mouth, and erectile dysfunction. Its unfavorable effect on quality of life resulted in methyldopa being gradually replaced by more effective drugs, although it is still extensively used in the management of hypertension of pregnancy, which is now its main indication.

Clonidine is now rarely used because of its short duration of action and risk for withdrawal syndrome, which occurs when sudden discontinuation results in a rebound rise in catecholamines with features that may resemble those of pheochromocytoma, such as severe hypertension, tachycardia, and sweating. This is exacerbated when patients are also receiving nonselective β-blockers such as propranolol. The syndrome is treated by readministration of the drug and then gradual discontinuation or the intravenous infusion of labetalol in an emergency. Clonidine is still used occasionally and can be effective in some patients with resistant hypertension. Extended-release formulations of clonidine are now available.

A newer centrally acting agent, moxonidine, is an imidazoline receptor agonist that reduces sympathetic outflow and BP. It has a lower incidence of side effects and is better tolerated than other centrally acting agents. Moxonidine has no clinical trial evidence to support its use as a preferred first-line agent but is used empirically in some patients intolerant of other agents or in resistant hypertension.

Direct Vasodilators

Hydralazine is no longer recommended as a first-line agent for hypertension management. The main disadvantages of hydralazine are sympathetic activation and the development of a lupus-like syndrome, particularly in patients with the slow acetylator genotype. Also, multiple daily dosing is required. It is still very occasionally used in severe hypertension and hypertension associated with pregnancy.

Minoxidil is a potent vasodilator, and its use is largely confined to occasional use in specialist centers for the treatment of severe and resistant hypertension. Its side effect profile includes stimulation of body hair growth; tachycardia and severe fluid retention reflect its potent vasodilator action and concomitant reflex SNS activation. For this reason, minoxidil is usually combined with a potent loop diuretic and a β-blocker as part of a triple-therapy approach to severe hypertension. Long-term use can be associated with insidious development of peritoneal and pericardial effusions (especially in patients with impaired kidney function), which usually respond to treatment withdrawal.

Emerging Drug Therapies for Hypertension

ARB/Neprilysin Inhibition

Treatment with an angiotensin receptor neprilysin inhibitor (ARNI; e.g., sacubitril) has become well established in heart failure and improves patient outcomes compared with prior standard of care.26 The ARNI effectively lowers BP over 24 hours, especially nocturnal BP, and is more effective than ARB alone.27,28 The BP lowering effect relates to the mechanism of action whereby neprilysin (NEP) inhibition blocks the breakdown and potentiates the actions of natriuretic peptides, producing a diuretic and vasodilator action that is augmented by concomitant RAS blockade with the ARB component. Although the ARNI has not been widely promoted to treat hypertension, there is ample data showing its efficacy at BP lowering, and it has the potential to be a highly effective and well-tolerated treatment, either alone or in combination with either a CCB and/or thiazide diuretic.

Sodium-Glucose Cotransporter-2 Inhibitors

These drugs (e.g., empagliflozin and dapagliflozin) were developed as treatments to lower blood glucose in patients with diabetes by inhibiting the active proximal convoluted tubular reabsorption of glucose via inhibition of sodium-glucose cotransporter-2 (SGLT2). Thus, SGLT2-inhibition also inhibits the proximal tubular reabsorption of sodium, promoting natriuresis, particularly if additional diuretics are present. This inevitably results in significant reductions in BP that are rarely commented upon but have been clearly documented.29,30 It is likely that the natriuresis and BP-lowering effects of SGLT2 inhibition have contributed to improved CV outcomes and kidney outcomes in patients with diabetes, and heart failure outcomes in patients with and without diabetes.30-32 In the context of difficult-to-control hypertension, especially in patients with diabetes, SGLT2 inhibition may complement and enhance the BP-lowering effect of other agents, even though not formally recommended for this purpose.

An intriguing aspect of treatment with drugs with diuretic actions that promote natriuresis is that they seem to be particularly effective at reducing nocturnal BP.28 This is often not appreciated as nocturnal BP is rarely recorded unless ABPM is performed. However, this may be important because nocturnal BP is the most powerful predictor of adverse outcomes and death in patients with hypertension and is more likely to be elevated in high-risk patients with diabetes and/or CKD, perhaps because of their predisposition to sodium retention.

Hypertension Treatment Strategies

Despite decades of guidelines for the treatment of hypertension, the control of BP has remained lamentably poor, with typically fewer than 50% of treated patients achieving optimal BP control.33 This relates to a number of factors that have been inadequately appreciated: (1) the complexity of guidance and overemphasis on specific indications for individual drug therapies versus the overriding importance of getting BP controlled; (2) treatment inertia (i.e., the slow uptitration of therapy and/or failure to escalate treatment by combining drugs to achieve BP control); and (3) poor recognition of the fact that poor adherence to therapy, especially multipill therapy, was a major factor in poor BP control; that is, the BP was not so much resistant to treatment as the patient was resistant to taking multiple drugs.

Recent iterations of the US and European guidance have aligned and dramatically shifted their approach by advocating the following:

1. Similar preferred drug classes for the routine treatment of hypertension, ACE inhibition or ARBs, CCBs, thiazide/thiazide-like diuretics (the US guidance specifically prefers chlorthalidone).
2. Simple and pragmatic treatment algorithms based on treatment with RAS blockade (ACE inhibition or ARB) as the foundation of therapy for most patients, in combination with a CCB and/or a thiazide/thiazide-like diuretic, or all three when required.
3. Initial therapy with two drugs, that is, RAS blockade plus a CCB or thiazide/thiazide-like diuretic for most patients when BP is 140/90 mm Hg or higher and certainly when 20/10 mm Hg or higher above the intended target—the exceptions being the frail elderly where monotherapy may be preferred, or patients with BP just above 140/90 mm Hg, when monotherapy may be sufficient. This recommendation effectively normalizes initiating therapy with two drugs for most people with hypertension.
4. Single-pill combination therapy for dual- and triple-drug therapy, when available at reasonable cost, to reduce the pill burden and improve patient adherence. The European guideline specifically advocates a “single-pill strategy” to treat hypertension.7
5. A three-drug combination (i.e., RAS blockade plus CCB plus thiazide/thiazide-like diuretic when the two-drug combination is insufficient).
6. Further diuretic therapy (usually spironolactone unless contraindicated) if further treatment is required (i.e., in resistant hypertension; see “Resistant Hypertension” section).
7. Use β-blockers when there is a guideline-directed indication for their use (e.g., in patients with symptomatic angina, heart failure with reduced ejection fraction, or in patients with atrial fibrillation to facilitate rate control) (Fig. 37.3). The US guidance does not contain a formal treatment algorithm, but the guidance in the US and Europe is very consistent on the treatment strategy8 (Table 37.9).

Initial Therapy With a Two-Drug Combination

The lower BP targets recommended in current guidelines makes twodrug combinations almost inevitable for the majority of patients as initial therapy, with the preferred combinations RAS blockade plus diuretic or RAS blockade plus CCB. This will often be a “low-dose” two-drug combination therapy. The recommendation of a two-drug

European Core Drug Treatment for Uncomplicated Hypertension

1 pill

Initial therapy
Dual combination

ACEi or ARB + CCB or diuretic

1 pill

Step 2
Triple combination

ACEi or ARB + CCB + diuretic

Step 3
Triple combination +
spironolactone or
other drug

Resistant hypertension
Add spironolactone (25–50 mg once daily)
or other diuretic, α-blocker or β-blocker

2 pills

Consider monotherapy in
low-risk grade 1 hypertension
(systolic BP < 150 mm Hg), or in
very old (≥80 years) or
frailer patients

Consider referral to a specialist
center for further investigation

β-Blockers
Consider β-blockers at any treatment step, when there is a specific indication for their use, e.g., heart failure, angina, post-MI, atrial fibrillation,
or younger pregnant women or those planning pregnancy

Fig. 37.3 European Core Drug Treatment Algorithm for Uncomplicated Hypertension. This algorithm is also considered appropriate for patients with hypertension-mediated organ damage, cerebrovascular disease, diabetes, or peripheral vascular disease. ACEi, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; MI, myocardial infarction.
(From Williams B, Mancia G, Spiering W, et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Eur Heart J. 2018;39[33]:3021-3104. Erratum Eur Heart J. 2019;40[5]:475.)

US Guidance for Approach to
Drug Therapy for Hypertension

TABLE 37.9
Grade

	LOE	Recommendation
Recommendation for Choice of Initial Medication		
I	A	For initiation of antihypertensive drug therapy, firstline agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.
Recommendation for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy		
I	C	Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, recommended in adults with stage 2 hypertension and an average BP >20/10 mm Hg above their BP target.
IIa	C	Initiation of antihypertensive drug therapy with a single antihypertensive drug reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve BP target.

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; LOE; level of evidence.

From Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127–e248. Erratum J Am Coll Cardiol. 2018;71(19):2275–2279.

combination is in part driven by concern that the upward titration of treatment in people at high risk may be too slow and leave them at risk for too long. A two-drug combination is also logical because the response to a single drug is often limited by counteractivation of pressor systems. This also explains why many BP-lowering drugs in monotherapy have a relatively flat dose-response curve. For example, sodium and water loss caused by diuretics or vasodilation with CCBs will activate the renin-angiotensin-aldosterone system, which limits the BP lowering. Thus, a two-drug combination as initial therapy (1) will produce much greater BP lowering than even the most effective monotherapy; indeed, studies have shown this approach is twice as effective as monotherapy at achieving BP control within 3 to 4 months[34]; (2) will reduce heterogeneity in the BP-lowering response, ensuring that all patients get a response because more than one mechanism is being targeted by a two-drug approach; and (3) will cause the dose-response to be steeper to upward titration of either component because counterregulatory mechanisms are blocked.

The main concern has been adverse events related to potentially large initial BP falls in treatment-naïve patients, but in practice this has not been a major problem, even in older patients, and guidelines already highlight the one group where there may be a need for a more cautious approach to lowering BP (i.e., frail older patients). Ironically, adverse effects may actually be minimized rather than enhanced by the recommended combinations of therapy (i.e., less CCB-mediated peripheral edema) or diuretic-induced hypokalemia when either is combined with RAS blockade.

Further advantages of combination therapy. Now that the major classes of antihypertensive therapy recommended by guidelines are available as generic agents, the costs have reduced substantially, and the same is true for single-pill combinations of two drugs as well

Nonadherence to Antihypertensive Therapy

% of nonadherent individuals

80

60

40

20

0
1

2
3
4
5
6+
Number of prescribed antihypertensive medications

Fig. 37.4 Nonadherence to Antihypertensive Therapy According to Number of Antihypertensive Medications, as Detected by Urine Drug Testing. Green bars denote data from the United Kingdom; red bars denote data from the Czech Republic. (Modified from Gupta P, Patel P, Štrauch B. Risk factors for nonadherence to antihypertensive treatment. Hypertension. 2017;69[6]:1113–1120.)

as two drugs. This makes guideline implementation more feasible globally, especially for single-pill combinations, because the number of pills used to treat hypertension is inversely related to patient adherence35 (Fig. 37.4). If a patient’s BP is not controlled on three or more drugs, then poor adherence to at least some of the drugs should be considered and excluded as a likely cause of the poor treatment response. The converse is also true; that is, if the patient receives two or three drugs as a single-pill combination, then they are more likely to be adherent to their therapy and are more likely to achieve their BP treatment target.

Registry data shows that patients starting treatment with a twodrug combination are more likely to achieve BP control faster and more likely to escalate to a three-drug combination if needed compared with patients starting treatment with monotherapy and a traditional stepped care approach, many of whom remain on monotherapy despite inadequate BP control. This indicates that the two-drug initial therapy approach, especially with a single-pill combination, is effective at overcoming clinical inertia36 37 (Fig. 37.5).

Finally, whereas no RCTs have compared initial combination therapy versus a standard stepped care approach, large-scale registry studies have suggested that initial combination therapy for hypertension is associated with improved CV outcomes compared with a standard initial monotherapy, stepped care approach, most likely due to faster and more effective BP control with the combination therapy38 (Fig. 37.6).

Triple or quadruple low-dose combination therapy as initial therapy for hypertension. Enthusiasm for low-dose combinations of therapy involving multiple drugs is growing, fueled by the philosophy that targeting multiple pressor mechanisms simultaneously produces more effective BP lowering, and that most BP lowering and fewer side effects occur when drugs are used in low dose. Indeed, studies thus far have found that a pill containing four agents (quad pill) in low dose is more effective at lowering BP than standard dose monotherapy,39 but what has not been studied is whether the quad pill would be more effective than low-dose dual therapy, which is now becoming the standard of care and is also much more effective than standard dose monotherapy. Thus, low-dose combination of three or four drugs is considered experimental and not currently recommended.

Combining Renin-Angiotensin System Blockade Is Not Recommended

The view that RAS blockade may help prevent or regress hypertensionmediated structural and functional damage led to the use of dual RAS blockers. However, data from numerous trials has demonstrated that dual RAS blockade was no more effective than RAS blocker monotherapy at preventing major CV events in high-risk populations, including those with diabetes,6 7 but increased the risk for adverse events, especially kidney impairment. These findings have prompted all international guidelines to state that dual RAS blockade should not be used to treat hypertension.

Resistant Hypertension

Standardizing the routine treatment of hypertension has also helped refine the definition of resistant hypertension (RH). RH is defined as a BP that remains above target despite the concurrent use of three guideline recommended antihypertensive agents, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic in optimal or maximum tolerated doses. The US guidance also includes patients with controlled BP when four different drugs have been required to achieve BP control. The definitions emphasize that causes of “pseudoresistant” or “apparent resistant” hypertension should be excluded. These include (1) ensuring proper measurement of office BP with an appropriately sized cuff (note that a cuff that is too small for the arm can lead to overestimation of BP); (2) the use of ABPM or home BP to exclude a significant white coat effect, which elevates BP only in the doctors’ office setting; and (3) exclusion of nonadherence to therapy. Finally, secondary causes of hypertension, such as primary aldosteronism and renovascular disease, should be excluded. Other causes of resistant hypertension also should be considered (Table 37.10). Once this screen is complete, analysis of recruitment into clinical trials of patients with resistant hypertension has consistently shown that as many as 9 out of 10 patients originally considered to have resistant hypertension are excluded, principally because of suboptimal therapy, controlled BP on ABPM or home measurements, or nonadherence to their prescribed therapy. Most patients with resistant hypertension are older, obese, and/or have evidence of target organ damage.40-42

Multidrug Therapy Categorized by Start With Monotherapy or
Two-Drug Combination Therapy
100
6 months

Patients under multidrug treatment (%)

90

1 year

2 years

3 years

80
70
60
50
85

40

82

79

78

30
20
10

27

22

36

32

0
Monotherapy

Combination
Monotherapy Combination
Monotherapy Combination
Monotherapy Combination
therapy
therapy
therapy
therapy

Fig. 37.5 Percent of patients receiving multidrug combination therapy according to whether they started treatment with monotherapy or two-drug combination therapy. (From Rea F, Corrao G, Merlino L, Mancia G. Initial antihypertensive treatment strategies and therapeutic inertia. Hypertension. 2018;72[4]:846–853.)

Major Outcomes of Monotherapy or Two-Drug Combination Therapy

Treatment strategy

Outcome

HR (95% CI)

P value

Any CV events
Monotherapy
Combination therapy

1.00 (Ref)
0.84 (0.79 to 0.90)

< .001

Heart failure
Monotherapy
Combination therapy

1.00 (Ref)
0.65 (0.51 to 0.82)

< .001

Cerebrovascular disease
Monotherapy
Combination therapy

1.00 (Ref)
0.85 (0.74 to 0.98)

.027

Ischemic heart disease
Monotherapy
Combination therapy

1.00 (Ref)
0.80 (0.71 to 0.91)

< .001

Death
Monotherapy
Combination therapy

1.00 (Ref)
0.80 (0.72 to 0.89)

Favors combination
therapy
0.50
0.75
1.00

Fig. 37.6 Major outcomes in patients initially treated for hypertension with monotherapy or two-drug combination therapy. CI, Confidence interval; CV, cardiovascular; HR, hazard ratio. (From Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial 2-drug fixed-dose combination treatment vs. monotherapy in hypertension. Eur Heart J. 2018;39[40]:3654–3661.)

< .001

TABLE 37.10

Considerations in the Patient With Resistant Hypertension

Patient Factors
Demographics
Older age, especially >75 y
Obesity
Women > men
More common in Blacks
Excess dietary sodium
High baseline BP and chronicity of uncontrolled hypertension
Concomitant Disease
Target organ damage: LVH or CKD
Diabetes
Atherosclerotic vascular disease
Aortic stiffening

Secondary Causes of Resistant Concomitant Medications That
Hypertension
May Raise BP
Common causes
Primary hyperaldosteronism (Conn adenoma)
Atherosclerotic renovascular disease
Sleep apnea
CKD
Uncommon Causes
Pheochromocytoma
Aortic coarctation
Cushing disease
Hyperparathyroidism

Prescription
Oral contraceptives
NSAIDs
Sympathomimetics (e.g., decongestants in cold remedies)
Cyclosporine
Erythropoietin
Corticosteroids (e.g., prednisone, hydrocortisone)
Nonprescription
Drug abuse (e.g., cocaine, amphetamines)
Excess licorice ingestion
Herbal remedies (e.g., ephedra, also known as ma huang)

Causes of “Pseudoresistant Hypertension”
Poor patient adherence to medications
Check BP response to directly observed medication
Errors in BP Measurement
Including BP cuff too small for arm circumference
White coat hypertension
Check BP with ABPM or home BP

measurements

ABPM, Ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; NSAIDs, nonsteroidal antiinflammatory drugs.
Modified from Williams B. Resistant hypertension: an unmet treatment need. Lancet. 2009;374:1396–1398.

The PATHWAY-2 study of resistant hypertension showed resistant hypertension is most commonly a sodium-retaining state with an inappropriately suppressed plasma renin level, despite background treatment with diuretic therapy and other drugs (i.e., CCB and RAS blockade) that would be expected to raise plasma renin.19 This has two important therapeutic implications: (1) there should be increased emphasis on dietary sodium restriction, and (2) treatment with further diuretic therapy is likely to be the most effective additional therapy as the fourth-line drug treatment for RH. This was tested and most convincingly proven in the PATHWAY-2 study, which showed that low-dose spironolactone (25 mg daily, titrated to 50 mg daily) was the most effective drug at lowering BP compared with placebo, a β-blocker (bisoprolol), or α-blocker (doxazosin).17 This emphasizes a key point: although spironolactone is a relatively weak diuretic as a sole agent, when combined with other diuretics acting at a different site in the nephron (as in the treatment of resistant hypertension on a background of thiazide/thiazide-like diuretic), this multisegment nephron blockade can be highly effective at offloading sodium in sodium-resistant states. It is also conceivable that spironolactone was particularly effective because some of these patients may have undetected primary aldosteronism.

However, the PATHWAY-2 study was conducted in patients with normal GFR, and careful monitoring for hyperkalemia is required when using spironolactone, especially in patients with a baseline potassium level above 4.5 mmol/L or GFR less than 45 mL/min/1.73 m2. shiftenterA more recent study in patients with advanced CKD (GFR 25 to ≤45 mL/min/1.73 m2) and resistant hypertension (the AMBER study) evaluated whether coadministration of patiromer (as potassium-binding polymer) with spironolactone could facilitate the safer use of spironolactone in these patients.43 The study showed that hyperkalemia with spironolactone occurred much less commonly (1%) in patients coadministered patiromer versus spironolactone (7%), and BP was lowered significantly after the addition of spironolactone in these patients. The PATHWAY-2 study showed that amiloride in higher doses that were usually administered (10–20 mg daily) was as effective at spironolactone at lowering BP in resistant hypertension,19 but as with all potassium-sparing diuretics, similar caution is needed with respect to potassium levels. Other theoretical (but not proven) alternatives to spironolactone for treatment of resistant hypertension include eplerenone, higher doses of thiazide-type diuretics, loop diuretics in place of thiazide diuretics in patients with GFR less than 45 mL/min/1.73 m2, the newer generation of nonsteroidal mineralocorticoid receptor antagonists, or even potentially newer drugs with multinephron segment diuretic actions such as ARNIs and SGLT2 inhibitors (see earlier).

Finally, treatments beyond further diuretic therapy may be effective for some patients with RH; for example, both doxazosin and bisoprolol did lower BP more effectively than placebo in the PATHWAY-2 study, though not as effectively as spironolactone. Alternatively, clonidine has also been shown to be effective at lowering BP in RH.44 For patients where all else has failed, it may be necessary to resort to a combination of minoxidil, loop diuretic, and β-blocker to improve BP control.

Pharmacologic Treatment of Hypertension With Specific Comorbidities or in Specific Patient Groups

Hypertension With Diabetes, or Cerebrovascular Disease, Peripheral Vascular Disease, or Hypertension-Mediated Organ Damage

The core drug treatment algorithm in the European guidance (Fig. 37.3) is recommended for patients with uncomplicated hypertension, those with hypertension-mediated organ damage (e.g., LVH), or those with diabetes, cerebrovascular, or peripheral vascular disease.7 The only caveat is that the core algorithm may need to be modified in those with other comorbidities such as coronary artery disease (CAD), heart failure, or significant CKD (see later). The US guidance6 does not show a specific treatment algorithm but instead emphasizes which drug classes have compelling indications for specific clinical comorbidities—this generally leads to similar treatment as the European guidance for these conditions.

Hypertension in Patients With Coronary Artery Disease

All guidance acknowledges that in hypertensive patients with stable CAD, RAS blockers and β-blockers may improve outcomes post-MI, and that in patients with symptomatic angina, β-blockers and CCBs would be preferred components of the drug treatment strategy. Thus, combination therapy for patients with stable CAD differs little from the core treatment strategy, except for the addition of β-blockers as required.

Hypertension in Patients With Heart Failure

Heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) are common consequences of long-standing hypertension. Patients with HFrEF and hypertension should already be treated with guideline-directed therapy for their heart failure, including ACE inhibitors or ARBs, β-blockers, and mineralocorticoid receptor antagonists (e.g., spironolactone and eplerenone). If further BP lowering is required, thiazide/thiazide-like diuretics or DHP CCBs may be considered. ARNI therapy (sacubitril/valsartan) lowers BP (see earlier) and improves outcomes in patients with HFrEF, and it is indicated for the treatment of HFrEF as an alternative to ACE inhibitors or ARBs. In addition, SGLT2 inhibitors improve outcomes for patients with HFrEF (both diabetic and nondiabetic patients) and also more recently in HFpEF, and they may be considered for patients with heart failure to further reduce BP if required. Non-DHP CCBs (diltiazem and verapamil), α-blockers, and centrally acting agents, such as moxonidine, should not be used in patients with heart failure.

BP lowering is commonly required in patients with HFpEF. Effective treatments for HFpEF are less clearly defined, and in most patients, treatment will follow similar principles to the treatment of HFrEF. If volume overload is present, diuretics will be required.

Hypertension in Patients With Chronic Kidney Disease

There is consensus that RAS blockade should be part of drug treatment for hypertension in patients with CKD, especially when albuminuria or proteinuria are present.6,7,9 This would usually be prescribed with a CCB or diuretic, the latter specifically required when volume overload is evident, but required in most patients with more advanced CKD when three or more drugs may be required to control BP. Other key considerations are that (1) thiazide/thiazide-like diuretics often become less effective when eGFR is less than 45 mL/min/1.73 m2 and certainly when less than 30 mL/min/1.73 m2, and will need to be replaced with a loop diuretic if a diuretic is required; and (2) hyperkalemia becomes more of a concern, especially with potassium-sparing diuretics when eGFR is less than 45 mL/min/1.73 m2 or baseline potassium levels are greater than 4.5 mmol/L.

Hypertension in Women

For a detailed discussion of this topic, the reader is referred to the US and European guidance,6,7 but it is important to highlight some specific considerations: (1) oral contraceptives (OCP), particularly those containing estrogen, may result in a significant rise in BP in about 5% of women, and thus BP should be carefully monitored and an alternative OCP formulation or form of contraception will usually be required in those who develop significant elevations of BP; (2) menopause is associated with an increased risk of hypertension, and the presence of hypertension is not a contraindication to hormone replacement therapy, provided that BP can be controlled; (3) in patients who are hypertensive and planning a pregnancy (i.e., prepregnancy hypertension), careful consideration should be given to whether BP medication is needed before consensus; when treatment is required, RAS blockers should be avoided, and the safest options are methyldopa, labetalol, or CCBs; there is controversy about whether diuretics should be used; and (4) postpregnancy, prescribers should refer to local formulary guidance regarding which drugs are safe to use when breastfeeding.

Hypertension in People of Black African Origin

Hypertension is more prevalent in Black patients, is associated with more target organ damage, and carries a worse prognosis, with a particularly high risk for stroke.45 Black patients tend to respond better to diuretics, CCBs, and dietary salt restriction than White patients. ACE inhibitors, ARBs, and β-blockers are generally less effective as initial therapy in Black patients but become more effective in combination with diuretics or CCBs. When a RAS blocker is used as part of the treatment strategy, an ARB may be preferred because of the increased risk for angioedema with ACE inhibitors in Black patients.

Hypertension in Older People

If a BP of 140/90 mm Hg or higher is used to define hypertension, more than 70% of people older than 60 years will be hypertensive—most of these patients having isolated systolic hypertension (ISH). Surveys suggest that physicians consistently underestimate the risks and undertreat hypertension in older people. However, important considerations in treating older people include the following:

1. The arterial wall stiffening that gives rise to systolic hypertension and increased pulse pressure is also associated with impaired baroreflex sensitivity with increased risk for orthostatic hypotension. Thus, it is important to record lying and standing BP readings in elderly patients. However, contrary to popular perception, BPlowering therapy has not been associated with increased risk of falls, even with lower BP goals now being advocated.
2. GFR declines with age, and older patients are more susceptible to reductions in GFR with BP lowering. In addition, they also often have impaired kidney conservation of sodium and fluid and may be more susceptible to volume depletion as a result of diuretic therapy.
3. Clearance of drugs and their active metabolites is decreased as a result of reduced hepatic and kidney function.
4. Cardiac function and reserve are often reduced, and patients are therefore much more likely to develop cardiac failure. Trials in elderly patients have consistently shown that treatment of hypertension reduces morbidity and mortality from cardiac failure.
5. Multiple comorbidities are much more common with advancing age, and this heterogeneity of patients means that actual age is a less important determinant of an individual patient’s tolerability of BP lowering than their functional independence.
6. Communication and adherence with therapy may be more difficult with decline in cognitive function.

Despite these considerations, age should never be considered a contraindication to treatment, as most older patients will generally tolerate BP-lowering medications well, and BP reduction leads to substantial benefits, reducing the risk for stroke, coronary events, heart failure, and possibly dementia.46 As a general rule, dosages should be increased more gradually and monotherapy initiation should be considered in older patients who are frail. Therapy needs to be tailored to individuals, remembering that elderly participants in clinical trials tend to be fitter and more independent than the many millions of elderly patients to whom guidelines are applied. However, it is reassuring for patients and families that the benefits are substantial if effective BP lowering can be achieved and is tolerated. Finally, there is a paucity of data with regard to treatment strategies for the most frail and dependent elderly patients, often with limited life expectancy, which in many cases is unlikely to be influenced by treatment of hypertension. Treatment decisions for such patients have to be individualized in consultation with the patient, family, and carers.

Concomitant Medication to Reduce Cardiovascular Risk

Treating hypertension should be considered part of a more comprehensive strategy to reduce CVD risk. Various tools to assess CVD risk, usually over a 10-year time frame, are available. The proposed level of CVD risk considered sufficient to warrant additional interventions has been progressively reduced toward 10% CVD risk over 10 years, and more recently, estimation of lifetime risk has been advocated.47 Patients at high risk (i.e., with established CVD, organ damage, or diabetes or with a high calculated CVD risk) should be considered for additional interventions to reduce risk (i.e., reinforcement of lifestyle advice, especially smoking cessation). In addition, routine use of statins to reduce total cholesterol values by 40 mg/dL (~1 mmol/L) reduces the risk for coronary events by about one-third and for stroke by about one-fifth above the benefit already accrued from BP lowering.48,49 Moreover, this risk reduction associated with statin therapy is not dependent on a high baseline cholesterol value. Hypertensive patients should be considered for treatment with antiplatelet drugs once BP has been controlled for secondary prevention (i.e., in those with established CVD or cerebrovascular disease).

Follow-up

In the early stages of treatment, the frequency of monitoring will be determined by the patient’s response to therapy, the comorbidities, and the complexity of the treatment regimen required to control the BP. After initiating therapy, patients should be reviewed frequently to adjust treatment, monitor for adverse effects, and establish BP control. Once BP is controlled, patients should be reevaluated at least annually for a formal review, and most will be reevaluated every 6 months.

Patients are increasingly monitoring their own BP between appointments, and this trend is likely to increase.

Withdrawal of Therapy

Most patients with hypertension require lifelong therapy. Some with milder hypertension who make major adjustments to their lifestyle may obtain sufficient fall in their BP to warrant safe withdrawal of monotherapy. However, patients with target organ damage or those at high CVD risk usually should not have their therapy withdrawn unless there is a compelling clinical reason.6 7 In patients with previously severe hypertension that has subsequently been well controlled, treatment withdrawal may not result in an immediate increase in BP, which can sometimes take many months to return to dangerously high values. Any patient who discontinues therapy must remain under review with regular BP monitoring. All but a very few will require treatment again.

Indications for Specialist Referral

Referral to a specialist center is sometimes indicated for the patient in management of hypertension. Indications include uncertainty about

Patient Characteristics That Should Raise Suspicion of Secondary Hypertension, and/or Circumstances That Should Prompt Consideration of Patient Referral to a Specialist Center for Further Evaluation

BOX 37.1

- Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
- Acute worsening of hypertension in patients with previously documented chronically stable normotension
- Resistant hypertension (BP uncontrolled despite treatment with optimal best-tolerated doses of three or more drugs including a diuretic, and confirmed by ABPM or HBPM)
- Severe (grade 3) hypertension or a hypertension emergency
- Presence of extensive HMOD
- Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD
- Clinical features suggestive of an OSA
- Symptoms suggestive of pheochromocytoma or family history of pheochromocytoma

Modified from Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104. Erratum Eur Heart J. 2019;40(5):475.

ABPM, Ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; HBPM, home blood pressure monitoring; HMOD, hypertension-mediated organ damage; OSA, obstructive sleep apnea.

the decision to treat, investigations to exclude secondary hypertension, severe and complicated hypertension, and resistant hypertension (Box 37.1).

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is true about combination therapy for the treatment of hypertension?
A. Combination therapy with two drugs is recommended as initial therapy only for patients younger than 65 years.
B. There are three- or four-drug single-pill combinations now available, which are recommended as initial therapy for patients with hypertension.
C. The recommended combinations of drug therapy for most patients with hypertension usually involve a RAS blocker combined with a CCB or diuretic.
D. Single-pill combination therapy is associated with worse adherence with therapy than free combination of the same drugs.
E. Combinations of an angiotensin-converting enzyme inhibitor and ARB are recommended for some specific patient groups with hypertension.
2. Which of the following statements is true of recommended BP targets for treated hypertensive patients?
A. Lowering BP to at most 140/90 mm Hg in all treated patients, if tolerated, is recommended by all guidelines.
B. The US guideline recommends routinely lowering BP to less than 120/80 mm Hg in high-risk patients.
C. The evidence for optimal BP targets is stronger for diastolic versus systolic BP.
D. All guidelines recommend the routine use of ambulatory or home BP monitoring for checking BP control in all patients.

E. The BP targets are similar for office, home, and ambulatory BP measurements.
3. Which of the following statements is true of drugs used to treat hypertension?
A. Thiazide diuretics are more effective than thiazide-like diuretics at lowering BP.
B. RAS-blocking drugs are suitable treatment for women of childbearing potential, either alone or as part of combination treatment, as long as they are discontinued by the third trimester in pregnant women.
C. β-Blockers are only used for specific guideline-directed indications and are especially effective as part of combination therapy in reducing the risk for stroke in older patients.
D. CCBs are less likely to reduce BP variability compared with other drug classes, especially in older patients.
E. Angiotensin receptor-neprilysin inhibitors are significantly more effective at lowering BP than ARBs alone.
4. Which of the following statements is true for RH?
A. RH is common, affecting approximately 30% of treated patients.
B. When patients are thoroughly investigated, RH is usually found to be due to a secondary cause of hypertension.
C. RH is more common in younger patients.
D. It is only rarely possible to control BP in RH with additional drug therapy.
E. RH is most effectively treated with further diuretic therapy.

REFERENCES

1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–1913.
2. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383:1899–1911.
3. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet. 2018;392(10159):2052–2090.
4. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–967.
5. The Blood Pressure Lowering Treatment Trialists’ Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet. 2021;397:1625–1636.
6. Whelton, P.K., Carey, R.M., Aronow, W.S., et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a Report of the American College of Cardiology/American heart association Task Force on clinical practice guidelines. J Am Coll Cardiol . 2018;71(19):e127–e248. Erratum: J Am Coll Cardiol. 2018;71(19):2275-2279.
7. Williams B, Mancia G, Spiering W, et al. ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104.
8. Whelton PK, Carey RM, Mancia G, Kreutz R, Bundy JD, Williams B. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: Comparisons, Reflections, and Recommendations. Circulation. 2022;146(11):868–877.
9. Philip R, Beaney T, Appelbaum N, et al. Variation in hypertension clinical practice guidelines: a global comparison. BMC Med. 2021;19(1):117.
10. Muntner, P., Einhorn, P.T., Cushman, W.C., et al. 2017 National Heart, Lung, and Blood Institute Working Group. Blood pressure assessment in adults in clinical practice and clinic-based research: JACC scientific expert panel. J Am Coll Cardiol . 2019;73(3):317–335.
11. Stergiou GS, Palatini P, Parati G, et al. European society of hypertension council and the European society of hypertension working group on blood pressure monitoring and cardiovascular variability. 2021 European society of hypertension practice guidelines for office and out-of-office blood pressure measurement. J Hypertens. 2021;39(7):1293–1302.
12. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–2116.
13. Zhang W, Zhang S, Deng Y, et al. Trial of intensive blood-pressure control in older patients with hypertension. N Engl J Med. 2021;385(14):1268–1279.
14. Drawz PE, Agarwal A, Dwyer JP, et al. Concordance between blood pressure in the systolic blood pressure intervention trial and in routine clinical practice. JAMA Intern Med. 2020;180(12):1655–1663.
15. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–2229.
16. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385(24):2252–2263.
17. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–2068.

18. Brown MJ, Williams B, Morant S, et al. Amiloride-hydrochlorothiazide versus individual diuretic effects on glucose tolerance and blood pressure

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(PATHWAY-3): a double-blind randomised trial. Lancet Diabetes Endocrinol. 2016;4(2):136–147.
Williams B, MacDonald TM, Morant SV, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. Lancet Diabetes Endocrinol. 2018;6(6):464–475.
Pepine CJ, Cooper-DeHoff RM. Cardiovascular therapies and risk of the development of diabetes. J Am Coll Cardiol. 2004;44:609–612.
Mason JM, Dickinson HO, Nicolson DJ, et al. The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension. J Hypertens. 2005;23:1777–1781.
Wiysonge C, Bradley H, Myose B, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2007;1:CD002003.
Webb AJS, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensivedrug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet. 2010;375:906–915.
Barnett AH, Bain SC, Bouter P, et al. Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin receptor blockade versus converting enzyme inhibition in type 2 diabetes with nephropathy. N Engl J Med. 2004;351:1952–1961.
ONTARGET Study Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547–1559.
McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.

Ruilope LM, Dukat A, Böhm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375(9722):1255–1266.

Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER study. Hypertension. 2017;69(3):411–420.

Kario K, Okada K, Kato M, et al. 24-Hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. Circulation. 2018;139(18):2089–2097.

Kario K, Ferdinand KC, Vongpatanasin W. Are SGLT2 inhibitors new hypertension drugs? Circulation. 2021;143(18):1750–1753.

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424.

NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 highincome countries: an analysis of 123 nationally representative surveys. Lancet. 2019;394(10199):639–651.

MacDonald TM, Williams B, Webb DJ, et al. Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. J Am Heart Assoc. 2017;6(11):e006986.

Gupta P, Patel P, Štrauch B, et al. Risk factors for nonadherence to antihypertensive treatment. Hypertension. 2017;69(6):1113–1120.

Rea F, Corrao G, Merlino L, Mancia G. Initial antihypertensive treatment strategies and therapeutic inertia. Hypertension. 2018;72(4):846–853.

Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77(2):692–705.

Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. Eur Heart J. 2018;39(40):3654–3661.

Chow CK, Atkins ER, Hillis GS, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, activecontrolled trial. Lancet. 2021;398(10305):1043–1052.

References

40. Myat A, Redwood SR, Qureshi AC, et al. Resistant hypertension. BMJ. 2012;345:e7473.
41. Williams B. Resistant hypertension: an unmet treatment need. Lancet. 2009;374:1396–1398.
42. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American heart association. Hypertension. 2018;72(5):e53–e90.
43. Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10208):1540–1550.
44. Krieger EM, Drager LF, Giorgi DMA, et al. Spironolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT randomized study (resistant hypertension optimal treatment). Hypertension. 2018;71(4):681–690.
45. Douglas JG, Bakris GL, Epstein M, et al. The Hypertension in African Americans Working Group. Management of high blood pressure in African Americans. Arch Intern Med. 2003;163:525–541.

46. Huang CJ, Chiang CE, Williams B, et al. Effect modification by age on the benefit or harm of antihypertensive treatment for elderly hypertensives: a systematic review and meta-analysis. Am J Hypertens. 2019;32(2):163–174.
47. Visseren FLJ, Mach F, Smulders YM, et al. ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2021;zwab154.
48. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. ASCOT Investigators. Lancet. 2003;361:1149–1158.
49. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediaterisk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–2031.

38

Evaluation and Treatment of Hypertensive Urgencies and Emergencies

Pantelis A. Sarafidis, George L. Bakris

Severe elevations in blood pressure (BP) can present as hypertensive emergencies or hypertensive urgencies.1–3 A hypertensive emergency is defined as severe elevation in BP associated with evidence of new or worsening target-organ damage, such as coronary ischemia, dissecting aortic aneurysm, pulmonary edema, acute kidney failure, papilledema, hypertensive encephalopathy, cerebral hemorrhage, and eclampsia. In these cases, both the rate and magnitude of an increase in BP are at least as equally important to the absolute BP level in determining the magnitude of organ injury. As such, although in most of these cases BP is usually greater than 180/120 mm Hg,1,2 there is no specific BP threshold to define hypertensive emergencies, and previously normotensive subjects can present with hypertension-mediated organ damage at lower BP levels.3 Hypertensive emergencies require immediate and careful intervention to reduce BP (not necessarily to normal), preferably with intravenous (IV) drug therapy in an intensive care unit (ICU) to limit further target-organ damage.1–3 A hypertensive urgency is the clinical situation of a patient who presents with severe BP elevation without acute or impending target organ dysfunction. These patients require a gradual BP reduction within hours with oral medications and do not normally require hospitalization.1,2,4

The term malignant hypertension first appeared in 1928 and described patients with extremely high BP values to emphasize that because of rapid target organ damage, their average prognosis was similar to that of most cancer patients.5 Subsequently, malignant hypertension is used to describe patients with greatly elevated BP and vascular damage that manifests as the bilateral presence of retinal flame hemorrhages and/or papilledema, which can be accompanied by encephalopathy, acute kidney injury, or thrombotic microangiopathy.2,3,6 Dramatic advances in both in-hospital and outpatient treatment have led to an improved prognosis of such cases and a decrease in 1-year mortality from 80% in 1928 to 50% in 1955 and to less than 10% after 1990.5,7

ETIOLOGY AND PATHOGENESIS

Hypertensive emergencies and urgencies can develop de novo in normotensive individuals but usually complicate underlying primary or secondary hypertension.4,8 Box 38.1 shows the most common clinical situations identified as hypertensive emergencies, along with cases of severe BP elevation without target-organ damage. In some hypertensive emergencies, an underlying condition is the clear cause of acute BP elevation. For example, in acute glomerulonephritis, renal crisis in patients with systemic sclerosis, and renal artery stenosis, severe BP elevations usually result from increased activity of the renin-angiotensin system (RAS). In pheochromocytoma, cocaine intoxication, or spinal cord injury, acutely elevated BP is the result of excess catecholamine release. In other patients, acute sustained elevations in BP itself are the etiologic factor, resulting in conditions such as hypertensive encephalopathy or severe hypertension with acute left ventricular failure and pulmonary edema. In some cases, however, it may be difficult to differentiate whether BP elevation is the cause or the result of a hypertensive emergency. For example, in a patient with intracerebral hemorrhage, an acute marked BP increase may be the primary cause; alternatively, a hemorrhage of other etiology (i.e., coagulation deficit) may have occurred, followed by BP elevation to preserve cerebral tissue blood supply. Thus, a careful diagnostic evaluation of hypertensive emergencies and urgencies is essential to guide proper treatment.

The most common clinical setting for hypertensive urgency is a patient with chronic hypertension (often undiagnosed, untreated, or uncontrolled) whose usual BP is greater than 180/120 mm Hg. In many of these patients, chronically elevated BP does not affect target organ perfusion because of autoregulation, which is the ability of blood vessels to dilate or constrict in response to changes in perfusion pressure and thereby maintain normal organ perfusion.9,10 In the brain, autoregulation primarily preserves blood flow, whereas in the kidney, it preserves glomerular hydrostatic pressure. Arteries from normotensive individuals can maintain flow over a wide range of mean arterial pressures (70–170 mm Hg, reflecting systolic blood pressure [SBP] of around 90–200 mm Hg). Chronic BP elevations cause compensatory functional and structural changes in the arteriolar circulation and shift the autoregulatory curve to the right, which allows hypertensive patients to maintain normal perfusion and avoid excessive blood flow at higher BP levels (Fig. 37.1).9,10 As such, most patients with chronically elevated BP greater than 180/120 mm Hg visiting the emergency department (ED) have no evidence of acute target-organ damage, and thus have hypertensive urgencies rather than emergencies.

The factors that lead to the severe and rapid BP elevation causing a hypertensive emergency are poorly understood. In some cases, the rapidity of the onset suggests a triggering factor (i.e., release of a humoral vasoactive factor) superimposed or not on preexisting hypertension. Most often, the hypertensive emergency is likely again a nonspecific consequence of chronically elevated BP, as with time, further structural and functional changes in cerebral and renal arterioles can lead to a progressive inability of the arterioles to autoregulate properly.9–12 Calcium channel blockers (CCBs) may also paradoxically increase glomerular pressure because of their ability to impair the renal autoregulatory response if systemic BP is not controlled. One way or another, target organ damage occurs when the autoregulatory mechanisms cannot maintain normal perfusion pressures in certain vascular beds (especially the retina, brain, and kidney) when systemic BP rises markedly.11–13 This results in high-shear forces causing extensive endothelial injury, with detachment and exposure of subendothelium to blood, and with activation of platelets and the coagulation cascade, leading to fibrin formation, increased vascular wall permeability, and vascular smooth muscle cell proliferation culminating in vasculopathy, occasionally with fibrinoid necrosis.

Thrombotic microangiopathy may result after formation of platelet-rich

Common Hypertensive Emergencies and Urgencies

BOX 38.1

Cardiovascular Conditions
- Acute myocardial ischemia/infarction caused by coronary artery disease
- Acute left ventricular failure/pulmonary edema
- Acute aortic dissection
- Severe hypertension after coronary bypass or other vascular surgery

Impaired autoregulation

Intraglomerular pressure

Acceleration of Chronic Hypertension
- With papilledema ± encephalopathy ± kidney failure
- With features of thrombotic microangiopathy (thrombocytopenia, hemolytic anemia, renal failure, ± papilledema, ± encephalopathy)

Renal Autoregulation

Normal autoregulation

80

120

160

Kidney Conditions
- Acute or rapidly progressive glomerulonephritis
- Renovascular hypertension
- Renal crises from scleroderma or collagen vascular disease
- Severe hypertension after kidney transplantation

Systemic pressure (mm Hg)

Fig. 38.1 Renal Autoregulation. Relationship of systemic to glomerular pressure in the setting of normal or abnormal renal autoregulation.

Neurologic Conditions
- Hypertensive encephalopathy
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Cerebral embolism or atherothrombotic cerebral infarction
- Severe hypertension after thrombolysis for atherothrombotic stroke
- Acute head trauma
- Guillain-Barré syndrome

In normotensive or minimally hypertensive individuals, such as children or pregnant women, the symptoms and signs of a hypertensive emergency may occur at lower BP levels than in hypertensive patients because adaptive chronic microvascular changes are absent. In such cases, the rate and magnitude of BP increase are more important than the actual BP level, which may be lower than the commonly used threshold of 180/120 mm Hg.[12]

Excess Circulating Catecholamine Conditions
- Pheochromocytoma crisis
- Interactions of tyramine-containing foods with monoamine oxidase

inhibitors
- Rebound hypertension after sudden withdrawal of centrally acting α2 agonists (clonidine, methyldopa, or other)
- Use of sympathomimetic drugs (phencyclidine, phenylpropanolamine, cocaine, or other)
- Automatic hyperreflexia after spinal cord injury

Pregnancy-Related Condition
- Severe preeclampsia/HELLP syndrome
- Eclampsia

Surgical Conditions
- Severe hypertension in patients requiring immediate surgery
- Perioperative hypertension
- Epistaxis unresponsive to anterior/posterior packing

Hypertension Associated With Severe Burns

HELLP, Hemolysis, elevated liver enzymes, and low platelets.

thrombi with obliteration of the microcirculation, platelet consumption, and intravascular hemolysis because of trapping and destruction of erythrocytes within the fibrin network. Activation of hormonal systems and release of vasoactive substances (RAS, catecholamines, endothelin, vasopressin) may create a vicious cycle in which elevated BP can both cause and result from vascular injury.3 4 13 14 In patients with hypertensive emergency, the typical structural kidney changes are onion-skin appearances of small arteries and arteriolar and glomerular collapse (Fig. 38.2) with electron-lucent widening of the subendothelial zone and wrinkling of the glomerular capillary walls, whereas fibrinoid necrosis of small arteries is less common.15

EPIDEMIOLOGY

The incidence of hypertensive emergencies and urgencies can be estimated from large observational studies of patients with hypertension.

Among 333,407 patients visiting 10 EDs in Italy over a 1-year period, 1155 had a hypertensive urgency, defined as BP at or greater than 220/120 mm Hg (3.46/1000/year), and 391 patients had a hypertensive emergency (1.17/1000 visits/year).16 The most common manifestations of hypertensive emergency were acute pulmonary edema (30.9%), stroke (22%), myocardial infarction (MI; 17.9%), acute aortic dissection (7.9%), acute kidney failure (5.9%), and hypertensive encephalopathy (4.9%). A systematic review of seven studies with variable definitions reported an incidence of hypertensive urgency between 1.64 and 24 patients/1000 ED visits/year and of hypertensive emergency between 1.17 and 7.6 patients/1000 ED visits/year.17

Furthermore, a wide-scale retrospective analysis of the Nationwide Emergency Department Sample (NEDS), representing about 20% of all hospital-based ED visits in the United States, showed that both hypertensive emergencies and urgencies may be increasing. Between 2006 and 2013 the incidence of acute hypertension (diagnosed by International Classification of Diseases [ICD]-9 Clinical Modification [CM] coding) increased from 1.8 to 4.6/1000 ED visits/year, and the incidence of hypertensive emergencies increased from 0.7 to 1.7/1000 visits/year.18 There is also evidence that hypertensive urgencies and emergencies are more common in middle- and low-income countries,19 20 and in deprived urban populations and ethnic minorities of high-income countries,21 that is, in patients who often have poor BP control.

People with a history of chronic kidney disease, coronary artery disease (CAD), or stroke also are at higher risk of hypertensive crises. Hypertensive emergency is more common in men, older individuals, and those with diabetes and hyperlipidemia.22 Importantly, 24% of patients presenting with a hypertensive crisis are suggested to be completely nonadherent (none of the prescribed drugs detected

A

B

Fig. 38.2 Common Kidney Biopsy Findings in Patients With Hypertensive Emergency–Related Renal Dysfunction. (A) Concentric subendothelial edematous thickening (“onion skin” appearance) of an arteriole. (B) Collapsed glomerulus (PAS stain). (From Nonaka K, Ubara Y, Sumida K, et al. Clinical and pathological evaluation of hypertensive emergency-related nephropathy. Intern Med. 2013;52:45–53.)

in urine) and another 34% partially nonadherent to their prescribed treatment.[23] Another study in patients presenting with hypertensive urgency showed that 38% had skipped antihypertensive medications and 45% had pain of noncardiac origin.[24]

Hypertensive emergencies are associated with an increased risk for mortality, with an acute in-hospital mortality of 11% to 12.5% and a 1-year mortality of 38.9%. Mortality was greater in those who experienced neurologic or cardiovascular emergencies.[25,26] As expected, mortality associated with hypertensive urgency is lower (in-hospital mortality between 0.3%– and .8% and 1-year mortality of 8.9%).[25,26]

With regards to kidney function, about 70% of patients with malignant hypertension have an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 at presentation; among these patients, 7% would need permanent kidney replacement therapy and another 20% to 25% would develop end-stage kidney disease (ESKD), requiring dialysis over long-term follow-up.[27,28]

DIAGNOSTIC EVALUATION

The primary goal of the diagnostic process is to differentiate a true hypertensive emergency from a hypertensive urgency because of the different therapeutic approaches. The second goal is rapid assessment of the type and severity of ongoing target-organ damage. In some hypertensive emergencies, the history (e.g., acute head trauma, preeclampsia, scleroderma) or overt symptoms and signs (e.g., chest/back pain, dyspnea, focal neurologic deficit, throbbing abdominal mass) may quickly guide the diagnosis; in patients with more general symptoms (headache, visual disturbances, dizziness, nausea, or altered mental status), however, the evaluation must be more comprehensive.

The diagnostic approach begins with the patient’s history, with attention to duration, severity, and treatment of preexisting hypertension and associated conditions, and to adherence to prescribed agents and possible use of substances that increase BP[2–4,8] (Box 38.2). BP readings should be performed in both arms and a leg to detect BP differences caused by aortic dissection and, if possible, in both sitting and standing positions.[3] Repeated BP measurements should be performed at regular intervals because in one-third of patients with hypertensive urgencies, BP will fall considerably without antihypertensive drugs.[29] Physical examination of cardiac, pulmonary, peripheral vascular, and neurologic systems with assessment of mental status should follow. Funduscopic (ophthalmoscopic) examination should look for hemorrhages, exudates (cotton wool spots), and papilledema as a crucial part of the diagnostic process.[4,8,12]

Diagnostic Evaluation for Hypertensive Emergencies and Urgencies

BOX 38.2

History

- Previous diagnosis and treatment of hypertension
- Symptoms, previous diagnoses, and treatment of cardiac, cerebral, renal, and visual damage
- Intake of pressor agents: sympathomimetics, illicit substances

Blood pressure

Physical examination

- Cardiac
- Vascular
- Pulmonary
- Neurologic
- Optic fundi

Laboratory studies

- Complete blood count, creatinine, urea, electrolytes, urinalysis,
- Specific tests by indication: fibrinogen, LDH, schistocytes, urine microscopy for red blood cells and casts, urine albumin/creatinine ratio, troponin, CK-MB, NT-proBNP, pregnancy test
- Plasma renin activity, aldosterone, and catecholamines if secondary hypertension is suspected

12-Lead electrocardiogram

Chest radiograph

Further investigations (according to clinical presentation)

- Kidney ultrasound including assessment of renal artery flow with Doppler
- Brain CT scan or MRI
- Transthoracic echocardiography
- Thoracoabdominal CT scan or MRI

CK-MB, Creatinine kinase-MB fraction; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NTproBNP, N-terminal pro-B natriuretic peptide.

This initial examination should not miss signs of secondary hypertension. An abdominal bruit may indicate renovascular hypertension; a pulsatile abdominal mass suggests abdominal aneurysm; palpable kidneys may be because of polycystic kidney disease; a radial-femoral pulse delay suggests aortic coarctation; abdominal striae and central obesity are observed with Cushing syndrome; and exophthalmos may indicate hyperthyroidism.

Initial laboratory studies in a hypertensive emergency include a complete blood count (CBC) with peripheral smear, urinalysis, creatinine and urea concentrations, and electrolytes.4,8,12 Comparison of kidney function with a patient's recent measurement is important. Further tests should be guided by clinical suspicion.2 High troponin and creatine kinase-MB (CK-MB) or high N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) can guide the diagnosis of acute MI or decompensated heart failure (HF). Acute deterioration in kidney function, microscopic hematuria with red blood cell casts, or nephritic urine sediment suggest acute glomerulonephritis. Features of hemolytic anemia and thrombocytopenia characterize patients with malignant hypertension–associated TMA. Differentiating hypertension-induced TMA from thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) can be difficult.3,30 The coexistence of severe BP elevation and advanced retinopathy are helpful, along with the fact that malignant hypertension is usually accompanied by less pronounced thrombocytopenia and fewer schistocytes present in a peripheral blood smear than TTP and HUS; however, some cases would require measurement of ADAMTS13 and other tests.

If a secondary form of hypertension is suspected, samples for plasma renin activity, aldosterone concentration, and plasma-free catecholamines and metanephrines should also be drawn before initiation of treatment with the patient supine. If the patient is already receiving RAS inhibitors, diuretics, or β-blockers, the diagnostic accuracy of these tests changes considerably, and results should be interpreted with caution.

Electrocardiography to rule out myocardial ischemia and left ventricular strain or hypertrophy, as well as chest radiography, should be performed in every patient. Kidney ultrasound, with renal artery Doppler, if available, is also useful to rule out abnormalities such as differences in kidney size or perfusion,31 especially in patients with reduced eGFR or with abnormalities on urinalysis.

Neurologic syndromes associated with hypertension, including subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic stroke, and hypertensive encephalopathy, are difficult to distinguish from one another only by means of clinical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) provides a definite diagnosis of a hemorrhagic or thrombotic stroke. Echocardiography, thoracoabdominal CT or MRI, or abdominal ultrasound may be needed in patients with suspected aortic dissection or pheochromocytoma.2–4

TREATMENT

General Principles and BP Treatment Thresholds for Hypertensive Emergencies

No randomized controlled trials (RCTs) examine the effect on hard outcomes of treatment strategies with different speed and degree of BP reduction for hypertensive emergencies, with the exception of acute stroke. Recommended strategies are based on consensus from clinical experience and observations on intermediate outcomes.1–3 Nevertheless, clinical data document that lowering BP in hypertensive emergencies is beneficial: papilledema and exudates regress, hypertensive encephalopathy vanishes, pulmonary edema resolves, and kidney function improves. On the other hand, abrupt or excessive BP lowering may cause or contribute to cerebral, coronary, or renal ischemia. Oral loading of antihypertensive agents can have cumulative undesirable effects; the most typical example is use of sublingual nifedipine with potent but unpredictable decrease in BP that may shunt blood away from the cerebral penumbra, resulting in ischemic events.32 Overall, understanding autoregulation and consideration of comorbidities, such as age and extent of vascular disease, are crucial for therapeutic decisions. Thus, the goal of therapy is not to normalize BP rapidly but rather to limit target-organ damage by gradually reducing BP, while minimizing the risk of tissue hypoperfusion.11

There are three major considerations before initiating treatment: (1) establishing whether there is a distinct cause of BP elevation (e.g., eclampsia, acute head trauma) or a distinct target-organ damage (acute MI, aortic dissection) that would require specific interventions in addition to BP lowering; (2) the timescale and magnitude of BP lowering required; and (3) the optimal type of drug treatment.2 In hypertensive emergencies, IV treatment with a short-acting and easily titratable agent is recommended to allow tight control of BP response (Tables 38.1 and 38.2). This treatment may be initiated in the ED but should be continued in an ICU or a high dependency unit (HDU) to enable continuous BP/hemodynamic monitoring and continuous clinical surveillance.1–3 A further consideration before initiation of IV therapy is assessment of the patient’s volume status. With the obvious exceptions of patients presenting with volume overload and/or pulmonary edema, several patients with a hypertensive emergency may be volume depleted because of pressure natriuresis, and diuretics should not be used; rather, fluid administration may help restore organ perfusion and prevent a precipitous fall in BP.4 Diuretics should be especially avoided in hypertensive emergencies caused by catecholamine excess states (pheochromocytoma, monoamine oxidase inhibitor crisis, cocaine intoxication) because these patients are usually volume depleted.

Current guidelines have minor differences with regards to the recommended timescale and magnitude of BP fall for major hypertensive emergencies.1–3 The 2017 American College of Cardiology/American Heart Association (AHA/ACC) Guidelines recommend reducing BP by a maximum of 25% within the first hour to SBP/diastolic blood pressure [DBP] levels of 160/100 to 160/110 mm Hg over the next 2 to 6 hours and to normal over the next 24 to 48 hours in most patients. In patients with severe preeclampsia or eclampsia and those with pheochromocytoma crisis, SBP should be reduced to less than 140 mm Hg within an hour and in those with aortic dissection to less than 120 mm Hg in the same timeframe.1

The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines differ in recommending immediate BP reduction to less than 160/105 mm Hg in patients with severe preeclampsia or eclampsia and to SBP less than 140 mm Hg in those with acute coronary event and acute cardiogenic pulmonary edema.2

With regard to acute ischemic stroke, evidence from RCTs does not conclusively suggest a benefit from BP-lowering in short-term and midterm mortality risk and functional outcomes.33 Therefore, current recommendations suggest that patients who are candidates for treatment with IV tissue plasminogen activator or mechanical thrombectomy should have their BP reduced to less than 185/110 before treatment.1–3,34 For patients that are not candidates for such interventions and have BP greater than 220/120 mm Hg, most guidelines agree that the evidence is uncertain, but it is reasonable to reduce BP by 15% within the first 24 hours.1,2,34 With regards to acute intracerebral hemorrhage (ICH), a previous RCT showed that lowering SBP to less than 140 mm Hg within an hour is safe and may improve functional outcome35; however, a subsequent RCT that examined BP lowering within 4.5 hours of an acute ICH found that treatment to SBP levels of 110 to 139 mm Hg did not lead to better outcomes compared with treatment to 140 to 179 mm Hg and was associated with more renal adverse effects.36 Thus, in patients with acute ICH presenting with SBP levels greater than 220 mm Hg, BP should be lowered using IV drugs to goal levels of 140 to 180 mm Hg.1,2

After the BP has been controlled for a suitable period, typically 12 to 24 hours, which allows autoregulation to reestablish, the IV medication can gradually be reduced and replaced by oral agents. Typically, a dihydropyridine CCB, α- and β-blocker, or RAS blocker is used, depending on the suspected cause and possible ongoing investigations for secondary hypertension.11

TABLE 38.1

Specific Aspects of Antihypertensive Drug Use for Hypertensive Emergencies

The need for gradual and tightly controlled BP reduction requires the use of IV drugs (see Table 38.1), the effects of which can be promptly reversed if the response is excessive. Previous systematic

Pharmacologic Agents for Treatment of Hypertensive Emergencies

Drug

Mechanism of Action

Onset of Action

Duration of Action

Vasodilators

Nicardipine hydrochloride

Calcium channel blocker

Initial 5 mg/h IV; increase every 5 min up to 15 mg/h

5–15 min

Clevidipine butyrate

Calcium channel blocker

1–2 mg/h IV; increase every 5–10 min up to 16 mg/h

Isradipine

Calcium channel blocker

Fenoldopam mesylate

Adverse Effectsa

Special Indications

15–30 min, may exceed 4 h

Tachycardia, headache, flushing, nausea, vomiting, local phlebitis

Most hypertensive emergencies except acute HF

2–4 min

5–15 min

Tachycardia, headache, flushing, HF deterioration

Most hypertensive emergencies;
caution with severe aortic stenosis

0.15 µg/kg/min IV, increase by 0.0025 µg/kg/min every 15 min
Maintenance infusion 0.15 µg/kg/min

1–10 min

1–2 h

Headache, flushing, peripheral edema, dizziness, tachycardia

Perioperative, pregnancy

Dopamine-1 receptor agonist

Initial 0.1–0.3 µg/kg/min IV; increase by 0.05–0.1 µg/kg/min every 15 min up to 1.6 µg/kg/min

>5 min

30 min

Tachycardia, headache, nausea, flushing

Most hypertensive emergencies;

caution with
glaucoma

Sodium
nitroprusside

↑ Cyclic GMP, blocks
intracellular Ca2+
increase

Initial 0.25–0.5 μg/
kg/min IVb;
increase by 0.5 μg/
kg/min up to 10
μg/kg/min

Immediate

1–2 min

Nausea, vomiting, muscle
twitching, thiocyanate
and cyanide intoxication,
impaired cerebral
autoregulation, coronary
steal syndrome

Caution in situations
associated
with CNS
manifestations,
hepatic failure
or renal failure;
probably should
be avoided if
given other
agents, especially
fenoldopam

Nitroglycerin

↑ Nitrate receptors

Initial 5
μg/min IV; increase
by 5 μg/min every
3–5 min up to 20
μg/min

2–5 min

5–10 min

Headache, vomiting,
methemoglobinemia,
tachyphylaxis, tolerance with
prolonged use

Coronary ischemia,
pulmonary edema

Enalaprilat

ACE inhibitor

Initial 1.25 mg over
5 min IV; increased
up to5 mg every 6 h

15–30 min

6–12 h

Precipitous fall in BP in
high-renin states, variable
response, acute renal failure

Acute left ventricular
failure; avoid in
acute MI

Hydralazine
hydrochloride

Opens K+ channels

Initial 10–20 mg IV;
repeat every 4–6 h

10–20 min

1–4 h

Tachycardia, flushing,
headache, vomiting,
aggravation of angina

Must be given with
concomitant IV
β-blockers to avoid
precipitation of
angina but not a
preferred initial
choice or treatment

Dose

Continued

Pharmacologic Agents for Treatment of Hypertensive Emergencies—cont’d

TABLE 38.1
Drug

Mechanism of
Action

Adrenergic Inhibitors
Labetalol
α1-, β-Blocker
hydrochloride

Onset of
Action

Duration of
Action

Initial 0.3–1.0 mg/
kg dose (maximum
80 mg) in slow IV
injection and
repeat after 10 min
or 0.4–1.0 mg/kg/h
IV infusion up to 3
mg/kg/h
Maximum dose
300 mg; can be
repeated every
4–6 h

5–10 min

3–6 h

Nausea, vomiting, scalp
tingling, bronchoconstriction,
dizziness, heart block, heart
failure

Most hypertensive
emergencies except
acute HF

Dose

Special
Indications

Adverse Effectsa

Esmolol
hydrochloride

β1-Blocker

0.5–2 mg/min IV
infusion or
250–500 μg/kg/

min IV bolus, then 50–100 µg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min

1–2 min

10–30 min

Nausea, asthma, firstdegree heart block, HF, thrombophlebitis, COPD

Aortic dissection, perioperative, increased heart output or heart rate

Urapidil

α1-Blocker, serotonin (5-HT1A) receptor agonist

12.5–25 mg IV bolus followed by 5–40 mg/h IV infusion

3–5 min

4–6 h

Headache, dizziness

Perioperative

Phentolamine

α-Blocker

Initial 5–15 mg IV bolus; repeat after 10 min

1–2 min

10–30 min

Tachycardia, flushing, headache

Catecholamine excess

aHypotension

may occur with all agents.
light-resistant delivery system.
ACE, Angiotensin-converting enzyme; BP, blood pressure; CNS, central nervous system; COPD; chronic obstructive pulmonary disease; GMP, guanosine monophosphate; HF, heart failure; IV, intravenous; MI, myocardial infarction.

bRequires

TABLE 38.2

Management of Specific Types of Hypertensive Emergencies
First-Choice Drug(s)

Second-Choice or
Additional Drug(s)

Nicardipine, clevidipine,
labetalol, nitroglycerin

Heart failure, pulmonary
edema

Clevidipine, nitroglycerin,
fenoldopam,

Aortic dissection

Labetalol or combination
of esmolol with sodium
nitroprusside or fenoldopam
or nicardipine

Type of Emergency
Cardiac
Coronary ischemia/infarction

Renal
Acute glomerulonephritis,
collagen vascular renal
disease, or renal artery
stenosis

Fenoldopam

Drugs to Avoid

Aim of BP Reduction

Sodium nitroprusside, esmolol
if heart failure absent

Diazoxide, hydralazine

Improvement in cardiac perfusion

Sodium nitroprusside,
enalaprilat; loop diuretics

Diazoxide, hydralazine;
β-blockers

Decrease in afterload

Diazoxide, hydralazine

Decrease of aortic wall stress
with systolic BP reduction
<120 mm Hg in 1 hour

Sodium nitroprusside; ACE

inhibitors and ARBs

Reduction in vascular resistance
and volume overload without
compromise of renal blood flow
or glomerular filtration rate

Nicardipine, labetalol,
clevidipine; diuretics for
volume overload

TABLE 38.2

Management of Specific Types of Hypertensive Emergencies—cont’d

Type of Emergency

First-Choice Drug(s)

Second-Choice or Additional Drug(s)

Scleroderma crisis

Enalaprilat or other ACE inhibitor

Angiotensin receptor blocker, fenoldopam

Nicardipine, fenoldopam, labetalol, clevidipine

Nitroprusside, esmolol, urapidil

Decrease BP up to 25% over 1 hour

Ischemic stroke

Nicardipine, labetalol, clevidipine

Nitroprusside, nimodipine, esmolol, urapidil

Reduction of BP if >220/120 mm Hg by up to 15% within first 24 hours to avoid impairing cerebral blood flow in penumbra
Reduction of BP if >185/110 in candidates of thrombolysis

Intracerebral hemorrhage

Nicardipine, labetalol, clevidipine

Fenoldopam, nitroprusside, esmolol, urapidil, nimodipine for subarachnoid hemorrhage

For patients presenting with SBP >220 mm Hg, it is reasonable to reduce SBP to 140–180 mm Hg. For patients presenting with SBP 150–220 mm Hg, decreasing to <140 mm Hg is not of benefit.

Neurologic
Hypertensive
encephalopathy

Catecholamine Excess States
Pheochromocytoma
Phentolamine or labetalol

Ingestion of cocaine or other
sympathomimetic

Phentolamine or labetalol

Perioperative/Postoperative Hypertension
Coronary artery surgery
Nitroglycerin, nicardipine,
clevidipine

Noncardiac surgery

Pregnancy Related
Eclampsia

Drugs to Avoid

Aim of BP Reduction

Corticosteroids,a diuretics

Decrease BP up to 25% over
1 hour

β-Blocker in the presence
of phentolamine, sodium
nitroprusside

Diuretics, β-blockers alone

Control of BP paroxysms from
sympathetic stimulation; reduce
SBP <140 mm Hg over 1 hour

β-Blocker in the presence
of phentolamine, sodium
nitroprusside

Diuretics

Control of BP paroxysms from
sympathetic stimulation

Esmolol, labetalol,
fenoldopam, isradipine,
urapidil

Protection against target
organ damage and surgical
complications (keep BP <140/90
mm Hg)

Esmolol, labetalol,
fenoldopam, nicardipine,

clevidipine, urapidil,
nitroglycerin
Labetalol, urapidil

Protection against target
organ damage and surgical
complications

Isradipine, nicardipine,
MgSO4, methyldopa,
hydralazine

Nitroprusside, ACE
inhibitors, ARBs

Reduce BP <140–160/105 mm
Hg over 1 hour and protect
placental blood flow

aCorticosteroids

may worsen hypertension in scleroderma renal crisis.
ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BP, Blood pressure; SBP, systolic blood pressure.

reviews and meta-analyses showed minor differences in the degree of BP lowering and no differences in morbidity or mortality among these agents because of the relative paucity of large RCTs with appropriate follow-up.37,38 Thus, treatment practices were mainly empiric. More recent evidence, however, suggests some benefits of novel agents.

Nicardipine is a dihydropyridine CCB with intermediate onset and duration of effect and strong cerebral and coronary vasodilatory activity. It is useful for most hypertensive emergencies, especially in patients with CAD. Nicardipine potentiates curare effects and interacts with inhalant anesthetics.4,11,39,40 In an RCT of 226 patients with acute SBP of 180 mm Hg or higher, those receiving nicardipine reached physician-specified target range slightly more often (92% vs. 83%, P = .039) than those receiving labetalol.41A systematic review of studies comparing nicardipine with labetalol suggested that the two drugs had comparable efficacy and safety, but nicardipine showed more predictable and consistent BP response.42 Nicardipine can be particularly useful in patients with acute coronary syndromes or hypertensive emergencies involving the brain because it reduces myocardial and cerebral ischemia.

Clevidipine butyrate is an ultrashort-acting (within 1–2 minutes) thirdgeneration CCB that acts through inhibition of extracellular calcium influx and reduces peripheral vascular resistance without affecting venous vascular tone or cardiac filling pressure. Clevidipine is rapidly hydrolyzed by blood esterases, and thus its metabolism is not affected by renal or hepatic function.4,39,40 In clinical studies, clevidipine was effective and safe for the control of perioperative hypertension and hypertensive emergencies. Three RCTs including more than 1500 patients with perioperative acute hypertension that compared clevidipine, nitroglycerin, sodium nitroprusside, and nicardipine found no difference between clevidipine, nitroglycerin, and nicardipine in the primary endpoint of death, MI, stroke, or reduced eGFR at 30 days, but clevidipine was more effective in maintaining BP within the prespecified range and was associated with lower mortality than nitroprusside.43 A factor that has limited the widespread use of clevidipine is its relatively high cost.

Fenoldopam mesylate is a selective agonist of dopaminergic 1 receptors located mainly in the renal and splanchnic arteries, with lesser density in the coronary and cerebral arteries.4,39,40 IV fenoldopam does not cross the blood-brain barrier and has no central nervous system activity because it is a poorly lipid-soluble molecule and, unlike dopamine, it lowers rather than raises BP. In clinical studies, compared with sodium nitroprusside, fenoldopam demonstrated similar BP-lowering efficacy and beneficial renal effects (increased diuresis, natriuresis, creatinine clearance).44 Thus, fenoldopam is mostly useful for BP reduction in patients with renal impairment, those with HF, and those undergoing vascular surgery. Fenoldopam must be administered with caution, if at all, to patients with glaucoma because it increases intraocular pressures.4,11,39,40

For several years, sodium nitroprusside was considered the first-choice drug for almost all hypertensive emergencies. It is easily titrated, inexpensive, and has a long record of effectiveness.4,11 However, sodium nitroprusside has several drawbacks, including accumulation of toxic metabolites (thiocyanate and cyanide) when used for more than 48 hours, especially in patients with renal or hepatic dysfunction, and the need for invasive BP monitoring and an administration system that protects it from light. High-dose nitroprusside also increases intracranial pressure, obliterates cerebral autoregulation, and reduces regional coronary blood flow. These attributes limit its usefulness in patients with neurologic complications or acute coronary syndromes.4,11

Labetalol is a nonselective α1- and β-blocker (in 1:7 ratio) that can be used in many hypertensive emergencies because when given intravenously it has rapid onset of action, potent and sustained effect, and low toxicity. Labetalol reduces peripheral vascular resistance without a reflex increase in systolic volume, and cerebral, renal, and coronary blood flow are maintained. Its main indications are for hypertension associated with aortic dissection, acute coronary syndromes, hypertensive encephalopathy, and adrenergic crisis.4,39,40 Labetalol can be used in pregnancy-induced hypertensive crisis because little placental transfer occurs as a result of its negligible lipid solubility.4 Labetalol may be used in chronic obstructive pulmonary disease if the patient has no history of an asthmatic component.45 Esmolol is a β1-blocker with an immediate onset and a short duration of action, whose metabolism is not dependent on kidney or hepatic function. Esmolol is used particularly in patients with severe postoperative hypertension, and it can be useful in those with increased cardiac output and heart rate.4,39,40

Table 38.1 provides pharmacologic characteristics and adverse effects of the aforementioned agents, as well as other agents that have been used in the treatment of hypertensive emergencies. Table 38.2 includes a general guide for use of these drugs according to the type of hypertensive emergency.4,8,12,39,40

Treatment of Hypertensive Urgencies

Although hypertensive urgencies are particularly common, high-quality studies on the value of extensive diagnostic testing for target-organ damage, the need for hospitalization, the type of treatment, and the optimal follow-up in asymptomatic patients with BP elevation are missing.46,47 A retrospective cohort study with propensity matching that included all patients presenting with hypertensive urgency (BP > 180/110 mm Hg) to an office in a large health care system in the United States showed that patients sent home compared with those sent to the ED had an equally low risk of major cardiovascular events (0.9%) and equal chance to have uncontrolled hypertension (65% vs. 67%) at 6 months.48

Because there is no proven benefit from rapid BP reduction in asymptomatic patients without evidence of acute target-organ damage, current guidelines agree that BP lowering should occur over a longer time than for a hypertensive emergency, and no hospitalization is necessary.1,2 BP reduction to less than 160/100 mm Hg may be accomplished within 2 to 4 hours in the ED with resting and oral agents. This may be particularly important for patients without ongoing target-organ damage, who are judged to be at high risk for CV events over the next days because of severe hypertension (e.g., those with known history of aortic aneurysm or repeated episodes of pulmonary edema). However, there are many different types of patients who may present as a hypertensive urgency, the most common of which is the hypertensive patient with low treatment compliance and chronically elevated BP levels. Thus, less aggressive lowering of BP (over several hours to days) is also proposed by some, using strategies such as resumption of antihypertensive therapy (in nonadherent patients), initiation of antihypertensive therapy with long-acting agents (if patients are treatment naive), and treatment modification or addition of another antihypertensive drug (in patients who are already treated). In short, the most important aspect of treatment of hypertensive urgency is not achieving a BP goal but rather ensuring adequate follow-up, generally within 1 week, to an appropriate site of care for chronic hypertension to optimize care and improve chronic BP control.1,2,4,11

Patients with hypertensive urgency should be provided a quiet room in which to rest. An uncontrolled study showed this maneuver resulted in a BP fall of at least 20/10 mm Hg in one-third of these individuals,49 and a recent RCT showed that resting produced identical BP reductions to 40 mg of telmisartan over a 2-hour period.24 A large observational study showed that there were no differences in 1-week ED revisit rate and BP control between patients with hypertensive urgencies treated or not with oral medications.50 The importance of relaxation is further supported by data suggesting that techniques such as pursed-lip breathing combined with number counting or anxiolytic treatment are associated with greater BP reductions than usual care alone.51,52 Another major factor to consider before prescribing antihypertensive medication is assessment of pain. Patients with severe pain not of cardiac or cerebral origin should be given analgesics first to improve it because if they are given acute-acting medications, they could become hypotensive once pain is alleviated.

The choice of drugs for treatment of hypertensive urgencies is much broader than for emergencies because almost all antihypertensives lower BP effectively given sufficient time. Captopril, clonidine, labetalol, and other short-acting drugs have been used most often (Table 38.3).4,40,53 A careful history to assess chronic antihypertensive treatment and patient adherence to medication is critical for drug and dose selection, and clinical surveillance is always advisable during the first few hours after drug administration. If a pheochromocytoma is suspected, it is advisable to avoid β-blockers because they can increase BP because of unopposed α-adrenergic activity; this included labetalol because its α-blocking effect is very small. An α-blocker such as doxazosin or prazosin is preferred. Overall, if the patient admits to missing one or more doses of their usual antihypertensive agents, reinstituting these medications in an appropriate order is a reasonable option.

Oral captopril is typically given in a 12.5- to 25-mg dose; angiotensinconverting enzyme (ACE) inhibitors must be used with caution because they can cause or exacerbate renal impairment in the occasional patient

TABLE 38.3

Pharmacologic Agents for Treatment of Hypertensive Urgencies

Drug	Mechanism of Action	Dose	Onset of Action	Duration of Action	Adverse Effects
Captopril	ACE inhibitor	12.5–25 mg PO every 1–2 h	15–30 min	4–6 h	Angioedema, cough, acute renal failure
Clonidine	Central α2-agonist	0.1–0.2 mg PO every 1–2 h	30–60 min	6–8 h	Sedation, dry mouth, bradycardia, rebound hypertension after withdrawal
Labetalol	α1-, β-Blocker	200–400 mg PO every 2–3 h	30–120 min	6–8 h	Bronchoconstriction, heart block, congestive heart failure
Furosemide	Loop diuretic				

20–40 mg PO every 2–3 h

30–60 min

8–12 h

Volume depletion, hyponatremia, hypokalemia

Isradipine

Calcium channel blocker

5–10 mg PO every 4–6 h

30–90 min

8–16 h

Headache, tachycardia, flushing, peripheral edema

PO, By mouth.
Shown are short-acting agents commonly used in the emergency room setting. However, as noted in the text, sometimes longer-acting drugs can be used.

with critical renal artery stenosis.53 Sublingual captopril has a more pronounced BP lowering effect than oral captopril at 10 and 30 minutes but similar at 60 minutes after dosing.54 Oral clonidine, 0.1 to 0.2 mg, is one of the most common agents used in this setting. However, patients should not be discharged on clonidine if they have a history of nonadherence to drug regimens because of the risk for rebound hypertension if clonidine is abruptly stopped. Furosemide also can effectively lower BP if elevated pressure is related to volume overload, especially if renal dysfunction is present. However, a common physiologic response of the kidney to elevated BP is natriuresis, so many patients, especially those with normal renal function, are volume depleted, as previously discussed.4 53 Further, furosemide is not considered appropriate for treating primary hypertension because of its short duration of action and a rebound in sodium reabsorption if dosed once daily.
Sublingual short-acting nifedipine, although once frequently used, is now contraindicated secondary to a higher incidence of stroke, MI, and death related to precipitous hypotensive episodes after ED release.32 Intermediate-acting dihydropyridine CCBs, such as isradipine and nicardipine, may be used, because their onset of action is between 30 and 90 minutes. Longer-acting CCBs, such as once-daily

nifedipine, sustained-release isradipine, and amlodipine do not have a role in reducing BP in the ED. However, these and long-acting agents from other major antihypertensive classes are valuable tools for longterm BP control, which, as mentioned previously, is the most important aspect of management in these patients.
Despite existing recommendations,1 2 a substantial proportion of patients with hypertensive urgency are still treated with IV medications in everyday clinical practice, an intervention that produces similar BP reduction, readmission rates, and adverse outcomes with oral dosing.55 56 There are also data suggesting that most of these patients do not receive proper instructions in the ED as proposed in the literature, and providers overestimate how often they refer patients for follow-up, resulting in questionable improvement in long-term outpatient BP control.46 Finally, there is a justified concern on the optimal treatment of patients with severe BP elevation and unclear symptoms while they

are undergoing workup in the ED to determine whether they have target-organ damage, especially as health system practices and available ED resources vary considerably across the globe.57 Further research is needed to clarify these issues and inform decisions for short- and longterm management of patients with hypertensive urgencies.

SELF-ASSESSMENT QUESTIONS

1. A patient being evaluated for a routine history and physical is noted to have a BP of 220/130 mm Hg. He states he feels fine except for nightly reflux. Examination shows fundi with atrioventricular nipping and normal heart sounds. Chest radiograph is normal; serum creatinine is 1.3 mg/dL, and urinalysis shows rare red blood cells (RBCs). Management should include which of the following?

A. Immediate hospitalization to the intensive care unit with administration of intravenous labetalol
B. Stat electrocardiogram, cardiac enzymes, and admission to the cardiac care unit
C. Start oral isradipine 5 mg, let the patient rest in a quiet room, and observe for some hours
D. Perform a full workup for secondary causes with plasma metanephrines and catecholamines and aldosterone-renin ratio.
Start clonidine, 0.4 mg twice daily.

2. A patient presents with an acute hemorrhagic stroke and has a BP of 180/120 mm Hg. You are asked to consult on the patient. Which of the following is the best strategy?

A. Give hydralazine (10 mg IV) to bring the BP down as rapidly as possible.
B. Initiate nitroprusside therapy and titrate BP down to 140/90 mm Hg over a 1-hour period.
C. Start nicardipine infusion and reduce BP to 160/90 mm Hg within an hour.
D. Do not treat the hypertension because it may worsen the stroke.

3. A patient presents with acute chest pain. On examination, BP in the right arm is 190/120 mm Hg but in the left arm is only 160/90 mm Hg. The chest radiograph shows a widened mediastinum. What is the best initial treatment to lower the BP?

A. Start a nitroprusside infusion, targeting BP of 140/90 mm Hg in the right arm.
B. Start a labetalol infusion, targeting BP of 120 mm Hg systolic in the right arm.
C. Start an esmolol infusion, targeting BP of 120 mm Hg systolic in the left arm.
D. Do not treat the BP because it is important to preserve cerebral perfusion.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
3. van den Born B-JH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. Eur Heart J Cardiovasc Pharmacother. 2019;5:37–46.
4. Sarafidis PA, Georgianos PI, Malindretos P, Liakopoulos V. Pharmacological management of hypertensive emergencies and urgencies: focus on newer agents. Expert Opin Investig Drugs. 2012;21:1089–1106.
5. Keith NM, Wagener HP, Kernohan JW. The syndrome of malignant hypertension. Arch Intern Med. 1928;41:141–188.
6. Cremer A, Amraoui F, Lip GYH, et al. From malignant hypertension to hypertension-MOD: a modern definition for an old but still dangerous emergency. J Hum Hypertens. 2016;30:463–466.
7. Lane DA, Lip GYH, Beevers DG. Improving survival of malignant hypertension patients over 40 years. Am J Hypertens. 2009;22:1199–1204.
8. Adebayo O, Rogers RL. Hypertensive emergencies in the emergency department. Emerg Med Clin North Am. 2015;33:539–551.
9. Carlström M, Wilcox CS, Arendshorst WJ. Renal autoregulation in health and disease. Physiol Rev. 2015;95:405–511.
10. Shekhar S, Liu R, Travis OK, Roman RJ, Fan F. Cerebral autoregulation in hypertension and ischemic stroke: a mini review. J Pharm Sci Exp Pharmacol. 2017;2017:21–27.
11. Elliott WJ. Clinical features in the management of selected hypertensive emergencies. Prog Cardiovasc Dis. 2006;48:316–325.
12. Suneja M, Sanders ML. Hypertensive emergency. Med Clin. 2017;101:465–478.
13. Kaplan NM, Victor RG. Hypertensive crises. In: Kaplan’s Clinical Hypertension: Eleventh Edition. Wolters Kluwer Health Adis (ESP); 2014.
14. van den Born B-JH, Löwenberg EC, van der Hoeven NV, et al. Endothelial dysfunction, platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. J Hypertens. 2011;29:922–927.
15. Nonaka K, Ubara Y, Sumida K, et al. Clinical and pathological evaluation of hypertensive emergency-related nephropathy. Intern Med. 2013;52:45–53.
16. Pinna G, Pascale C, Fornengo P, et al. Hospital admissions for hypertensive crisis in the emergency departments: a large multicenter Italian study. PLoS One. 2014;9:e93542.
17. Astarita A, Covella M, Vallelonga F, et al. Hypertensive emergencies and urgencies in emergency departments: a systematic review and metaanalysis. J Hypertens. 2020;38:1203–1210.
18. Janke AT, McNaughton CD, Brody AM, Welch RD, Levy PD. Trends in the incidence of hypertensive emergencies in US emergency departments from 2006 to 2013. J Am Heart Assoc. 2016;5.
19. Pierin AMG, Flórido CF, Santos JD. Hypertensive crisis: clinical characteristics of patients with hypertensive urgency, emergency and pseudocrisis at a public emergency department. Einstein (Sao Paulo). 2019;17:eAO4685.
20. Gebresillassie BM, Debay YB. Characteristics, treatment, and outcome of patients with hypertensive crisis admitted to University of Gondar Specialized Hospital, northwest Ethiopia: a cross-sectional study. J Clin Hypertens (Greenwich). 2020;22:2343–2353.
21. Waldron FA, Benenson I, Jones-Dillon SA, et al. Prevalence and risk

factors for hypertensive crisis in a predominantly African American innercity community. Blood Press. 2019;28:114–123.

22. Benenson I, Waldron FA, Jadotte YT, Dreker MP, Holly C. Risk factors for hypertensive crisis in adult patients: a systematic review. JBI Evid Synth. 2021;19(6):1292–1327.
23. Wallbach M, Lach N, Stock J, et al. Direct assessment of adherence and drug interactions in patients with hypertensive crisis-A cross-sectional study in the Emergency Department. J Clin Hypertens. 2019;21:55–63.
24. Park SK, Lee D-Y, Kim WJ, et al. Comparing the clinical efficacy of resting and antihypertensive medication in patients of hypertensive urgency: a randomized, control trial. J Hypertens. 2017;35:1474–1480.
25. Katz JN, Gore JM, Amin A, et al. STAT Investigators. Practice patterns, outcomes, and end-organ dysfunction for patients with acute severe hypertension: the Studying the Treatment of Acute hyperTension (STAT) registry. Am Heart J. 2009;158:599–606.e1.
26. Guiga H, Decroux C, Michelet P, et al. Hospital and out-of-hospital mortality in 670 hypertensive emergencies and urgencies. J Clin Hypertens. 2017;19:1137–1142.
27. Amraoui F, Bos S, Vogt L, van den Born B-J. Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. BMC Nephrol. 2012;13:71.
28. González R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. Nephrol Dial Transplant. 2010;25:3266–3272.
29. Grassi G, Seravalle G, Quarti-Trevano F, et al. Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. Hypertension. 2008;52:925–931.
30. Bayer G, von Tokarski F, Thoreau B, et al. Etiology and outcomes of thrombotic microangiopathies. Clin J Am Soc Nephrol. 2019;14:557–566.
31. Tsioufis C, Andrikou I, Pruijm M, et al. Should renal color Doppler ultrasonography be a routine test in newly diagnosed hypertensive patient? J Hypertens. 2018;36:16–22.
32. Messerli FH, Grossman E. The use of sublingual nifedipine: a continuing concern. Arch Intern Med. 1999;159:2259–2260.
33. Georgianou E, Georgianos PI, Petidis K, Athyros VG, Sarafidis PA, Karagiannis A. Antihypertensive therapy in acute ischemic stroke: where do we stand? J Hum Hypertens. 2018;32:799–807.
34. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50:e344–e418.
35. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355–2365.
36. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375:1033–1043.
37. Cherney D, Straus S. Management of patients with hypertensive urgencies and emergencies: a systematic review of the literature. J Gen Intern Med. 2002;17:937–945.
38. Perez MI, Musini VM. Pharmacological interventions for hypertensive emergencies: a Cochrane systematic review. J Hum Hypertens. 2008;22:596–607.
39. Salvetti M, Paini A, Bertacchini F, et al. Acute blood pressure elevation: therapeutic approach. Pharmacol Res. 2018;130:180–190.
40. Maloberti A, Cassano G, Capsoni N, et al. Therapeutic approach to hypertension urgencies and emergencies in the emergency room. High Blood Press Cardiovasc Prev. 2018;25:177–189.
41. Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. Crit Care. 2011;15:R157.

42. Peacock WF, Hilleman DE, Levy PD, Rhoney DH, Varon J. A systematic review of nicardipine vs labetalol for the management of hypertensive crises. Am J Emerg Med. 2012;30:981–993.
43. Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008;107:1110–1121.

References

44. Murphy MB, Murray C, Shorten GD. Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. N Engl J Med. 2001;345:1548–1557.
45. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005; CD003566.
46. Wolf SJ, Lo B, Shih RD, Smith MD, Fesmire FM, American College of Emergency Physicians Clinical Policies Committee. Clinical policy: critical issues in the evaluation and management of adult patients in the emergency department with asymptomatic elevated blood pressure. Ann Emerg Med. 2013;62:59–68.
47. Campos CL, Herring CT, Ali AN, et al. Pharmacologic treatment of hypertensive urgency in the outpatient setting: a systematic review. J Gen Intern Med. 2018;33:539–550.
48. Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. JAMA Intern Med. 2016;176:981–988.
49. Grassi D, O’Flaherty M, Pellizzari M, et al. Hypertensive urgencies in the emergency department: evaluating blood pressure response to rest and to antihypertensive drugs with different profiles. J Clin Hypertens (Greenwich). 2008;10:662–667.
50. Sricharoen P, Poungnil A, Yuksen C. Immediate prescription of oral antihypertensive agents in hypertensive urgency patients and the risk of revisits with elevated blood pressure. Open Access Emerg Med. 2020;12:333–340.

51. Paštrović F, Okštajner PK, Vodanović M, et al. The role of anxiolytics in hypertensive urgency management. Psychiatr Danub. 2020;32:593–596.
52. Mitsungnern T, Srimookda N, Imoun S, Wansupong S, Kotruchin P. The effect of pursed-lip breathing combined with number counting on blood pressure and heart rate in hypertensive urgency patients: a randomized controlled trial. J Clin Hypertens (Greenwich). 2021:23(3):672–679.
53. Rosei EA, Salvetti M, Farsang C. European Society of Hypertension Scientific Newsletter: treatment of hypertensive urgencies and emergencies. J Hypertens. 2006;24:2482–2485.
54. Kaya A, Tatlisu MA, Kaplan Kaya T, et al. Sublingual vs. Oral captopril in hypertensive crisis. J Emerg Med. 2016;50:108–115.
55. Saladini F, Mancusi C, Bertacchini F, et al. Diagnosis and treatment of hypertensive emergencies and urgencies among Italian emergency and intensive care departments. Results from an Italian survey: progetto GEAR (Gestione dell’Emergenza e urgenza in ARea critica). Eur J Intern Med. 2020;71:50–56.
56. Allgaier J, Emmich M, Rastegar V, Stefan MS, Lagu T. Hypertensive urgency or emergency? The use of intravenous medications in hospitalized hypertensive patients without organ dysfunction. Heart Lung. 2020;49:824–828.
57. Koracevic G, Lovic D, Zdravkovic M, Stojanovic M, Djordjevic D. How should we treat very high blood pressure until we distinguish between hypertensive emergency and urgency? Hypertens Res. 2020;43:470–472.

39

Endocrine Causes of Hypertension: Aldosterone

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INTRODUCTION

Aldosterone is a steroid hormone produced in the adrenal glands that has critical roles in blood pressure (BP), plasma volume, and potassium homeostasis. Its production is normally under feedback regulation such that hypertension, intravascular volume expansion, and hypokalemia decrease its expression. When this feedback regulation is impaired, autonomous and inappropriate aldosterone production can lead to severe hypertension that is often refractory to treatment and to hypokalemia. Autonomous aldosterone production is also associated with an increased risk of major cardiovascular events, such as myocardial infarction, congestive heart failure, atrial fibrillation, and stroke, such that the rate of these complications is substantially greater than expected solely from the associated hypertension. Recent advances in the diagnosis of aldosterone-induced hypertension have led to the recognition that primary aldosteronism is surprisingly common. Effective diagnostic strategies are available, and treatment regimens are highly efficacious.

ETIOLOGY AND PATHOGENESIS

Aldosterone is produced under normal conditions in the zona glomerulosa of the adrenal glands (Fig. 39.1). The enzyme, aldosterone synthase, is encoded by the gene CYP11B2, and it is generally accepted as the rate-limiting enzyme for aldosterone production. Box 39.1 summarizes factors known to stimulate or inhibit aldosterone synthesis. The physiologically most important regulators of aldosterone production are angiotensin II (Ang II), which stimulates aldosterone production through activation of the AT1 receptor; adrenocorticotropic hormone (ACTH), which acutely stimulates aldosterone secretion; atrial natriuretic peptide (ANP), which is inhibitory; and extracellular potassium concentration (hyperkalemia is stimulatory and hypokalemia is inhibitory).1,2 A high NaCl (salt) diet suppresses aldosterone production; this likely occurs through changes in ANP and renin-dependent Ang II production. Finally, there is a significant circadian variation, with serum levels greatest in the late morning with peak values about 50% greater than the average concentration.

Aldosterone mediates its effects almost exclusively through activation of the mineralocorticoid receptor (MR). MR is a classic steroid hormone receptor, which upon activation translocates to the nucleus where it functions as a transcription factor altering the expression of many genes. The endogenous glucocorticoid hormone cortisol can also activate MR. However, in most MR-expressing cells, there is concomitant expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme that converts cortisol to cortisone, which does not activate MR. MR is expressed in a wide variety of tissues, including the kidney, endothelial cells, vascular smooth muscle cells, cardiomyocytes, fibroblasts, and macrophages and in the central nervous system

(CNS).3 In the kidney, MR is found in the aldosterone-sensitive distal nephron (ASDN), in glomerular mesangial cells and podocytes, and in interstitial fibroblasts.

Pathogenesis of Aldosterone-Dependent Hypertension

Aldosterone increases BP through several mechanisms. Its effects on renal NaCl retention, leading to intravascular volume expansion, are well known but are not the only mechanism. Extrarenal MR activation leads to effects on the vasculature, CNS, peripheral nervous system, and other hormones (Fig. 39.2). It also has nonhemodynamic effects, such as activation of interstitial fibroblasts, that can contribute to development of hypertension and to progression of chronic kidney disease (CKD).[4] These multiple effects help explain why primary aldosteronism can cause refractory hypertension.

In the kidney, aldosterone stimulates renal sodium chloride retention by increasing expression of the amiloride-sensitive epithelial sodium channel (ENaC) in the collecting duct and the chloridereabsorbing protein pendrin in the cortical collecting duct.[5,6] Through nongenomic mechanisms, aldosterone also acutely stimulates sodium reabsorption in these segments.[7] Furthermore, aldosterone-induced hypokalemia increases expression of the Na^+Cl^- cotransport protein (NCC), the sodium-chloride cotransporter present in the distal convoluted tubule. Together, these effects on multiple Na^+ and Cl^- transporters lead to NaCl retention, intravascular volume expansion, and volume-dependent hypertension.

A second renal-mediated mechanism through which aldosterone increases BP involves its generation of hypokalemia. Aldosterone increases extrarenal cellular potassium uptake by stimulating the ubiquitous Na^+,K^+-ATPase pump. As discussed in Chapter 10, potassium depletion raises BP through a variety of mechanisms, including increased expression of NCC in the distal convoluted tubule, induction of renal interstitial injury, and direct vascular effects.

In addition, aldosterone has multiple direct effects on the vasculature. Aldosterone increases both basal vascular tone and vascular reactivity to circulating vasoconstrictors, including norepinephrine, epinephrine, Ang II, and vasopressin.[8] Aldosterone decreases flowmediated vasodilation, in part by decreasing nitric oxide production as a result of decreased endothelial nitric oxide synthase expression.[9] In addition, aldosterone leads to vascular inflammation and fibrosis, vascular stiffness, increased expression of proteins involved in atherosclerosis, and endothelial oxidative stress.[10]

The CNS control of BP is another mechanism through which aldosterone regulates BP. Aldosterone, through activation of CNS MR, stimulates CNS-mediated sympathetic nervous tone, which further increases BP.[11] CNS MR activation may also contribute to salt-sensitive hypertension and to effects of peripheral aldosterone on BP.

Biochemical Pathway for Aldosterone Synthesis
Cholesterol

17α-OHase

Pregnenolone

17-(OH)-pregnenolone

3β-hydroxysteroid dehydrogenase

Progesterone

17-(OH)-progesterone

21-hydroxylase (Cyp21)

11β-deoxycortisol

11β-deoxycorticosterone

11β-hydroxylase (Cyp11B1)

Corticosterone

17α-OHase

Cortisol

Aldosterone synthase
(Cyp11B2)
Aldosterone

Fig. 39.1 Biochemical pathway for aldosterone synthesis.

BOX 39.1

Factors That Regulate Aldosterone Release

Aldosterone-Independent Mineralocorticoid Receptor Activation

Stimulatory
Angiotensin II
Adrenocorticotropic hormone[a]
Potassium
Serotonin
Vasopressin
Endothelin-1
Estrogen (via GPER-1 receptor)
Parathyroid hormone
Leptin

MR can also be activated through mechanisms not involving aldosterone. As previously noted, cortisol, a naturally synthesized glucocorticoid, has an affinity for MR that is similar to that of aldosterone but has plasma levels about 100-fold greater than aldosterone. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which is expressed in the aldosterone-sensitive distal nephron, metabolizes cortisol to cortisone, which does not effectively bind to MR, thereby preventing glucocorticoid-dependent MR activation. Either the genetic deficiency of 11β-HSD2 or the ingestion of inhibitors of this enzyme can result in excessive activation of the MR and development of severe hypertension (see Chapters 40 and 49).12

A second aldosterone-independent mechanism that can activate MR involves Ang II. In the vasculature, in smooth muscle cells, Ang II acting through the angiotensin receptor blocker (ARB)-sensitive Ang II type 1 receptor activates MR through mechanisms that may involve post-translation modifications, such as phosphorylation.10 13

Another aldosterone-independent mechanism involves the Rho family small guanosine triphosphatase, Rac1. Rac1 activation increases MR expression, and its expression is increased by increased dietary NaCl intake.10 This effect can lead to Rac1-dependent dietary salt–evoked paradoxical MR activation that can lead to increased renal NaCl reabsorption through reduced oxidative stress and direct regulation of Na transporters.14

Lastly, the concept of differential aldosterone sensitivity is being increasingly recognized. This concept in based on the observation that similar levels of aldosterone lead to highly different BP responses in

Inhibitory
Atrial natriuretic peptide
Dopamine
Somatostatin
Estrogen (via ERβ receptor)

Both extracellular potassium and numerous hormones exert significant effects on aldosterone release. The primary effectors under most clinical circumstances are noted in italics.

aOnly acutely.

Data from Quinn SJ, Williams GH. Regulation of aldosterone secretion. Annu Rev Physiol. 1988;50:409–426; and Stowasser M, Gordon RD. Primary aldosteronism: Changing definitions and new concepts of physiology and pathophysiology both inside and outside the kidney. Physiol Rev. 2016;96:1327–1384.

Effects of Aldosterone on Blood Pressure

Low BP or reduced plasma volume
Angiotensinogen
Renin

Angiotensin I
ACE
↑ Blood
Pressure

Increased peripheral
sympathetic tone
↑ Endothelin

Renal NaCl
retention

Increased
vasoconstriction

Decreased
NO-mediated
vasodilation

Angiotensin II

CNS
Adrenal
gland

Aldosterone

Fig. 39.2 Summary of aldosterone's effects on blood pressure (BP) regulation. ACE, Angiotensin-converting enzyme; CNS, central nervous system; NO, nitric oxide.

different individuals and that MR blocker (MRB) medications exert profound effects on BP in some patients, particularly those with suppressed plasma renin levels, whereas it has substantially less effect in others.15 The mechanism of this differential sensitivity is incompletely understood at present, but it is possible that differences in tissue MR expression and/or downstream signaling pathways mediate these differences.

Types of Primary Aldosteronism

Primary aldosteronism can result either from unilateral or bilateral autonomous aldosterone production (Fig. 39.3). Typically, unilateral disease results from an aldosterone-producing adenoma (APA) and bilateral disease from hyperplasia. This association is not absolute, and about 10% of patients with primary aldosteronism have either bilateral adenoma, which may be microscopic, or unilateral hyperplasia. In general, an APA causes more severe primary aldosteronism than does adrenal hyperplasia, but this distinction is not sufficient to solely guide clinical decision making.

Most APAs are unilateral and are large enough (≥10 mm) to be seen with thin-slice computed tomography (CT) (Fig. 39.4). However, APAs may also be microscopic, and they may be bilateral. Hyperplasia is typically bilateral but occasionally is unilateral, and it may develop asynchronously in the two adrenal glands. Because unilateral adrenal hyperplasia is potentially curable with adrenalectomy, the absence of an identifiable adrenal adenoma on CT or magnetic resonance imaging (MRI) does not exclude the possibility of surgically treatable primary aldosteronism.

Familial Hyperaldosteronism

Recognizing the presence of familial forms of primary aldosteronism is important for both case detection in affected family members and because it may result in changes in management for selected forms.

Fig. 39.3 Adrenal Adenoma. An aldosterone-producing adrenal adenoma with typical cholesterol-rich yellow appearance.

Although identification of familial hyperaldosteronism (FH) was previously based on an arbitrary definition of the presence of two or more family members, improved understanding of the genetic causes has led to a classification system based on genomic DNA sequencing findings. Table 39.1 summarizes the different forms of FH. In some cases, the clinical presentation suggests the presence of a familial etiology, and in some the presentation is indistinguishable from sporadic forms. Except for familial hyperaldosteronism type I, identification of these familial forms, beyond allowing specific genetic testing of family members of affected individuals, does not alter treatment decisions at this time. The first identified was familial hypertension type I (FH-I), which is also known as glucocorticoid-remediable aldosteronism (GRA). In FH-I there is crossover between the CYP11B1 and CYP11B2 genes. This leads to a chimeric aldosterone synthase gene whose expression is regulated by ACTH, leading to excessive aldosterone release.16 17 FH-I is transmitted in an autosomal dominant pattern and should be considered in children or young adults with refractory hypertension or who have a family history of hypertension at a young age or history of premature hemorrhagic stroke.18 If suspected, genetic testing is the preferred diagnostic approach because this offers improved sensitivity and specificity over measurement of steroid metabolites or dexamethasone suppression testing.18 When FH-I is found, administering corticosteroids at the lowest dose necessary to suppress ACTH release often dramatically improves BP control (see Chapter 49). Concomitant MRB and/or anti-ENaC therapy may be necessary to avoid high doses of glucocorticoids with their associated side effects.

Familial hyperaldosteronism type II. In the past several years, there has been a fundamental change in our understanding of FH

Adrenal adenoma

type II (FH-II). Previously, FH-II was based on the presence of at least two family members with primary aldosteronism after excluding a diagnosis of FH-I. This definition almost certainly overestimated the frequency of FH because of misclassification of sporadic primary aldosteronism in multiple family members as FH-II. FH-II is now known to result from germline mutations in the gene, CLCN2, which encodes the chloride channel, ClC-2.19 20 These mutations lead to gain-of-function, increasing cellular Cl exit, which causes membrane depolarization. Membrane depolarization increases Ca^{2+} entry through voltage-sensitive calcium channels. Increases in intracellular Ca^{2+} lead to cellular proliferation and increased CYP11B2 expression, which increases aldosterone production and secretion. FH-II appears to present in childhood with severe primary aldosteronism.

Familial hyperaldosteronism type III. FH type III (FH-III) is the result of germline mutations in the KCNJ5 gene.21–23 The KCNJ5 gene encodes a K^+-channel that is a major determinant of adrenal cortical cell membrane voltage. Mutations observed in FH-III result in loss of K^+ selectivity, leading to Na^+ influx and membrane depolarization. Consequently, there is voltage-gated Ca^{2+} channel activation, increased cytosolic calcium, and stimulation of aldosterone production and adrenal cell proliferation. Although initial studies characterized FH-3 as having severe, often childhood-onset of hypertension, subsequent studies suggest the presentation is more variable.24

Familial hyperaldosteronism type IV. FH type IV (FH-IV) results from mutations in the CACNA1H gene, which encodes for a T-type calcium channel (CaV3.2).25 These mutations appear to lead to increased Ca^{+2} entry, increased cytosolic calcium, and stimulation of aldosterone production and adrenal cell proliferation. Clinical penetrance of the mutation is incomplete.

Sporadic Forms

Fig. 39.4 Adrenal Adenoma by Computed Tomography Scan. A normal linear image of the right adrenal gland (arrowhead) and expansion of the left adrenal with aldosterone-producing adenoma (~1 cm) (arrow).

TABLE 39.1

Our understanding of the factors that lead to sporadic forms of primary aldosteronism has advanced substantially. This is true for both unilateral autonomous aldosterone production associated with an APA and for bilateral autonomous aldosterone production. DNA sequencing,

Familial Hyperaldosteronism (FH)

Form

Affected Gene

Pathogenic Effect

Classic Presentation

Targeted Treatment

FH-I

Crossover of CYP11B1
promoter with CYP11B2
coding sequence

Aldosterone synthase expression under control of
ACTH-sensitive promoter

Severe hyperaldosteronism in
childhood or young adults
with autosomal dominant
inheritance

Low-dose glucocorticoids,
to suppress endogenous
ACTH production. May need
concomitant ARB and/or ENaC
inhibitor therapy.

FH-II

CLCN2

FH-III

KCNJ5

FH-IV

CACNA1H

None available
Gain-of-function mutation in the Cl⁻ channel ClC-2, Early-onset hypertension
leading to increased Cl⁻ efflux and subsequent
membrane depolarization
Membrane depolarization increases Ca2+ entry,
which leads to hyperplasia and increased
CYP11B2 expression
Loss of Na⁺ selectivity of K+ channel, GIRK4,
Severe early-onset
None currently available at
hypertension associated with present
leading to membrane depolarization, which
profound hypokalemia
Macrolide antibiotics are effective
increases Ca2+ entry and subsequent hyperplasia
and increased CYP11B2 expression
in vitro, but in vivo effects have
not been well characterized
Early-onset primary
None currently available
Mutation in the pore-forming α1 subunit of the
aldosteronism
voltage-sensitive calcium channel Cav3.2,
leading to increased Ca2+ entry and subsequent May be associated with
hyperplasia and increased CYP11B2 expression

developmental delay or
attention deficit disorder

ACTH, Adrenocorticotropic hormone; ARB, angiotensin receptor blocker; ENaC, epithelial sodium channel.

either “classic” Sanger sequencing, or immunohistochemistry-guided next-generation sequencing, shows that acquired somatic mutations lead to many cases of sporadic primary aldosteronism.19 26 Unilateral autonomous aldosterone production associated with an APA is frequently associated with KCNJ5 mutation in the APA and is found in as many as 80% of APA, with a higher frequency in Asian populations.19 27 In African Americans, somatic CACNA1D mutations appear to be the most frequently acquired mutation.28 Other genes in which somatic mutations have been found frequently include ATP1A1 and ATP2B3. Less frequently, mutations in CTNNB1 and PRKACA have been identified.19 27

Recent advances have also been made in understanding the pathogenesis of primary aldosteronism from bilateral adrenal hyperplasia.

Activating autoantibodies directed against the angiotensin II type 1 (AT1) receptor may activate the AT1 receptor, both directly stimulating adrenal aldosterone secretion and contributing to the hypertension through an aldosterone-independent mechanism involving AT1 receptor activation in vascular tissue.29 30 To date, the presence of these antibodies has been examined in only a limited number of patients. Additional studies are needed to examine how widespread this mechanism is and what proportion of cases of bilateral adrenal hyperplasia results from this mechanism.

EPIDEMIOLOGY

The apparent incidence of primary aldosteronism varies with the patient population and the diagnostic criteria used. Early studies, which only recognized severe cases, suggested that primary aldosteronism was rare, with an incidence of less than 1% to 2%. More sensitive diagnostic criteria have now led to the recognition that primary aldosteronism is relatively common.31 Patients with treatmentresistant hypertension—inadequately controlled hypertension despite treatment with three medications at appropriate dosages, including a diuretic—are quite likely to have primary aldosteronism, with rates typically of 20% to 40% and as high as 67% in some studies.32

Primary aldosteronism causes adverse effects that are independent of hypertension and hypokalemia. This includes an increased risk of cardiac arrhythmias, both atrial and ventricular, cerebrovascular events, and coronary heart disease.33 Diagnosing and treating the primary aldosteronism, whether with adrenalectomy or with MRBs, as clinically appropriate, substantially reduces, and may even fully correct, this increased risk.34 35 Finally, primary aldosteronism is associated with a variety of neuropsychiatric disorders, ranging from depression and anxiety to lethargy, fatigue, and difficulties with concentration. Appropriate treatment of the primary aldosteronism may improve these symptoms.24

EVALUATION AND DIFFERENTIAL DIAGNOSIS

Who to Evaluate for Primary Aldosteronism

We recommend a liberal policy for testing patients for primary aldosteronism. This involves testing patients who have early-onset hypertension, baseline or easily provoked hypokalemia, or hypertension not effectively controlled with routine antihypertensive therapy. Some evidence suggests patients with hypertension and atrial fibrillation should be screened for primary aldosteronism.36 Patients with hypertension and a known adrenal adenoma should also undergo testing. Finally, hypertensive patients with a family history of primary aldosteronism should be tested. It is important to recognize that the absence of hypokalemia or metabolic alkalosis does not exclude the diagnosis of primary aldosteronism.

Evaluation of Suspected Primary Aldosteronism

Evaluation of patients with suspected primary aldosteronism is directed at identifying those who have autonomous aldosterone release, followed by determining whether treatment should be based on a pharmacologic or a surgical approach (Fig. 39.6).

The diagnosis of primary aldosteronism requires evidence of autonomous aldosterone production. As previously detailed, the major factors that stimulate aldosterone production involve Ang II-dependent and hyperkalemia-dependent stimulation of the adrenal gland. Thus, autonomous aldosterone production is identified by inappropriate aldosterone production in view of Ang II and serum/plasma K+.

Hyperkalemia, if present, should be corrected before screening to eliminate this possible stimulus for aldosterone production. Because Ang II cannot be assayed with routine clinical tests, plasma renin is used as a surrogate. A random blood sample is used to measure plasma aldosterone and renin. This test should be obtained in early morning because of diurnal variations in plasma aldosterone and plasma renin activity.

The question as to whether to hold medications that can alter the reninangiotensin-aldosterone system and, if so, for how long before testing is complex and is discussed in detail later. If the aldosterone/renin ratio (ARR) is elevated, this suggests there is significant Ang II–independent aldosterone release, providing presumptive evidence of autonomous aldosterone production consistent with primary aldosteronism.

Incidence of Primary Hyperaldosteronism in
Patients With Differing Degrees of Hypertension
13.2%
14

Identifying patients with primary aldosteronism purely on clinical characteristics is difficult. Some patients with primary aldosteronism have features suggestive of secondary hypertension, such as early onset of hypertension or the need for multiple drugs for BP control. Others present with either frank or easily provoked hypokalemia. In hypertensive patients with atrial fibrillation without a known cause of atrial fibrillation, primary aldosteronism may be present in as many as 42%.36 Many, however, have no distinguishing characteristics that differentiate them from individuals with essential hypertension. The incidence of primary aldosteronism in a hypertensive population parallels the severity of hypertension, although 1% to 2%, and possibly as many as 13%, of normotensive individuals show evidence of autonomous aldosterone production (Fig. 39.5).31 37

12
Incidence (%)

CLINICAL MANIFESTATIONS

8.0%

10
8
6
4

1.6%

2.0%

2
0

Normal
Stage 1
Stage 2

Stage 3
SBP <130
140-159
160-179
>180
DBP <85
90-99
100-109
>110

Fig. 39.5 Incidence of primary aldosteronism in patients with differing degrees of hypertension. DBP, Diastolic blood pressure; SBP, systolic blood pressure. (From Mosso L, Carvajal C, Gonzalez A, Barraza A, Avila F, Montero J, et al. Primary aldosteronism and hypertensive disease. Hypertension. 2003;42:161–165.)

Diagnostic Strategy for Evaluation of Primary Hyperaldosteronism
Refractory hypertension

Aldosterone/renin ratio

<25

>50 and [aldo] >8

ARR 25–50

Primary
aldosteronism
unlikely

Confirmatory testing

Negative

Start MRB

Positive

Surgical candidate?

Yes

No

Adrenal imaging
CT scan

Optimize MRB

Positive

Negative

Adequate
BP response?

Continue MRB

Adrenal vein
aldosterone sampling

Unilateral aldosterone
release

No

Yes

Bilateral aldosterone
release
Optimize MRB

Laparoscopic
adrenalectomy

Fig. 39.6 Diagnostic Strategy for Evaluation of Primary Aldosteronism. Aldosterone-renin ratio (ARR) is calculated using measurement of plasma renin activity. If direct renin immunoassay is used, the resulting ARR calculation should be multiplied by approximately 8 for use with this diagnostic algorithm. BP, Blood pressure; CT, computed tomography; MRB, mineralocorticoid receptor blocker.

Currently, two types of renin assays are in routine clinical use. One measures renin activity, assayed as the rate of conversion of angiotensinogen to angiotensin I (Ang I), and the second measures the amount of immunoreactive renin. These two techniques yield results that correlate well with each other, but the units and numerical values obtained differ. For the plasma renin activity, the normal range is 1.9 to 3.7 ng Ang I/mL/hr, and the lower level of detectability is approximately 0.1 ng Ang I/mL/hr in most clinical laboratories. For the direct renin assay, the normal range is typically 13 to 44 IU/mL and the lower level of detectability is approximately 28 IU/mL. Therefore, the typical ARR, for a patient with primary hypertension not receiving drugs that alter the renin-angiotensin system (RAS), is about 10:1 when using the plasma renin activity, and 1:1 with the direct renin assay. Currently, an ARR greater than 25 ng/dL per ng/(mL/h) or 650 pmol per µg/(L/h), depending on the units used for aldosterone measurement, is considered elevated. If using direct renin measurements, the cut-off is 2.3 ng/dL per mIU/L or 60 pmol per mIU/L.

TABLE 39.2

Confirmatory Testing for Primary Aldosteronism

Test

Method

Oral salt loading

Oral NaCl intake >200 mmol/d for 3 days, with oral KCl Urine aldosterone <10 µg/d, diagnosis
as needed to prevent hypokalemia, with subsequent
unlikely; >12 µg/d, primary aldosteronism
24-hr urine aldosterone measurement
likely

Saline infusion test

Patient in recumbent position for 1 hr before testing
Plasma aldosterone at end of infusion <5
Avoid if severe uncontrolled
and then throughout entire test
ng/dL, primary aldosteronism unlikely;
hypertension, CKD, CHF, cardiac
Begin test between 8 and 9:30 am; measure plasma
>10 ng/dL, diagnosis likely; 5–10 ng/dL,
arrhythmias, or severe hypokalemia
aldosterone, plasma renin activity, cortisol, and
indeterminate
potassium at beginning of test and then after
infusing 2 l NS IV over 4 hr
Oral fludrocortisone, 0.1 mg every 6 hr for 4 d, plus oral Upright plasma aldosterone on day 4 >6 ng/ Requires very close follow-up
NaCl, 30 mmol 3×/d, and high-salt diet combined
dL and plasma renin activity <1 ng/mL/hr,
to monitor blood pressure and
with sufficient KCl to avoid hypokalemia
primary aldosteronism likely
potassium
Plasma aldosterone and plasma renin activity obtained Plasma aldosterone decrease >30%, primary Probably more false-positive and falsealdosteronism unlikely
negative results than other tests
immediately before oral captopril, 25–50 mg, is
given and then 1–2 hr afterward, with patient seated
throughout test

Fludrocortisone
suppression test
Captopril challenge
test

Evaluation

Limitations
Avoid if severe uncontrolled
hypertension, CKD, CHF, cardiac
arrhythmias, or severe hypokalemia

CHF, congestive heart failure; CKD, chronic kidney disease; IV, intravenously; NS, normal saline.

Although an elevated aldosterone in combination with an elevated ARR strongly suggests primary aldosteronism, the ARR may be elevated even with suppressed plasma aldosterone production if plasma renin activity (or concentration) is substantially suppressed. In this event, the elevated ARR may represent a false-positive screening test. We recommend that a combination of an elevated ARR and a “nonsuppressed” aldosterone level should be used for case-screening for primary aldosteronism. The minimal plasma aldosterone level that may be associated with aldosteronism is unclear. We recommend using a minimal value of 8 ng/dL to make a diagnosis of primary aldosteronism.38 Others recommend using a cutoff of 15 or even 20 ng/dL.39 40 We recommend the lower cutoff because about 40% of patients with primary aldosteronism have plasma aldosterone levels between 9 and 16 ng/dL,37 41 and about 20% of those with unilateral autonomous adrenal aldosterone production have levels less than 15 ng/dL.41

Effect of Medications on Screening for Primary Aldosteronism

Many medicines commonly used for the treatment of hypertension can alter either plasma aldosterone or renin release and thereby alter the ARR.40 42 β-Adrenergic receptor antagonists (β-blockers) suppress renin but generally do not cause the nearly complete renin suppression typically seen in primary aldosteronism. Angiotensin-converting enzyme (ACE) inhibitors (ACE-I) and ARBs, along with diuretics, can increase renin release in normal individuals, which theoretically might decrease the sensitivity of ARR measurement. However, the effect of ACE-Is and ARBs to increase renin release can also be an advantage. In patients using either an ACE-I or an ARB, a suppressed renin in combination with a nonsuppressed aldosterone (>8 ng/dL) is highly specific for primary aldosteronism. MRBs such as spironolactone and eplerenone can elevate the plasma renin activity and impair the sensitivity of testing. Direct renin inhibitors have been reported to both increase and decrease plasma renin activity in patients who presumably have essential hypertension and to decrease plasma aldosterone. Their effect on plasma renin activity and ARR in patients with primary aldosteronism is presently not known.

When to Hold Medications That Affect the RAS System Before Screening

The decision whether to hold medications that affect the reninangiotensin-aldosterone system requires the clinician to balance competing priorities. Holding these medications, which includes diuretics, ACE-Is, ARBs, direct renin inhibitors, and β-blockers, improves the diagnostic accuracy of the plasma aldosterone and plasma renal activity. However, in the patient with poorly controlled hypertension, discontinuing these medications and attempting to control the blood pressure solely with calcium channel blockers, α-adrenergic blockers, and direct vasodilators can be problematic. In one study, as many as 38% of patients with difficult-to-control hypertension experienced one or more related adverse effects.43 Moreover, the amount of time drugs should be stopped to completely reverse their effects on the adrenal gland is not clear.

The observation that patients with refractory hypertension who do not have primary aldosteronism respond similarly well to MRB therapy as those who do44 45 suggests that accurate diagnosis may only be needed to guide whether to pursue evaluation of unilateral autonomous aldosterone production. If medications are to be withheld, it should be done carefully using standardized protocols with extensive safety monitoring.

In patients being evaluated because they have an adrenal adenoma and who do not have resistant hypertension or substantial hypokalemia, the risk/benefit balance may differ. In this latter group, the clinical difficulty and the risks to the patient from changing medications are less substantial, and the utility of accurately identifying clinical milder forms of primary aldosteronism may be greater.

Confirmatory Testing

If the diagnosis of primary aldosteronism is in doubt, several confirmatory tests can be used. Table 39.2 summarizes the various confirmatory testing methods in routine use. Recent studies suggest that confirmatory testing may not be needed in patients with spontaneous hypokalemia, plasma aldosterone greater than 20 ng/dL, and completely suppressed renin46 or in patients with plasma aldosterone greater than 30 ng/dL with a suppressed renin.47 Both the risks and the benefits of confirmatory testing must be considered.38 No confirmatory test has 100% sensitivity or specificity. Moreover, confirmatory testing has complicating issues associated with its performance. Salt loading, if used for testing, can raise BP and worsen hypokalemia and is problematic in the patient who already has poorly controlled hypertension. Testing also requires the patient not use any medications that interact with the RAS, which means discontinuing β-blockers, ACE-Is, ARBs, MRBs, direct renin inhibitors, and diuretics; this can lead to significant worsening of hypertension control.38 How long these medications should be held is not clear. Acute effects will dissipate within days as the medications are metabolized, but chronic effects on expression of proteins involved in adrenal aldosterone metabolism may persist longer.

Confirmatory testing should be considered if the diagnosis is in doubt and if it will substantially alter management. In general, patients with resistant hypertension respond to MRBs with significant BP improvement regardless of whether they have primary aldosteronism.44 45 Because of this, confirmatory testing may not alter the decision as to whether to use MRB therapy in this population. We generally reserve confirmatory tests for patients with an adrenal adenoma found for unrelated reasons who have mild hypertension and are under evaluation for possible adrenalectomy. In this latter patient population, the benefits of MRB therapy are less clear, and the clinical risks associated with holding RAS blockers are substantially less.

Unilateral Versus Bilateral Differentiation

Selection of Patients for Further Testing

Once primary aldosteronism is diagnosed, the clinician should consider the possibility that the patient has unilateral aldosterone release, in which case adrenalectomy may be curative. However, this step is important only if the patient is both an appropriate surgical candidate and the patient desires possible surgical intervention. If either condition is not met, then further evaluation is not necessary, and the patient can be treated with MRB therapy.

Imaging Approaches

Adrenal imaging is typically the next step in evaluation. Unilateral autonomous aldosterone production is often the result of an aldosterone-producing adenoma (see Fig. 39.3), which is frequently sufficiently large to be identified by thin-slice (1 mm) CT (see Fig. 39.4). However, in some cases, microadenoma that are not detectable with current imaging approaches are the cause of unilateral autonomous aldosterone release. Bilateral autonomous aldosterone production is typically not associated with the presence of a detectable functional adenoma, but nonfunctional adrenal adenomas are frequent, and their incidence increases with age. Consequently, the presence of an adenoma on imaging studies does not necessarily indicate unilateral disease, and its absence does not necessarily indicate bilateral aldosterone production. Overall, an adrenal adenoma in a patient with primary aldosteronism has an approximately 70% to 80% chance that it is functional (i.e., an APA is present) and a 20% to 30% chance that it is a nonfunctional adenoma.48 In patients younger than 40 years old, the likelihood of a nonfunctional adenoma is less, and the likelihood of an APA is greater. The absence of a detectable adenoma indicates bilateral aldosterone production in 70% to 80% of cases, but there is a 20% to 30% chance of unilateral aldosterone production.

Adrenal Vein Sampling

Adrenal vein sampling is the definitive test for determining whether autonomous aldosterone release is unilateral or bilateral. This is a technically difficult procedure and should be performed in a specialized center experienced with it. When interpreting adrenal vein sampling results, the first step is to confirm sampling of both the right and left adrenal veins. The right adrenal vein is short and may have a common insertion into the inferior vena cava (IVC) as the inferior accessory hepatic vein, making successful cannulation difficult. Accordingly, biochemical confirmation of successful adrenal vein sampling should be employed. This is done by measuring the concentration of a hormone produced in the adrenal gland and showing that the observed

Formulas Used to Interpret Adrenal Vein Sampling Results

TABLE 39.3

Name	Formula	Comment
Selectivity index (SI)	$SI_X = [Cortisol_X]/[Cortisol_{IVC}]$	Metanephrine or androstenedione measurements may be substituted for cortisol.
Lateralization index (LI)	$LI = \frac{[Aldo_A]/[Cortisol_A]}{[Aldo_B]/[Cortisol_B]}$	Calculate using the adrenal vein sample with the higher aldosterone concentration as sample A and the contralateral samples as sample B.

concentration is significantly greater than in the IVC. To quantitatively evaluate whether the adrenal veins were successfully cannulated, a selectivity index is calculated from the adrenal vein and IVC cortisol concentrations (Table 39.3). The higher the selectivity index, particularly if it is greater than 2 in unstimulated and greater than 5 in stimulated samples, the greater the confidence that the sample accurately reflects adrenal origin.[49] Cortisol is the most frequently measured analyte, but metanephrine or androstenedione can also be used.[50,51] Stimulation of cortisol production with cosyntropin can facilitate confirmation of adrenal vein cannulation by increasing adrenal cortisol production, which increases adrenal vein cortisol levels acutely with minimal effects on IVC cortisol. However, cosyntropin can also stimulate aldosterone secretion, which can lead to differing conclusions as to whether aldosterone production is unilateral or bilateral in as many as 25% of cases.[52]

The lateralization index (LI) is then determined to assess aldosterone lateralization. After confirming successful adrenal vein sampling, the ratio of adrenal vein aldosterone to adrenal vein cortisol is calculated for each adrenal vein (see Table 39.2). The LI is calculated by dividing the greater adrenal vein ratio by the lesser adrenal vein ratio. An LI greater than 2.0 supports a diagnosis of an aldosterone-producing adenoma, but this cutoff is not 100% specific. Our practice is to use an LI greater than 2.0 to indicate an aldosterone-producing adenoma if this is concordant with imaging findings. If the LI finding is discordant with imaging, we consider a LI between 2 and 4 an indeterminant finding. The importance of interpreting adrenal vein sampling in context of the clinical situation is exemplified by the finding that adrenal vein sampling performed twice within 5 minutes had a discordance rate of 13% for the selectivity index and 10% for the LI.53

Other Testing Options

Many other diagnostic tests have been suggested in the evaluation of primary aldosteronism to differentiate unilateral from bilateral disease, but none has widespread acceptance. Noninvasive physiologic tests, such as saline suppression test and postural stimulation tests, rely on the association that APA-mediated aldosterone release is typically not stimulated by Ang II, whereas in hyperplastic lesions, Ang IIdependent stimulation is generally retained. All medicines that affect the RAS, including diuretics, β-blockers, ACE-Is, and ARBs, must be stopped before testing, but the difficulty in controlling BP in these patients without these medicines often limits the utility of this test. In addition, the association of Ang II-stimulated aldosterone production is discordant with whether aldosterone release is unilateral or bilateral in as many as 20% of cases, leaving this test result insufficiently accurate to determine whether surgical therapy is appropriate in most cases. Its main role may be in the evaluation of the patient with an adrenal adenoma and unsuccessful adrenal vein sampling.54

Aldosterone Breakthrough

Approximately 30% to 40% of patients treated with an ACE-I or ARB respond with an initial decrease in the plasma aldosterone levels, which is then followed by a return of their aldosterone level to baseline, or even above baseline, levels. This is termed aldosterone breakthrough.55 Mechanisms that have been proposed to explain this include ACEindependent Ang II generation, Ang II–independent stimulation of aldosterone generation, possibly via either ACTH or ANP, and alterations in endothelial nitric oxide formation.55,56 Aldosterone breakthrough likely contributes to the development of resistant hypertension in patients being treated with an ACE-I or ARB and likely contributes to progressive kidney disease in CKD.

Metabolic Syndrome

The metabolic syndrome is associated with elevated plasma aldosterone levels,57 which may contribute to the associated, and often resistant, hypertension. However, it does not appear to be associated with changes in plasma renin activity.57 The mechanism of the increased plasma aldosterone may involve adipocyte production of cytokines that stimulate adrenal sensitivity to Ang II.58 It may also involve fructose, a common pathogenic factor in the metabolic syndrome, stimulating vasopressin release, which stimulates ACTH release59 and thereby increases aldosterone production. Vasopressin may also directly increase adrenal aldosterone secretion.60

NATURAL HISTORY

The natural history of untreated primary aldosteronism leads to a variety of significant complications. Clearly, it is a major cause of worsening hypertension, and it also increases the incidence of hypokalemia, with its adverse chronic effects. In addition, it leads to a wide variety of end-organ complications. These end-organ effects include increased risks of coronary heart disease, atherosclerotic peripheral vascular disease, cardiac arrhythmias, left ventricular hypertrophy, low bone mineral density, and development of CKD.33,61 The incidence of these complications appears to be twofold greater than in patients with essential hypertension of the same magnitude. These effects appear to be related to excessive activation of mineralocorticoid receptors in these end-organ tissues and therefore reflect a direct, and blood pressure-independent, disease association. Effective treatment of primary aldosteronism appears to substantially improve these risks. Therefore, treatment either with MRBs or with adrenalectomy is recommended for all patients with primary aldosteronism.

TREATMENT

Adrenalectomy

Patients with unilateral autonomous aldosterone production, typically from an APA, who are acceptable surgical candidates, can have a dramatic response to adrenalectomy. Patients with an APA who undergo adrenalectomy have a greater than 95% likelihood of biochemical cure and a 30% to 60% chance of hypertension cure.62,63 Patients most likely to have their hypertension cured are female, younger than 50 years, and have shorter duration of hypertension, lower body mass index, and few family members with primary hypertension. Those not cured have a greater than 95% chance of BP improvement.62,63 The lack of complete cure may reflect microvascular disease that developed because of the poorly controlled hypertension and/or hypokalemia. Adrenalectomy performed using a laparoscopic approach is associated with a relatively short hospital stay, low postoperative morbidity, and a

rather quick return to normal health, at least compared with a nonlaparoscopic surgical approach. Adrenalectomy should not be performed in patients with bilateral autonomous aldosterone production because unilateral adrenalectomy is not curative and bilateral adrenalectomy is associated with unacceptable long-term complications because of the induction of deficiency of other adrenal hormones, such as glucocorticoids and catecholamines.

Mineralocorticoid Receptor Blocker Therapy

Patients who are not candidates for surgical adrenalectomy or who have bilateral aldosterone production should be treated with MRBs. Current MRB treatment options are spironolactone and eplerenone. Many patients will find that their responses are delayed, and monthly dose adjustments are often needed until an optimal dose is identified. It is possible that some of the effects of MRB therapy may also be mediated through effects on pannexin.64

The choice of which MRB to use involves consideration of effectiveness and side effects. Importantly, the treatment efficacy of these two agents is quite different. Spironolactone is more effective than eplerenone at improving BP, yielding almost twice as great a BP reduction and a substantially greater proportion of patients experiencing a significant BP improvement.65 Spironolactone also has off-target effects on sex-steroid hormone receptors, which can lead to breast enlargement (gynecomastia) in men and breast tenderness (gynecodynia) and menstrual irregularities in women. These side effects are dose-dependent and are typically mild or absent at doses of 100 mg per day or less. Eplerenone is more selective than spironolactone for the mineralocorticoid receptor, and the risk of these side effects is less, but its efficacy is also less.

Based on its greater treatment efficacy, we recommend spironolactone as the preferred initial agent for medical treatment of primary aldosteronism. Treatment with an MRB usually results in dramatically improved BP control. Many patients will respond to a low dose of spironolactone (25–50 mg daily) as initial therapy. Both systolic BP and diastolic BP often decrease by about 25 mm Hg over a few weeks to months. Dosage of the MRBs can be increased as necessary but generally should not be changed more than every 2 to 4 weeks. If present, hypokalemia and metabolic alkalosis typically improve. Potassium supplements can often be stopped when MR therapy is initiated; if not, the dose can often be tapered rapidly. Because there is significant interpatient variability in the serum K+ response after initiating MRB therapy, close follow-up is needed.

With time, BP can be controlled in many patients with an MRB and a single alternative agent. We typically use ACE-Is or ARBs because renin activity, which is suppressed initially, typically increases after starting MRB therapy. Synergistic use of an ACE-I or ARB may prevent development of a renin-stimulated, Ang II–dependent component of hypertension. However, many antihypertensive combinations can be used successfully with the MRB.

Many of the side effects of MRBs can be easily managed. Muscle cramps occur with both spironolactone and eplerenone. Changing from one MRB to the other often allows resolution of the muscle cramps. MRBs can cause neuropsychiatric side effects that are often nonspecific and can include symptoms of feeling out of touch with reality, difficulty thinking, and decreased attention and performance in various memory tasks.65,66 In general, these effects are temporary and resolve within a few weeks.

Other MRBs are in development and may become available for use soon. Finerenone is a novel, selective, nonsteroidal MRB that may have less effect on serum potassium and slows the progression of diabetic nephropathy.67 This may make this medication useful in selected patients. Multiple other nonsteroidal MRBs are also in development.68

Plasma Renin Activity Predicts Risk of Cardiovascular Events During
Mineralocorticoid Receptor Blocker Therapy
Primary aldosteronism (PRA <1 μg/L per h) treated with MR antagonists (adjusted)
Primary aldosteronism (PRA <1 μg/L per h) treated with MR antagonists
(unadjusted)
Primary aldosteronism (PRA ≥1 μg/L per h) treated with MR antagonists (adjusted)
Primary aldosteronism (PRA ≥1 μg/L per h) treated with MR antagonists
(unadjusted)
Essential hypertension (adjusted)
Essential hypertension (unadjusted)

Cumulative incidence of composite cardiovascular events (%)

100

80

Adjusted HR (primary aldosteronism with PRA <1 μg/L per h vs
essential hypertension) = 2.83 (95% Cl 2.11–3.80)
Adjusted HR (primary aldosteronism with PRA ≥1 μg/L per h vs
essential hypertension) = 1.09 (95% Cl 0.56–2.10)

60

Adjusted HR (primary aldosteronism with PRA <1 μg/L per h vs
primary aldosteronism with PRA ≥1 μg/L per h)
2.60 (95% Cl 1.27–5.32)
40

20

0
0

2.5

5
Years

7.5

10

Primary
aldosteronismPRA <1 μg/L/h

134

83

52

31

13

Primary
aldosteronismPRA ≥1 μg/L/h

67

46

29

19

12

Number at risk

Essential
41,853
34,423
25,870
18,261
12,453
hypertension

Fig. 39.7 Plasma Renin Activity Predicts Risk of Cardiovascular Events During Mineralocorticoid Receptor Blocker (MRB) Therapy of Primary Aldosteronism. Patients with primary aldosteronism treated with MRBs that have plasma renin activity of at least 1 ng/mL/hr have a composite risk of cardiovascular events not significantly different from matched patients with essential hypertension. Those patients with plasma renin activity less than 1 ng/mL/hr have a significantly increased hazard ratio (HR) for composite cardiovascular events 2.83-fold greater. CI, Confidence interval; PRA, plasma renin activity; MR, mineralocorticoid receptor. (From Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018;6:51–59.)

Monitoring Mineralocorticoid Receptor Blocker Therapy With Plasma Renin Measurements

Primary aldosteronism is associated with end-organ complications, particularly affecting the cardiovascular system, whose frequency is greater than that expected from the associated hypertension. This suggests that treatment of primary aldosteronism directed solely at controlling BP may not fully reverse the adverse consequences of primary aldosteronism. Assessment of the plasma renin activity response during therapy may be helpful (Fig. 39.7). Recent studies show that MRB therapy that results in reversal of the plasma renin suppression, to greater than 1 ng/mL/hr, is associated with major cardiovascular events, mortality, and atrial fibrillation rates similar to matched patients with essential hypertension.34 35 In contrast, in those treated with MRB therapy who continue to have suppressed plasma renin activity, less than 1 ng/mL/hr, these rates remain approximately twofold elevated.34 35 Although alternative explanations other than therapy effectiveness are possible, we recommend using a plasma renin-guided therapeutic approach, adjusting the MRB dose on a 1- to 2-month basis targeting a plasma renin activity greater than 1 ng/mL/hr.

Choice of Adrenalectomy Versus MRB Therapy

The choice of adrenalectomy versus MRB therapy for the patient with unilateral autonomous aldosterone production is often not easy. Adrenalectomy is associated with a greater than 95% biochemical cure, and with clinical cure (normotension and normokalemia without medications) of 30% to 60%. Studies comparing outcomes in patients with unilateral primary aldosteronism treated with adrenalectomy versus medical therapy have suggested benefits from adrenalectomy in terms of lower all-cause mortality, reduced risk of stroke and atrial fibrillation, and regression of left ventricular hypertrophy in patients treated with adrenalectomy rather than MRB therapy.19 69 However, whether the patients treated with MRB therapy had normalization of the plasma renin is unknown, and if they did not, whether renin-guided medical therapy would have resulted in equivalent outcomes as adrenalectomy is also unknown. Finally, many patients are elderly, have significant comorbid medical conditions that make adrenalectomy relatively contraindicated, or prefer not to undergo elective surgery.

Nonmineralocorticoid Receptor Blocker Therapy

In occasional patients, high doses of MRBs will not be sufficient to block the effects of aldosterone on BP, potassium, and plasma renin. In this case, addition of a medication that specifically blocks aldosterone's effect on renal NaCl reabsorption can be helpful. Aldosterone specifically stimulates the distal epithelial cell Na+ transporter, ENaC, which contributes to the volume expansion and resultant hypertension. Use of ENaC inhibitors, such as amiloride or triamterene, in combination with MRBs may be helpful. We typically use amiloride, starting at 5 mg by mouth daily and titrating as needed.

Aldosterone synthase inhibitors are a new treatment option under development.70 These medications directly inhibit adrenal aldosterone synthesis, leading to decreased plasma aldosterone levels and improvements in BP control. Because they do not target MR, their side effect profile is likely to differ from that seen with MRBs, although the development of hyperkalemia is not likely to differ.

Considerations in the Treatment of Patients With Chronic Kidney Disease

CKD is common in patients with primary aldosteronism,71 72 which leads to several concerns regarding changes in serum/plasma K+ and GFR. This frequency may be because of direct effects of aldosterone to stimulate renal fibrosis and glomerular injury, manifested initially as albuminuria, and to indirect effects resulting from the associated hypertension and, if present, hypokalemia. Because aldosterone also stimulates glomerular hyperfiltration, which may contribute to renal injury, the full extent of renal injury may not be evident until the primary aldosteronism is adequately treated. Anticipating and then appropriately responding to these effects is helpful for the management of the patient with CKD and primary aldosteronism.

Patients with CKD who are treated with an MRB may be more likely to develop clinically significant hyperkalemia during treatment. Treatment with a K+-binding polymer, such as patiromer or sodium zirconium cyclosilicate, can facilitate treatment, enabling continued MRB use with less risk of hyperkalemia,73 and the beneficial effect is maintained even if eGFR is between 25 and less than 30 mL/min/1.73 m2 74 Our recommendation is to follow closely patients who have CKD who are started on MRB therapy for the development of hyperkalemia. If it occurs, we then start therapy with a K+-binding resin (see above), dosed as needed to control the serum/plasma K+. Although this approach is supported by the benefit of MRB treatment to improve BP and to slow the progression of CKD, whether correcting the hyperkalemia by addition of a K+ binder versus discontinuation of MRB deserves further study.

Second, initiation of MRB therapy can be associated with an acute decrease in eGFR in patients with CKD. However, patients with a greater acute decrease had a slower long-term eGFR decline.75 Acute decreases in eGFR after initiating therapy with an MRB does not need to be an indication to discontinue therapy.

SELF-ASSESSMENT QUESTIONS

1. The most common genetic cause of primary aldosteronism because of an APA is related to a mutation in which protein?
A. Aldosterone synthase
B. Mineralocorticoid receptor
C. AT1 receptor
D. Potassium channel (KCNJ5)
E. Sodium channel (ENaC)
2. Based on recent comparative studies, which of the following MR antagonists for primary aldosteronism is preferred and for what reason?
A. Eplerenone because of greater efficacy

B. Eplerenone because of fewer side effects and less drug discontinuation
C. Spironolactone because of greater efficacy
D. Spironolactone because of fewer side effects and less drug discontinuation
3. Which of the following is the preferred first-line test for identification of primary aldosteronism?
A. Serum potassium
B. Plasma aldosterone
C. Plasma renin activity
D. ARR in combination with absolute level of plasma aldosterone
E. Urinary sodium and potassium excretion rate

REFERENCES

1. Quinn SJ, Williams GH. Regulation of aldosterone secretion. Annu Rev Physiol. 1988;50:409–426.
2. Spat A, Hunyady L. Control of aldosterone secretion: a model for convergence in cellular signaling pathways. Physiol Rev. 2004;84:489–539.
3. Nishiyama A. Pathophysiological mechanisms of mineralocorticoid receptor-dependent cardiovascular and chronic kidney disease. Hypertens Res. 2019;42:293–300.
4. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney Int. 2019;96:302–319.
5. Verlander JW, Hassell KA, Royaux IE, et al. Deoxycorticosterone upregulates PDS (Slc26a4) in mouse kidney: role of pendrin in mineralocorticoid-induced hypertension. Hypertension. 2003;42:356–362.
6. Blazer-Yost BL, Liu X, Helman SI. Hormonal regulation of ENaCs: insulin and aldosterone. Am J Physiol. 1998;274:C1373–C1379.
7. Wingo CS, Kokko JP, Jacobson HR. Effects of in vitro aldosterone on the rabbit cortical collecting tubule. Kidney Int. 1985;28:51–57.
8. Berecek KH, Stocker M, Gross F. Changes in renal vascular reactivity at various stages of deoxycorticosterone hypertension in rats. Circ Res. 1980;46:619–624.
9. Nishizaka MK, Zaman MA, Green SA, Renfroe KY, Calhoun DA. Impaired endothelium-dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism. Circulation. 2004;109:2857–2861.
10. DuPont JJ, Jaffe IZ. 30 years of the mineralocorticoid receptor: the role of the mineralocorticoid receptor in the vasculature. J Endocrinol. 2017;234:T67–T82.
11. Gomez-Sanchez EP. Brain mineralocorticoid receptors: orchestrators of hypertension and end-organ disease. Curr Opin Nephrol Hypertens. 2004;13:191–196.
12. Rogerson FM, Fuller PJ. Mineralocorticoid action. Steroids. 2000;65:61–73.
13. Jaffe IZ, Mendelsohn ME. Angiotensin II and aldosterone regulate gene transcription via functional mineralocortocoid receptors in human coronary artery smooth muscle cells. Circ Res. 2005;96:643–650.
14. Nagase M. Role of Rac1 GTPase in salt-sensitive hypertension. Curr Opin Nephrol Hypertens. 2013;22:148–155.
15. Gray Z, Tu W, Chertow GM, Bhalla V. Aldosterone sensitivity: an opportunity to explore the pathogenesis of hypertension. Am J Physiol Renal. 2021;320. F325-F35.
16. Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;355:262–265.
17. Pascoe L, Curnow KM, Slutsker L, et al. Glucocorticoid-suppressible hyperaldosteronism results from hybrid genes created by unequal crossovers between CYP11B1 and CYP11B2. Proc Natl Acad Sci U S A. 1992;89:8327–8331.
18. Zennaro MC, Jeunemaitre X. SFE/SFHTA/AFCE consensus on primary aldosteronism, part 5: genetic diagnosis of primary aldosteronism. Ann Endocrinol (Paris). 2016;77:214–219.
19. Zennaro MC, Boulkroun S, Fernandes-Rosa FL. Pathogenesis and treatment of primary aldosteronism. Nat Rev Endocrinol. 2020;16:578–589.
20. Scholl UI, Stolting G, Schewe J, et al. CLCN2 chloride channel mutations in familial hyperaldosteronism type II. Nat Genet. 2018;50:349–354.
21. Geller DS, Zhang J, Wisgerhof MV, Shackleton C, Kashgarian M, Lifton RP. A novel form of human mendelian hypertension featuring nonglucocorticoid-remediable aldosteronism. J Clin Endocrinol Metab. 2008;93:3117–3123.
22. Choi M, Scholl UI, Yue P, et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science. 2011;331:768–772.
23. Mulatero P, Tauber P, Zennaro MC, et al. KCNJ5 mutations in European

families with nonglucocorticoid remediable familial hyperaldosteronism. Hypertension. 2012;59:235–240.

24. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both inside and outside the kidney. Physiol Rev. 2016;96:1327–1384.
25. Scholl UI, Stolting G, Nelson-Williams C, et al. Recurrent gain of function mutation in calcium channel CACNA1H causes early-onset hypertension with primary aldosteronism. Elife. 2015;4:e06315.
26. Mulatero P, Monticone S, Deinum J, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the working group on endocrine hypertension of the european society of hypertension. J Hypertens. 2020;38:1919–1928.
27. Lenzini L, Rossitto G, Maiolino G, Letizia C, Funder JW, Rossi GP. A meta-analysis of somatic KCNJ5 K(+) channel mutations in 1636 Patients with an aldosterone-producing adenoma. J Clin Endocrinol Metab. 2015;100:E1089–E1095.
28. Nanba K, Omata K, Gomez-Sanchez CE, et al. Genetic characteristics of aldosterone-producing adenomas in blacks. Hypertension. 2019;73:885–892.
29. Rossitto G, Regolisti G, Rossi E, et al. Elevation of angiotensin-II type1-receptor autoantibodies titer in primary aldosteronism as a result of aldosterone-producing adenoma. Hypertension. 2013;61:526–533.
30. Kem DC, Li H, Velarde-Miranda C, et al. Autoimmune mechanisms activating the angiotensin AT1 receptor in ‘primary’ aldosteronism. J Clin Endocrinol Metab. 2014;99:1790–1797.
31. Hundemer GL, Kline GA, Leung AA. How common is primary aldosteronism? Curr Opin Nephrol Hypertens. 2021;30:353–360.
32. Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. J Hypertens. 2004;22:2217–2226.
33. Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med. 2008;168:80–85.
34. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Incidence of atrial fibrillation and mineralocorticoid receptor activity in patients with medically and surgically treated primary aldosteronism. JAMA Cardiol. 2018;3:768–774.
35. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018;6:51–59.
36. Seccia TM, Letizia C, Muiesan ML, et al. Atrial fibrillation as presenting sign of primary aldosteronism: results of the Prospective appraisal on the prevalence of primary aldosteronism in hypertensive (PAPPHY) study. J Hypertens. 2020;38:332–339.
37. Mosso L, Carvajal C, Gonzalez A, et al. Primary aldosteronism and hypertensive disease. Hypertension. 2003;42:161–165.
38. Weiner ID. Endocrine and hypertensive disorders of potassium regulation: primary aldosteronism. Semin Nephrol. 2013;33:265–276.
39. Nishikawa T, Omura M, Satoh F, et al. Guidelines for the diagnosis and treatment of primary aldosteronism-the Japan Endocrine Society 2009. Endocr J. 2011;58:711–721.
40. Seiler L, Rump LC, Schulte-Monting J, et al. Diagnosis of primary aldosteronism: value of different screening parameters and influence of antihypertensive medication. Eur J Endocrinol. 2004;150:329–337.
41. Stowasser M, Gordon RD. Primary aldosteronism-careful investigation is essential and rewarding. Mol Cell Endocrinol. 2004;217:33–39.
42. Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. Hypertension. 2002;40:897–902.
43. Beeftink MM, van der Sande NG, Bots ML, et al. Safety of temporary discontinuation of antihypertensive medication in patients with difficultto-control hypertension. Hypertension. 2017;69:927–932.

44. Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007;49:839–845.
45. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension. 2010;55:147–152.

References

46. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:1889–1916.
47. Umakoshi H, Sakamoto R, Matsuda Y, et al. Role of aldosterone and potassium levels in sparing confirmatory tests in primary aldosteronism. J Clin Endocrinol Metab. 2020;105:1284–1289.
48. Sam D, Kline GA, So B, Leung AA. Discordance between imaging and adrenal vein sampling in primary aldosteronism irrespective of interpretation criteria. J Clin Endocrinol Metab. 2019;104:1900–1906.
49. Mulatero P, Sechi LA, Williams TA, et al. Subtype diagnosis, treatment, complications and outcomes of primary aldosteronism and future direction of research: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. J Hypertens. 2020;38:1929–1936.
50. Dekkers T, Deinum J, Schultzekool LJ, et al. Plasma metanephrine for assessing the selectivity of adrenal venous sampling. Hypertension. 2013;62:1152–1157.
51. Ceolotto G, Antonelli G, Maiolino G, et al. Androstenedione and 17-alpha-Hydroxyprogesterone are better Indicators of adrenal vein sampling selectivity than cortisol. Hypertension. 2017;70:342–346.
52. Rossi GP, Bisogni V, Bacca AV, et al. The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism. Int J Cardiol Hypertens. 2020;5:100029.
53. Almarzooqi MK, Chagnon M, Soulez G, et al. Adrenal vein sampling in primary aldosteronism: concordance of simultaneous vs sequential sampling. Eur J Endocrinol. 2017;176:159–167.
54. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:3266–3281.
55. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol. 2007;3:486–492.
56. Nakagawa T. Diabetic nephropathy: aldosterone breakthrough in patients on an ACEI. Nat Rev Nephrol. 2010;6:194–196.
57. Bochud M, Nussberger J, Bovet P, et al. Plasma aldosterone is independently associated with the metabolic syndrome. Hypertension. 2006;48:239–245.
58. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, et al. Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci U S A. 2003;100:14211–14216.
59. Salata RA, Jarrett DB, Verbalis JG, Robinson AG. Vasopressin stimulation of adrenocorticotropin hormone (ACTH) in humans. In vivo bioassay of corticotropin-releasing factor (CRF) which provides evidence for CRF mediation of the diurnal rhythm of ACTH. J Clin Invest. 1988;81:766–774.
60. Perraudin V, Delarue C, Lefebvre H, Do Rego JL, Vaudry H, Kuhn JM. Evidence for a role of vasopressin in the control of aldosterone secretion in primary aldosteronism: in vitro and in vivo studies. J Clin Endocrinol Metab. 2006;91:1566–1572.

61. Salcuni AS, Palmieri S, Carnevale V, et al. Bone involvement in aldosteronism. J Bone Miner Res. 2012;27:2217–2222.
62. Sawka AM, Young WF, Thompson GB, et al. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med. 2001;135:258–261.
63. Meyer A, Brabant G, Behrend M. Long-term follow-up after adrenalectomy for primary aldosteronism. World J Surg. 2005;29:155–159.
64. Good ME, Chiu YH, Poon IKH, et al. Pannexin 1 channels as an unexpected new target of the anti-hypertensive drug spironolactone. Circ Res. 2018;122:606–615.
65. Parthasarathy HK, Menard J, White WB, et al. A double-blind,

randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens. 2011;29:980–990.

66. Cornelisse S, Joels M, Smeets T. A randomized trial on mineralocorticoid receptor blockade in men: effects on stress responses, selective attention, and memory. Neuropsychopharmacology. 2011;36:2720–2728.

67. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219–2229.

68. Kolkhof P, Nowack C, Eitner F. Nonsteroidal antagonists of the mineralocorticoid receptor. Curr Opin Nephrol Hypertens. 2015;24:417–424.

69. Wu VC, Wang SM, Chang CH, et al. Long term outcome of Aldosteronism after target treatments. Sci Rep. 2016;6:32103.

70. Hargovan M, Ferro A. Aldosterone synthase inhibitors in hypertension: current status and future possibilities. JRSM Cardiovasc Dis. 2014;3: 2048004014522440.

71. Reincke M, Rump LC, Quinkler M, et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. J Clin Endocrinol Metab. 2009;94:869–875.

72. Iwakura Y, Morimoto R, Kudo M, et al. Predictors of decreasing glomerular filtration rate and prevalence of chronic kidney disease after treatment of primary aldosteronism: renal outcome of 213 cases. J Clin Endocrinol Metab. 2014;99:1593–1598.

73. Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394:1540–1550.

74. Agarwal R, Rossignol P, Budden J, et al. Patiromer and spironolactone in resistant hypertension and advanced CKD: analysis of the randomized AMBER trial. Kidney360. 2021;2:425–434.

75. Kobayashi H, Abe M, Nakamura Y, et al. Association between acute fall in estimated glomerular filtration rate after treatment for primary aldosteronism and long-term decline in renal function. Hypertension. 2019;74:630–638.

40
Other Endocrine Causes of Hypertension
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Endocrine causes of hypertension often are undiagnosed. Some studies suggest endocrine causes make up over 20% of all secondary hypertension cases, of which primary aldosteronism is most common.1

Endocrine hypertension frequently occurs in the absence of readily observed signs and symptoms, but certain features should trigger consideration (Fig. 40.1). Chapter 39 discusses primary aldosteronism; this chapter describes the other causes of endocrine-related hypertension.

CUSHING SYNDROME
Definition
Cushing syndrome is defined by sustained glucocorticoid excess that does not follow a circadian rhythm. Cushing syndrome can be caused by overproduction of adrenocorticotropic hormone (ACTH) by a pituitary adenoma (i.e., Cushing disease); by cortisol overproduction from an adrenal adenoma, adrenal nodular hyperplasia, or adrenal cortical carcinoma; or rarely as secondary to ectopic ACTH (corticotrophin) secretion from neuroendocrine tumors.2-4 Approximately 0.5% of patients with bronchogenic carcinoma (more common in men than women) develop ectopic ACTH syndrome. Even more rare, ectopic corticotropin-releasing hormone (CRH) from tumors can cause hypercortisolism. Another rare cause of Cushing syndrome is Carney complex, an autosomal dominant disorder featuring cardiac myxomas and pigmented skin/mucosal lesions and Cushing syndrome. The most common cause of Cushing syndrome is exogenous corticosteroid administration, including from steroids present in joint injections, creams, inhalers, nasal sprays, and oral steroids. The incidence of endogenous Cushing syndrome is 5 to 10 cases per 1 million population per year. Cushing disease and cortisol-secreting adrenal tumors are four times more common in women than in men.

the vasodilator nitric oxide (NO) by cortisol may contribute to the hypertension, along with enhanced pressor responsiveness to catecholamines and angiotensin II (Ang II), heightened cardiac inotropic sensitivity to β-adrenergic stimulation, and increased plasma volume.5

The sympathetic nervous system and renin-angiotensin system (RAS) may be suppressed, even though circulating levels of renin substrate are increased. Adipokines, including leptin and resistin, plus release of proinflammatory cytokines (tumor necrosis factor-α, interleukin-6), also may contribute to the increased cardiovascular (CV) risk observed in Cushing syndrome.2–4,6–8

Successful treatment of Cushing disease or removal of an underlying adrenal adenoma usually results in blood pressure (BP) reduction and partial return of the previously impaired nocturnal fall in arterial pressure, although hypertension persists in some patients.8

Clinical Manifestations
Clinical features in Cushing disease result from elevated circulating levels of hormones, including ACTH (increased pigmentation) and cortisol (central adiposity, insulin resistance or diabetes, muscle wasting/weakness, plethoric facies, purple striae [Fig. 40.2], easy bruising, osteoporosis, psychological problems). In some patients, androgen effects are observed (hirsutism, acne, virilization) and may be striking in those with adrenal adenoma or adrenal cortical carcinoma. Ectopic ACTH syndrome caused by small cell lung carcinoma or other tumors (e.g., bronchial or thymic neuroendocrine tumors) manifests typically as a wasting disease, often with hyperpigmentation (from the very high ACTH levels) and hypokalemia (from the MR binding in very high cortisol states). Hypertension is often associated with left ventricular hypertrophy, which can be disproportionate to the blood pressure, and frank cardiac failure is occasionally the presenting feature.2,5

Etiology, Pathogenesis, and Epidemiology

Differential Diagnosis

Hypertension is present in 80% of patients with Cushing syndrome (less often when caused by exogenous synthetic corticosteroid administration) and results from an increase in both cardiac output and total peripheral resistance.5
In some patients, Cushing syndrome may be caused by concurrent overproduction of mineralocorticoids such as aldosterone, 11-deoxycorticosterone, and corticosterone. Although cortisol can bind to the mineralocorticoid receptor (MR) in the kidney, it usually does not because 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) inactivates cortisol to cortisone, thereby preventing its binding to the MR. However, in patients with extremely high cortisol levels (e.g., severe Cushing syndrome as in ectopic ACTH syndrome), 11βHSD is overwhelmed, and excess cortisol can bind the MR and lead to a pseudohyperaldosterone state.
Cardiac and vascular MR activation may foster cardiovascular inflammatory, hypertrophic, and fibrotic changes. Inhibition of

Pseudo-Cushing syndrome can occur with a sustained high intake of alcohol by inducing augmented cortisol secretion and reduced cortisol metabolism caused by hepatic damage. Routine diagnostic tests are unable to distinguish alcoholic pseudo-Cushing syndrome from true Cushing syndrome, and reassessment after alcohol withdrawal may be required.9 Depression is associated with an increased cortisol level. Careful psychological and physical evaluation will usually differentiate these patients from those with Cushing syndrome.

Diagnosis

Initial evaluation should test for one or more of the following: (1) an elevated 24-hour urinary free cortisol excretion (at least two collections), (2) increased late night salivary cortisol (at least three samples), (3) absence of suppression of 7 to 8 am serum cortisol after a 1 mg dose of dexamethasone taken at midnight the night before the morning blood draw (1 mg dexamethasone suppression test), and (4) failure

Testing for Endocrine Hypertension

Triggers for endocrine investigation in hypertension

Family history

Pheochromocytoma/
paraganglioma
Neurofibromatosis
Multiple endocrine neoplasia
Aldosteronism

Refractory hypertension:
high blood pressure
resistant to 2–3 drugs

Consider:
Iatrogenic source
Noncompliance with
medication
Renal/renovascular
disease
Endocrine disorder
Renal angiography
Measure:
Serum electrolytes Na +/K+
Urinalysis
Aldosterone/PRA
Plasma metanephrines

Hypokalemia: persistent(?)
K+ wasting(?) (i.e., >30 mmol/
24 h excreted when plasma
K+ <3.5 mmol/L)

Consider:
Iatrogenic (diuretics,
licorice)
Accelerated primary
hypertension
Aldosteronism
Pseudoaldosteronism
Cushing syndrome
Renin-producing tumor
Liddle syndrome

Symptoms/signs

Pheochromocytoma/
paraganglioma
Hyperadrenergic: sweating/
tachycardia/headache
Thyroid
Change in:
Temperature tolerance
Weight
Skin/hair
Bowel habits
Eyes
Tremor
Sweating

Acromegaly
Size of face/hands/feet
Sweating
Cushing syndrome
Striae, acne, central weight gain

Hyperglycemia

Diabetic nephropathy
Cushing syndrome
Pheochromocytoma
Acromegaly

Fig. 40.1 Testing for Endocrine Hypertension. Clinical observations suggesting investigation into endocrine causes of hypertension in hypertensive patients.

Fig. 40.2 Striae and central obesity in a patient with Cushing syndrome.

of suppression of serum cortisol on low-dose dexamethasone (0.5 mg four times daily) for 48 hours. Random blood cortisol measurements are not reliable.

A positive screening test result should trigger involvement of an endocrinologist. Once the screening tests suggest hypercortisolism, early morning cortisol, ACTH, and dehydroepiandrosterone sulfate (DHEAS) can be measured; high levels of ACTH suggest ACTHdependent causes of hypercortisolism (pituitary adenoma or ectopic ACTH), whereas low ACTH suggests ACTH-independent causes (adrenal adenomas or adrenal cortical carcinoma). Magnetic resonance imaging (MRI) of the pituitary is recommended for ACTH-dependent causes, and computed tomography (CT) of the adrenal glands is recommended for ACTH-independent causes. ACTH-producing pituitary adenomas, corticotroph adenomas, are often small and may not

be well visualized on MRI. For ACTH-dependent cases, further tests may include a high-dose dexamethasone suppression test (8 mg dexamethasone suppression test) that partially suppresses ACTH (at least 50% reduction) in patients with pituitary tumors but not with ectopic ACTH. The response of plasma ACTH to a dose of corticotrophinreleasing hormone (≥20% rise in response to CRH points to a pituitary source) may help distinguish pituitary from adrenal or ectopic tumors.

The gold standard to differentiate Cushing disease from ectopic ACTH production is bilateral inferior petrosal sinus sampling (IPSS) for ACTH measurements performed by experienced interventional radiologists. IPSS will show higher ACTH from the petrosal sinus sampling compared with the peripheral blood levels if the source is from the pituitary; no gradient will be seen between the petrosal sinus and the peripheral blood if the source is ectopic. If an ectopic source is suspected, imaging of the thorax/abdomen/pelvis is indicated to detect the most common sources of ectopic ACTH (e.g., lung cancer, pancreatic neuroendocrine tumors, pheochromocytomas/paragangliomas, medullary thyroid cancers). If cross-sectional imaging is unhelpful, 68Ga-DOTATATE positron emission tomography (PET)/CT may be used to highlight tissues with somatostatin receptors and identify the location of ectopic ACTH production.10

Treatment and Prognosis

Untreated patients with Cushing syndrome have 50% 5-year mortality because of CV risk from hypertension, along with glucose intolerance, insulin resistance, hyperlipidemia, and obesity.4 5

Surgical removal of a pituitary microadenoma in Cushing disease results in 80% to 90% cure rates, whereas 50% cure rates occur for

5 cm

Fig. 40.3 Large adrenal pheochromocytoma with areas of hemorrhagic necrosis.

pituitary macroadenomas. Cushing syndrome due to adrenal adenoma is almost always cured by unilateral adrenalectomy. However, prognosis is poor when Cushing syndrome is from adrenocortical carcinoma or ectopic causes such as small cell lung cancer. If the ectopic ACTH-producing tumor can be located, and complete removal occurs, there is a substantial reduction of mortality. After cure of Cushing syndrome, approximately 30% of patients have persistent hypertension.[11]

No evidence supports the use of any antihypertensive class over another. Potassium-losing diuretics can exacerbate both hypokalemia and glucose intolerance, whereas potassium-sparing diuretics, usually in combination with other antihypertensive agents, may correct hypokalemia and reduce edema while lowering BP.

PHEOCHROMOCYTOMA/PARAGANGLIOMA

Definition

Pheochromocytoma and paraganglioma (PPGLs) can mimic a wide spectrum of other disorders, and the diagnosis is frequently delayed or missed.[12] PPGLs are tumors of the autonomic nervous system that arise from chromaffin tissue in the adrenal medulla (Fig. 40.3) and from sympathetic extra-adrenal ganglia, which secretes catecholamines and metanephrines, or the parasympathetic ganglia, which are nonsecretory, especially those in the head and neck (Fig. 40.4). PPGLs occur in 2 to 8 per million people and are a rare cause of hypertension (0.2%–0.6% of all patients with hypertension),[13] yet pheochromocytomas make up 4% to 7% of adrenal incidentalomas.[14] Making the diagnosis is key because, when undiagnosed, these tumors are associated with high morbidity and mortality secondary to the uncontrolled catecholamine levels leading to hypertension, heart disease, stroke, and death. Although most tumors are localized, up to 25% can be metastatic and associated with a poor prognosis.[15] There are no good predictors of metastatic disease, and histologic features are not a reliable predictor for aggressive behavior. Large tumor size, extra-adrenal location, SDHB germline pathogenic variant, and very high dopamine/methoxytyramine secretion are associated with metastatic disease but are not specific.

Prevalence and Genetic Association With Pheochromocytoma and Paraganglioma

The prevalence of diagnosed pheochromocytoma in patients with hypertension in general medical outpatient clinics is 0.1% to 0.6%[16]; the true prevalence may be considerably higher.[12,16] PPGLs can be

sporadic or familial. Up to 40% of patients with PPGLs will have a germline pathogenic variant in one of over 14 genes known to increase risk of PPGL[12,15] (Table 40.1). Guidelines recommend that all patients with these tumors be referred for clinical genetic testing because of the high rate of hereditary predisposition[12] and the screening implications for both the patient and family members.

The classic tumor suppressor syndromes of neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2), and von Hippel–Lindau disease (vHL) were the first discovered to be associated with increased risk of pheochromocytomas, often bilateral, and all are autosomal dominant syndromes (see Table 40.1). The hereditary paraganglioma-pheochromocytoma syndromes are caused by germline pathogenic variants in the Succinate Dehydrogenase Subunit

(SDH) genes, which make up complex II of the mitochondrial respiratory chain and convert succinate to fumarate in the Krebs cycle.

Germline pathogenic variants in any of the four genes SDHA, SDHB, SDHC, or SDHC and a cofactor, SDHAF2, increase risk for PPGLs. Table 40.1 describes more information. SDHB is associated with a higher risk of metastatic disease (~25%) compared with the other SDHx genes (<5%).17 SDHD and SDHAF2 germline pathogenic variants are paternally expressed, meaning a carrier will only develop PPGL if the variant was inherited from their father, with extremely rare exception.18 Carriers of SDHx pathogenic variants are at risk for multiple primary PPGLs, clear cell renal cell carcinoma, gastrointestinal stromal tumors, and pituitary adenomas.15 SDHx carriers must undergo lifelong screening, starting between 6 and 10 years of age with annual biochemistry panels and full-body imaging every 2 to 3 years,19 usually with MRI rather than CT to minimize radiation exposure.

Clinical Manifestations

Classic symptoms from overproduction of catecholamines include headache, sweating, palpitations, anxiety, and pallor; however, patients may be asymptomatic or present with a variety of symptoms; therefore a high level of suspicion is required to make the diagnosis.20 Although less than 1% of resistant hypertension cases are because of pheochromocytoma/paraganglioma, new or worsening hypertension or diabetes mellitus, with or without symptoms, may be the presenting manifestation. PPGL also may present with symptoms of mass effect because of enlarging tumors. On occasion, a metastatic lesion may be the presenting sign. Physical examination may reveal labile (66%) or persistent (33%) hypertension, and some patients may be normotensive or even hypotensive if epinephrine is the predominant catecholamine secreted. Patients may also present with catecholamine (takutsubo) cardiomyopathy. Hypertensive crisis with or without heart failure may be precipitated by surgery, general anesthesia, pregnancy, or rarely on exposure to radiocontrast material. This also may occur after minor or major trauma and from sudden spontaneous release of catecholamines from the tumor or on hemorrhage into it.

Diagnosis

Diagnosis of pheochromocytoma is based on clinical suspicion and biochemical confirmation. Measurement of plasma-free metanephrines or urinary fractionated metanephrines is used for diagnosis or exclusion of pheochromocytoma. Both plasma and urine metanephrine tests have over 90% sensitivity for PPGLs. Plasma metanephrines are favored because of their ease of collection and higher specificity compared with the 24-hour urine tests (ranging from 79%–98% vs. 69%–95%, respectively).12 Catecholamine and metanephrine measurements are susceptible to false-positive elevations for many reasons. Interfering medications (Box 40.1) are the most common cause.

Plasma tests should ideally be performed with the patient resting for 20

*
ICA

ECA

A

ICA

*

B
Post resection

Ligated external carotid
artery stump
Common carotid
artery

Internal carotid
artery
Vagus
nerve

C

Fig. 40.4 (A) Carotid paraganglioma. (B) Carotid paraganglioma pre- and postembolization before surgery. (C) Carotid paraganglioma intraoperatively and after resection. ECA, External carotid artery; ICA, internal carotid artery.

TABLE 40.1

Genetic Syndromes and Clinical Features Associated With PPGL
Primary PPGL
location

Mode of
inheritance

Neurofibromatosis
type 1 (NF1)

Adrenal
pheochromocytoma
Can be bilateral

Autosomal
dominant
1:3000

RET

Multiple endocrine
neoplasia type 2
(MEN2)

Adrenal
pheochromocytoma
Bilateral
pheochromocytoma
50% (synchronous or
metachronous)

Autosomal
dominant
1:30 000

VHL

von Hippel–Lindau

Adrenal
pheochromocytoma in
10%–20%
Bilateral
pheochromocytomas

Autosomal
dominant
1:36 000

Gene

Syndrome

NF1

Hereditary Paraganglioma-Pheochromocytoma Syndromes
SDHA
Any location but more

Autosomal
commonly in head and
dominant
neck region
SDHB
Any location but
Autosomal
commonly extraadrenal dominant
and HNPGL
SDHC
Any location but
Autosomal
commonly HNPGL or
dominant
thoracic PGL
SDHD
Any location but
Autosomal
commonly multifocal
dominant
and often HNPGL
and paternal
inheritance
Other Germline Susceptibility Genes
TMEM127 Familial PPGL
Adrenal
syndrome
pheochromocytoma
Can be extraadrenal or
HNPGL
MAX
Familial PPGL
Adrenal
syndrome
pheochromocytoma
Can be bilateral

Autosomal
dominant

Autosomal
dominant

Clinical Features

Risk of
Malignancy

≥2 of the following clinical criteria: Up to 12%
• 6 or more café-au-lait spots
• Lisch nodules (benign iris
hamartomas)
• ≥2 cutaneous neurofibromas
• Plexiform neurofibroma
• Axillary or inguinal freckling
• Optic glioma
• Sphenoid dysplasia (thinning of
the long bones)
• First-degree relative with NF1
MEN2A (90%):
<5%
• Medullary thyroid carcinoma
• Pheochromocytoma
• Primary hyperparathyroidism

MEN2B (10%):
🐧•🐧 Medullary thyroid carcinoma
🐧•🐧 Pheochromocytoma
🐧•🐧 Mucosal neuromas
🐧•🐧 GI ganglioneuromas
🐧•🐧 Marfanoid habitus
Multiple different tumors and cysts 5%
🐧•🐧 Pheochromocytoma
🐧•🐧 Hemangioblastomas of the central nervous system, including retina
🐧•🐧 Renal cysts
🐧•🐧 Clear cell renal cell carcinoma
🐧•🐧 Pancreatic cysts
🐧•🐧 Pancreatic neuroendocrine tumors
🐧•🐧 Endolymphatic sac tumors
🐧•🐧 Epididymal cysts
PPGL
GIST

May be high at ~12%

PPGL
Renal cell carcinoma
GIST

23%–50%

<5%

Clinical Pearls
All patients with NF1 and HTN must be screened for pheochromocytoma

Annual biochemical screening for pheochromocytoma
🐧•🐧 Age 11 in patients with high-risk mutations (including those in codons 634 and 918)
🐧•🐧 Age 16 for those with moderate risk mutations
Annual biochemical screening for pheochromocytoma should begin at age 5 y

Most experts recommend screening starting between age 6 and 10 y with annual biochemistries and full body imaging (MRI preferred) every 3 y

<5%

PPGL

Renal cell carcinoma

<5%

Rare cause of PPGL

Unknown; may
be high

Rare cause of PPGL

Continued

TABLE 40.1

Genetic Syndromes and Clinical Features Associated With PPGL—cont'd

Gene

Syndrome

Primary PPGL
location

Mode of
inheritance

FH

HLRCC syndrome

Any location

MDH2

Familial PPGL
syndrome
Polycythemia
paraganglioma
syndrome

Any location

Autosomal
dominant
Autosomal
dominant
Somatic mosaic

EPAS1

Any location

Clinical Features

Risk of
Malignancy

Leiomyomas of the uterus and skin; May be high
renal cell carcinoma

Clinical Pearls
Rare cause of PPGL
Rare cause of PPGL

Can have polycythemia and/or
somatostatinomas

Rare cause of PPGL

GI, Gastrointestinal; GIST, gastrointestinal stromal tumors; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HNPGL, head and neck paraganglioma; HTN, hypertension; MRI, magnetic resonance imaging; PPGL, pheochromocytoma and paraganglioma.

Medications That Interfere With Screening Tests for Pheochromocytomas and Paragangliomas

BOX 40.1

Acetaminophen
Levodopa
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Sympathomimetics
Tricyclic antidepressants
Some β-blockers (especially nonselective)
Some α-blockers (i.e., phenoxybenzamine)
Cyclobenzaprine
Cocaine

minutes in the supine position,12 although this is not always practical. Most laboratories have different reference ranges for tests drawn in the supine and upright positions to help when interpreting the results. In patients with advanced chronic kidney disease (CKD), there are additional challenges with interpreting test results because catecholamines and their metabolites are renally cleared21 and patients with advanced CKD or kidney failure have sympathetic hyperactivity.22 Plasma-free metanephrines appear to be the least dependent on kidney function relative to plasma catecholamines and deconjugated metanephrines but remain higher in patients with kidney disease than hypertensive controls.21 Different cutoffs for plasma metanephrine concentration have been suggested based on the severity of CKD, which would reduce false-positive screening results from 7.6% to 5% in patients with CKD stage 3 and from 21.9% to 4.1% in patients with CKD stage 4 or higher.23 Another study suggested that 24-hour urine normetanephrine measurements can be used to detect PPGLs in people with CKD provided that the glomerular filtration rate (GFR) is greater than 15 mL/min/m2 24 End-stage kidney disease patients are often anuric; urinary measurements are not possible, and plasma metanephrines have been found to be approximately twofold higher than hypertensive controls.21

Imaging

Once the biochemical diagnosis is secured, the lesion must be localized. Cross-sectional imaging with MRI or CT scan (with contrast) of the abdomen and pelvis is recommended first because most lesions will be within the abdomen and pelvis. For patients with known susceptibility gene mutations, imaging of other anatomic locations may be necessary. Paragangliomas, particularly of the head and neck, that are derived from the parasympathetic chain are often nonsecretory;

therefore, if suspected, imaging should be performed regardless of biochemical testing results. If patients with a known head and neck paraganglioma have elevated metanephrines, abdominal/pelvic imaging studies must be performed to evaluate for additional sympatheticderived primary PPGLs. Imaging with 123I-metaiodobenzylguanidine (MIBG) should be reserved for patients in whom cross-sectional imaging did not reveal a tumor despite markedly abnormal biochemical testing or patients with metastatic disease to assess if the lesions are amenable to treatment with 131I-MIBG.12 68GA DOTATATE PET/CT or 18F-FDG PET/CT scanning is preferred (particularly in patients with SDHB germline pathogenic variants) over 123I-MIBG imaging for diagnosis of metastatic disease because of higher sensitivity and specificity.25–28

Treatment

Once a PPGL has been localized, the patient should be prepared for surgery with a collaborative team approach by the surgeon, anesthesiologist, and physician. Perioperative blockade is important to reduce the morbidity and mortality associated with tumor resection (down to 0%–2%[29]) and should be used before other surgical procedures and biopsies and considered before treatment for metastatic disease such as chemotherapy, radiation, and ^{131}I-MIBG therapy, particularly when catecholamine levels are very elevated. Independent of medication regimen, treatment should also include a high-sodium diet and increased fluid intake. The typical drugs and dosing regimens are shown in Table 40.2

Medications

α-Blockers

Secretory PPGLs cause α-receptor activation in response to excess catecholamine secretion leading to severe vasoconstriction, which can result in hypertension, arrhythmias, and myocardial ischemia. Therefore, selective or nonselective α-blockers are recommended as first-line therapy in perioperative management.[12] A prospective randomized controlled trial suggested no major differences in using phenoxybenzamine (nonselective) versus doxazosin (α-1 selective) α blockade.[30] The nonselective α-blocker phenoxybenzamine is a noncompetitive inhibitor that covalently (irreversibly) binds to α-1 and α-2 receptors and provides more complete blockade of α receptors. This significantly lowers the risk of an intraoperative hypertensive crisis but can also cause hypotension once the tumor is resected, so vasopressors and IV fluids may be required for 24 to 48 hours postoperatively.

Selective α-1 receptor blockers include doxazosin, terazosin, and prazosin. These competitive inhibitors are relatively short-acting, and their effects can be overcome by the excess catecholamine released during surgery, potentially causing an intraoperative hypertensive crisis. However, their shorter half-life results in less postoperative hypotension.

Common Medications for Perioperative Blockade of Patients With
Pheochromocytoma and Paraganglioma

TABLE 40.2
Drug

Mechanism of Action

Common Dosing

Nonselective α-Blocker
Phenoxybenzamine

Noncompetitive antagonist

10 mg 2–3 times daily (maximum Orthostasis, nasal congestion
60–100 mg/d)

Selective α-Blockers
Doxazosin
Prazosin
Terazosin

Competitive antagonist
Competitive antagonist
Competitive antagonist

4–8 mg twice daily
5 mg three times daily
1–4 mg once daily

Orthostasis, dizziness
Orthostasis, dizziness
Orthostasis, dizziness

Calcium Channel Blockers
Nicardipine
Amlodipine

Dihydropyridine long acting
Dihydropyridine long acting

30 mg twice daily
5–10 mg daily

Headache, edema, vasodilation
Headache, edema, palpitations

250–500 mg 4 times daily (dose
escalated every 2 days)

Severe lethargy, extrapyramidal neurologic
side effects and gastrointestinal upset

25–50 mg 1–2 times daily

Fatigue, dizziness

25–100 mg/d

Fatigue, dizziness

Tyrosine Hydroxylase Inhibitor
Metyrosine
Decreases catecholamine production
β-Blockers
Metoprolol tartrate (selective β-1 blocker)
Atenolol (nonselective β-1 blocker)

Used to treat reflex tachycardia only after full α-blockade achieved
Used to treat reflex tachycardia only after full α-blockade achieved

β-Blockers

Preoperative coadministration of β-adrenergic receptor blockers is indicated to control reflex tachycardia only after administration of α adrenergic receptor blockers and sufficient volume expansion to avoid the potential for hypertensive crisis because of unopposed stimulation of α-adrenergic receptors. This tachyarrhythmia is a desired side effect indicating complete α-blockade has been achieved.

Calcium Channel Blockers

Calcium channel blockers are second-line therapy or add-on therapy.12 No prospective studies compare α-blockade and calcium channel blockers for preoperative blockade.

Metyrosine

Methyl-paratyrosine (metyrosine) inhibits catecholamine synthesis and may be used in combination with α-adrenergic receptor blockers for a short period before surgery to further stabilize BP or to help control symptoms related to catecholamine excess in those with metastatic PPGL. Metyrosine is infrequently used because it is expensive, its efficacy is controversial, it is not readily available, and it has significant side effects.

Acute Hypertensive Crisis

Acute hypertensive crisis can be the presenting sign in patients with an undiagnosed PPGL and can occur in patients with a known tumor. Intravenous (IV) α-blockade with phentolamine can be used to control BP, with or without other IV vasodilators such as sodium nitroprusside or nicardipine.

Surgery

Surgical resection is the treatment of choice for PPGLs. Laparoscopic surgery for PPGL is associated with better outcomes than open adrenalectomy31 for small PPGLs. Cortical-sparing surgery should be attempted in patients with or without genetic predisposition for bilateral adrenal pheochromocytomas (MEN2 and vHL) because it may avoid the need for lifelong glucocorticoid and mineralocorticoid replacement. However, there is a risk of recurrence with corticalsparing surgery. Continuous hemodynamic and cardiovascular monitoring is required during surgery and perioperatively. Postoperatively, patients may require BP support with fluids, colloids, and sometimes α-adrenergic agonists for 24 to 48 hours. BP usually returns to normal within a few days of surgery, but patients may remain hypertensive, particularly if they have chronic underlying hypertension or widespread metastatic disease.

Common Side Effects

Follow-up

All patients should have plasma metanephrines checked about 4 to 6 weeks after surgery; if levels remain elevated, this may indicate residual or metastatic disease. All patients should have annual plasma metanephrines levels checked for life because recurrence or metastatic disease can occur even 20 years later, and patients also can develop additional primary tumors. All patients with PPGL should be referred for genetic testing because of the high rate of inherited disease (up to 40%).12 Follow-up imaging is not required for most patients with complete sympathetic PPGL resection unless they have a known germline susceptibility gene mutation. Imaging also should be considered if catecholamines remain elevated or if metastatic disease is suspected.

Pheochromocytoma and Paraganglioma in Pregnancy

PPGL in pregnancy can be dangerous, even fatal, for both the mother and fetus. Perioperative blockade is the same as for nonpregnant patients; however, timing of surgery is often tricky. It is usually recommended to proceed with surgical resection around 18 to 22 weeks of pregnancy. If diagnosis is not made until the third trimester, it is recommended to perform a cesarean section and surgical resection of the PPGL at the same surgery. Spontaneous labor and delivery should be avoided. In patients with genetic predisposition, screening with plasma metanephrine levels is recommended when contemplating conception and/or when pregnancy is confirmed to avoid morbidity from an undetected PPGL. If patients develop a hypertensive crisis during pregnancy, treatment is the same as for nonpregnant patients except nitroprusside should be avoided because of the risk of cyanide toxicity in the fetus. A recent large multicenter, retrospective study of patients with PPGL and pregnancy included 249 pregnancies in 232 patients with PPGL, and 66% had an underlying germline mutation.32 Adverse outcomes were associated with unrecognized PPGL during pregnancy, abdominal or pelvic tumor location, and very high catecholamine levels at least 10 times the upper limit of the normal range. For patients diagnosed during pregnancy, α-adrenergic blockade therapy was associated with fewer adverse outcomes, and the outcome was similar if surgery was performed during pregnancy or delayed until after pregnancy.

Metastatic Pheochromocytoma and Paraganglioma

PPGLs should be described as metastatic or nonmetastatic PPGL rather than malignant or benign.13 Common metastatic sites include lymph nodes, liver, bones including the skull, lung, and peritoneum. Metastases occur in approximately 10% of pheochromocytomas and 20% of paraganglioma and are more likely to occur in large tumors, extra-adrenal paragangliomas, and patients with SDHB mutations.33 Metastases can be detected at the time of primary tumor diagnosis or even 20 years later and are associated with 5-year survival of 50%.33 Unfortunately, there are no reliable histopathologic markers to predict metastatic disease.

Treatment Options

Treatments for metastatic disease can slow disease progression, but none are curative. Surgical debulking is still the best option when tumor burden is low. If the tumor is MIBG avid, 131I-MIBG therapy can be used. Recently high-specific-activity 131I-MIBG was US Food and Drug Administration (FDA) approved for treatment of patients with metastatic PPGL. Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs is FDA approved for gastrointestinal and pancreatic neuroendocrine tumors and is in clinical trials for PPGL. External beam radiation therapy and proton therapy often are used for bone metastases and control of unresectable head and neck paragangliomas. Cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) can control disease but is not curative.

ADRENAL INCIDENTALOMA

Definition and Epidemiology

Adrenal incidentaloma refers to the incidental discovery of an adrenal mass in the absence of any prior suspicion of adrenal disease.34 35 The prevalence of unsuspected adrenal masses of adults undergoing highresolution CT or MRI abdominal studies is approximately 1% in those younger than 30 years, rising to 10% in the elderly.34

Hypertension is more common in those with incidentalomas (40%) than in the general population. About 75% prove to be nonsecretory benign adenomas. However, an important minority show hormone secretion, including aldosterone-producing adenomas (2.5%, frequently normokalemic), pheochromocytoma (7%, often normotensive), and, most often, cortisol-secreting tumors (12%).34

Subclinical Cushing syndrome (SCS), now referred to as mild autonomous cortisol secretion (MACS) without clinical manifestations of Cushing syndrome, is the most frequent hormonal abnormality detected in patients with adrenal incidentalomas. Cortisol excess should be ruled out by performing a 1-mg overnight dexamethasone suppression test (DST). If the 8 am serum cortisol concentration after 1 mg of dexamethasone given at midnight the evening before is greater than 1.8 μg/dL, this suggests hypercortisolism. Typically, a level greater than 5 μg/dL is considered overt hypercortisolism, whereas levels

between 1.8 and 5 μg/dL are considered MACS. In addition, DHEAS is low in adrenal cortisol excess. A baseline morning ACTH and cortisol can confirm if this hypercortisolism is ACTH independent (ACTH should be low) and from an adrenal nodule. Hypercortisolism, even mild hypercortisolism, is frequently complicated by hypertension (~65% of cases), diabetes (~33%), obesity, and osteoporosis and carries increased risk for CV events and related mortality.36,37 A recent retrospective study of 632 patients with either MACS (n = 212) or nonsecreting adenomas (n = 420) demonstrated a higher prevalence of atrial fibrillation in those with MACS (8.5%) compared with the nonsecreting group (3.1%).38

Adrenal cortical carcinoma (ACC) is rare, affecting 1 to 2 per million people39 and accounts for a very small percentage of adrenal tumors, but is deadly with 5-year survival of less than 30%. Most ACC are greater than 4 cm on imaging and may or may not be functional (e.g., with evidence of Cushing syndrome, primary aldosteronism, and/or virilization).

Management

Investigation of adrenal incidentalomas should address two key issues: whether the tumor is malignant and whether it is hormonally active. Every adrenal incidentaloma should be evaluated for pheochromocytoma (plasma-free metanephrines or 24-hour urine fractionated metanephrines), glucocorticoid excess (early-morning plasma cortisol concentration after 1 mg dexamethasone given the night before), and, if the patient has hypertension, also evaluated for primary aldosteronism (plasma renin and serum aldosterone levels), as outlined here and in Chapter 39. Tumors with an appearance that is worrisome for malignancy (e.g., noncontrast Hounsfield units [HU] >10), tumors that are growing, tumors more than 4 to 6 cm in diameter, and those that are functional should be surgically resected.34,35 Adrenal incidentaloma guidelines suggest benign-appearing (HU < 10), small adenomas (less than 4–6 cm) that are nonfunctional no longer need imaging or biochemical follow-up,34 although some experts suggest even nonfunctional nodules may have long-term cardiometabolic consequences and should have some subsequent follow-up.

RENIN-SECRETING TUMOR

Definition

Primary renin-secreting tumors are rare, and less than 200 cases have been reported.40 Diagnostic criteria include an elevated plasma renin or prorenin level, which decreases on removal of the tumor, and demonstration of renin within the tumor. Most renin-secreting tumors are caused by benign renal juxtaglomerular cell tumors (JGCT) ranging from 5 mm to 6 cm in diameter (typically 2–4 cm). These tumors occasionally occur with nephroblastomas, renal cell carcinomas, and extrarenal neoplasms (bronchial or pancreatic carcinoma, ovarian tumors, carcinoma of ileum or colon, soft tissue sarcomas, orbital hemangiopericytoma).

Etiology and Pathogenesis

Autonomous hypersecretion of renin results in high circulating levels of Ang II that increase arterial pressure. Secondary hyperaldosteronism and hypokalemia result from stimulation of the adrenal glomerulosa by Ang II. High Ang II levels also induce hyponatremia in a minority of patients, by stimulation of thirst and arginine vasopressin (AVP) secretion, together with a direct renal water-retaining action of the peptide.40

Clinical Manifestations

Cases show female predominance; 75% of patients are aged less than 30 years, presenting usually with severe, occasionally paroxysmal

Clinical Workup of Secreting Pheochromocytoma or Paraganglioma
Clinical suspicion

Check plasma-free metanephrines

Normal

Elevated but <2× ULN

Elevated ≥2–3× ULN

Discontinue
search

Check for interfering
medications, herbs,
supplements

CT or MRI
abdomen/pelvis

Stop interfering
substances and
repeat tests

If none, repeat tests after
patient supine for ≥20 min
or obtain 24 hr urine
fractionated metanephrines
and catecholamines

If suspicion
high, move
to imaging
Still
<2×
ULN
If suspicion low,
repeat in 6–12
months

If negative, CT
chest, neck,
and head
If negative,
consider
MIBG scan

Fig. 40.5 Clinical workup of secreting pheochromocytoma or paraganglioma. CT, Computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; ULN, upper limit of normal.

hypertension (average 206/131 mm Hg), hypokalemia (<3.0 mmol/L in ~70% of cases), proteinuria (>0.4 g/day in ~50% of patients), and, in a minority, hyponatremia.[41] GFR is normal or high. BP may decrease substantially with the first dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Pathology

Renin-secreting tumors are encapsulated and tan or grayish yellow, with scattered hemorrhages. These masses consist largely of polygonal or spindle cells in close contact with capillary and sinusoidal vessels and contain cytoplasmic renin granules.40

Diagnosis and Differential Diagnosis

Patients presenting with hypertension and hypokalemia together with elevated renin (and prorenin) and aldosterone levels may harbor a renin-secreting tumor, most often a JGCT.

CT or MRI angiography or renal arteriography typically identify JGCTs as radiolucent, expansile, homogeneous, solid renal cortical neoplasms, usually 2 to 4 cm in diameter (Fig. 40.5).41 CT and MRI scans showing an isodense or hypodense lesion with little or no enhancement after injection of contrast material have proved helpful in the provisional localization of these tumors. Bilateral, simultaneous renal vein sampling may enable lateralization of the tumor. Because renal blood flow to the culprit kidney is not impaired, however, a renin ratio of more than 1.2:1 between the two renal veins may not be present, in contrast to unilateral renal artery stenosis, in which reduced blood flow to the stenosed kidney and renin oversecretion often lead to an elevated renal vein renin ratio. Selective segmental renal vein renin sampling may help localize the tumor. When no renal lesion can be visualized and lateralization of renin secretion is not evident, an extrarenal renin-secreting lesion must be considered and sought by appropriate radiographic investigations and venous sampling for renin measurements.

Apart from renal artery stenosis or occlusion, it may be necessary to exclude other renin-producing lesions, including Wilms tumor, renal carcinoma, neuroblastoma, hepatocellular carcinoma, and pheochromocytoma, which can either secrete renin or stimulate renal renin production.

Treatment

Preoperative BP control is achieved using an ACE inhibitor or ARB, introduced cautiously to avoid first-dose hypotension. For JGCTs, local excision is advisable, if possible, to preserve nephrons. When doubt exists, an intraoperative frozen section will differentiate a benign JGCT from malignant lesions and guide surgery. Removal of a JGCT results in the return of renin and aldosterone levels to normal. BP decreases rapidly but not always to normal if there is a history of primary hypertension.42

ACROMEGALY

Definition and Epidemiology

Acromegaly is caused by excessive circulating growth hormone (GH) originating from a somatotroph (or somatomammotroph) adenoma of the pituitary in more than 95% of cases.43 Rare causes include hypothalamic or neuroendocrine tumors secreting GH-releasing factor (GHRH) and, even more rarely, hemopoietic, breast, bronchial, and abdominal tumors may secrete GH. Multiple endocrine neoplasia type 1 is associated with pituitary adenomas, with somatotroph adenomas being the second-most common of the secreting tumors. Acromegaly may appear in other familial settings (e.g., McCune-Albright syndrome, Carney complex) or as an isolated disorder in familial isolated pituitary adenoma.

Acromegaly is rare, with an incidence of 6 to 8 cases per million population per year.44 The median age of diagnosis is 47 years. Hypertension is more common (~40%) in persons with acromegaly than in the general population, especially in female and older patients.45 Patients with acromegaly who have additional hypopituitarism or advanced cardiomyopathy may have BP reduction masking before hypertension. Most somatotroph adenomas are macroadenomas resulting in compression of the normal pituitary and hypopituitarism in 75% of cases.

Fig. 40.6 Facial features of acromegaly with enlargement of brow, nose, and jaw.

The pathogenesis of hypertension in acromegaly is complex but reflects sodium retention and volume expansion associated with an inappropriate compensatory response. Total exchangeable sodium, total body water, and extracellular fluid volume are increased. Volume expansion should suppress plasma renin levels, but although levels are low, they are not consistent with the sodium status. Aldosterone levels are also normal or only slightly suppressed. The kidneys are enlarged and GFR is increased, but sodium balance is not corrected unless the acromegaly is cured.

Clinical Manifestations

Excess circulating GH stimulates production of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 mediates the biologic effects of GH. Acromegaly is characterized by enlargement of the jaw (macrognathia), skull (Fig. 40.6), hands (Fig. 40.7), and feet because of bone and soft tissue overgrowth. Other symptoms result from local effects of an expanding pituitary tumor and include visual field defects and headache. The manifestations of disease are gradual, slowly progressing over many years, and diagnosis may be delayed until dysmorphic features are well developed, typically in the fourth to fifth decade. Other signs and symptoms include headache (40%), excessive sweating (50%), loss of libido (35%), amenorrhea (45%), carpal tunnel syndrome (25%), diabetes mellitus (19%), and visual field defects (5%).43 Thyroid enlargement occurs in 50% of patients and thyrotoxicosis in 6%; hirsutism occurs in 24% of women and galactorrhea in 10%. Other complications of acromegaly include cardiac hypertrophy, systolic and diastolic dysfunction, heart failure, arrhythmia, sleep apnea, osteoarthritis and osteopenia, and disturbed calcium metabolism.46 Acromegaly is associated with increased risk of malignancy, including a twofold increase in colorectal cancer.

Diagnosis

Clinical suspicion should be raised by symptoms and signs. Box 40.2 lists appropriate tests for acromegaly. Elevated levels of IGF-1 and GH, especially with lack of suppression of GH on oral glucose tolerance testing, are strongly suggestive of the diagnosis. MRI of the pituitary and visual field testing for those with macroadenomas are necessary to define the tumor extension.

Treatment

Treatment aims to lower IGF1 (GH) levels so that symptoms and signs resolve and metabolic abnormalities improve. However, bony

Fig. 40.7 Radiograph of the Hand in Acromegaly. “Arrowhead” distal phalanges, expanded joint spaces, and increased soft tissue can be seen.

BOX 40.2

Diagnostic Tests for Acromegaly

- Screen with serum insulin-like growth factor-1. If elevated:
- Serum growth hormone responses to glucose tolerance test to confirm
- Assessement of full pituitary function (thyroid-stimulating hormone, T4 [thyroxine], prolactin, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle-stimulating hormone, estradiol/testosterone)
- Magnetic resonance imaging of pituitary fossa; if macroadenoma,

visual field testing

overgrowth generally does not reverse. Resection of the pituitary adenoma by transsphenoidal surgery is the treatment of choice. Surgical cure (defined by normalization of plasma IGF-1 and a nadir oral glucose tolerance test GH of < 2 µg/L) is achieved in 81% to 100% of microadenomas and 45% to 68% of macroadenomas.43 Irradiation and drug therapy are valuable when complete removal of tumor tissue is not possible (approximately one-third of acromegalic cases overall) and when surgery is contraindicated. Somatostatin analogs are first-line medical therapy because they can decrease the size of the residual tumor in addition to lowering GH secretion. If IGF1 levels have not normalized, pegvisomant, a GH receptor antagonist, can be added or may be used as first-line therapy.43 47 Pegvisomant does not shrink the tumor. Dopaminergic agents, such as bromocriptine and cabergoline, may be helpful to reduce GH levels in mild cases but are not strongly effective. Radiotherapy is used in cases with persistent active disease despite all other treatments but may not exert its full effect for months or years. Patients must be monitored regularly for pituitary function because hypopituitarism may occur late after treatment (even 10 years out) and necessitate hormone replacement in about 40% of patients.48

Management of Hypertension in Acromegaly

Surgical removal of the pituitary adenoma with normalization of GH levels may reduce BP, but most patients with acromegaly will continue to require antihypertensive therapy. Antihypertensive treatment requires a diuretic, given the volume-expanded state. Additional antihypertensive agents are frequently required, and both calcium channel blockers and ACE inhibitors may be effective. β-Blockers also may be used, although theoretically such agents may increase GH concentration.

HYPOTHYROIDISM

Definition and Epidemiology

Hypertension is more common in hypothyroid patients than in the general population. The pathogenesis of the hypertension is multifactorial and associated with both increased total body sodium and increased peripheral vascular resistance.

Hypothyroidism is associated with increased aortic stiffness, loss of sensitivity to vasoconstrictors, and impaired endothelial function with loss of endothelial-dependent vasodilation plus reduced vasodilatory responses to NO donors.49 Hypothyroidism is associated with increases in arterial pressure, plasma catecholamines, aldosterone, and cortisol.50-52 The relationship between plasma catecholamine levels and BP is enhanced in hypothyroidism.53 Hypertension develops despite a low cardiac output.

Thyroid replacement therapy corrects the electrolyte, hemodynamic, and hormone changes and cures the hypertension in most patients.

Clinical Features

Bradycardia, mild hypertension with narrowed pulse pressure, and muffled heart sounds are the most frequent signs in overt hypothyroidism. Other features include weakness, dry skin, lethargy, slow slurred speech, cold intolerance, thick tongue, facial puffiness, coarse and thinning hair, failing memory, constipation, and weight gain with reduced appetite. In extreme cases, myxedema and coma ensue. Coronary heart disease is common, with dyslipidemia and hypertension accelerating atherogenesis.

Diagnosis

Hypothyroidism should be considered in any patient with hypertension. Because the clinical manifestations of hypothyroidism are often difficult to elicit, especially in elderly patients, thyroid function tests, including thyroid stimulating hormone (TSH), should be performed.

In patients with primary hypothyroidism who remain hypertensive despite full thyroxine replacement therapy, primary hypertension is likely also present. For those patients with known heart failure or angina who have overt or long-standing hypothyroidism, replacement thyroxine therapy should be given initially with low doses and increased slowly over time to minimize the chance of precipitating myocardial ischemia.

HYPERTHYROIDISM

Definition and Epidemiology

Hypertension is common in hyperthyroidism, with a prevalence of 60% in toxic adenoma and approximately 30% in Graves disease.2

Clinical Features

The clinical features depend on the underlying cause of the hyperthyroidism, the severity of the disorder, rapidity of onset, age of the patient, and concomitant disease. Abnormalities may be evident in the CV system (tachyarrhythmias, heart failure), skin (increased sweating, increasing pigmentation with vitiligo), eyes (lid lag, exophthalmos),

nervous system (hypertension, nervousness), gastrointestinal system (increased appetite yet weight loss, diarrhea), and muscles (proximal weakness).

Hypertension in hyperthyroidism is associated with an increased pulse pressure and elevated systolic BP with normal or low diastolic BP.54 It may be observed in both postpartum thyrotoxicosis and neonatal thyrotoxicosis. Elevation of diastolic BP is unusual unless there is concomitant primary hypertension.

The hemodynamic characteristics in hypertension of thyrotoxicosis are an increased cardiac output (by 50%–300%), increased myocardial contractility, tachycardia, decreased peripheral vascular resistance, and expanded blood volume. These indices return to normal in most patients on achieving the euthyroid state. Interestingly, catecholamine levels tend to be low (inversely to hypothyroid hypertension), and there is no sympathetic overactivity. The RAS tends to be activated and the aldosterone levels increased in hyperthyroidism, which may contribute to the development of systolic hypertension. Suspicion of hyperthyroidism should be high in the elderly patient with hypertension and a high pulse pressure, particularly if there is also atrial fibrillation. Such patients are prone to developing cardiac failure, in which case the increased systolic arterial pressure will diminish, masking previous hypertension. Hypertension with a high pulse pressure, although typical of hyperthyroidism, is observed in many elderly patients with primary hypertension because of the loss of compliance of the aorta with aging.

Diagnosis and Treatment

The diagnosis is confirmed by thyroid function tests, including measurement of TSH, and when suppressed, adding a T4 and T3. βBlockers are effective first-line therapy for hyperthyroidism-associated hypertension because they prevent hyperthyroidism-associated arrhythmias, such as tachycardia and atrial fibrillation. Treatment of hyperthyroidism, whether by antithyroid drugs, surgery, or radioiodine, often will promptly normalize the increased systolic arterial pressure, unless concomitant primary hypertension is present.

PRIMARY HYPERPARATHYROIDISM

The incidence of primary hyperparathyroidism (PHPT) is approximately 20 per 100,000 person-years.2,55 Full-blown PHPT may feature severe hypercalcemia, nephrolithiasis, acute and chronic kidney disease, and fractures, but patients are usually asymptomatic. The prevalence of hypertension in PHPT approaches 50% with an independent association between plasma ionized calcium levels and the presence of hypertension. In those with MEN2, the hypertension could be a sign of coincident pheochromocytoma.

Indications for surgery in PHPT include serum calcium at least 1 mg/dL above the upper limit of normal, presence of renal stones, decreased renal function with creatinine clearance less than 60 mL/min, elevated urinary calcium greater than 400 mg/day, osteoporosis or vertebral fracture, or age less than 50 years.56 Generally, mild PHPT in those aged older than 50 years is not an indication for parathyroidectomy, and management involves serial follow-up with monitoring of plasma calcium, renal function, and bone density. Coincident hypertension is not an accepted indication for parathyroidectomy and is managed according to standard guidelines with the notable difference that thiazide diuretics (which may increase plasma calcium) should be avoided. There is some evidence that surgical cure of PHPT and restoration of eucalcemia restores vascular function and BP toward normal.55

SELF-ASSESSMENT QUESTIONS

1. Each form of endocrine hypertension:
A. always manifests typical signs and symptoms.
B. can always be cured if correct specific therapies are applied.
C. is usually familial.
D. may present as hypertension resistant to multiple drugs.
2. Initial screening tests for Cushing syndrome include which of the following?
A. CT or MRI of pituitary and adrenal glands
B. 1 mg dexamethasone suppression test

C. High-dose dexamethasone suppression test
D. Bilateral inferior petrosal sinus sampling for ACTH
3. Pheochromocytomas/paragangliomas are hereditary in what percent of cases?
A. <5%
B. 10% to 15%
C. 30% to 40%
D. >70%

REFERENCES

1. Wang L, Li N, Yao X, et al. Detection of secondary causes and coexisting diseases in hypertensive patients: OSA and PA are the common causes associated with hypertension. BioMed Research International. 2017:8295010.
2. Pappachan JM, Buch HN. Endocrine hypertension: a practical approach. Adv Exp Med Biol. 2017;956:215–237.
3. Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jorgensen JO. mortality in cushing syndrome: a systematic review and meta-analysis. Eur J Intern Med. 2012;23(3):278–282.
4. Bancos I, Alahdab F, Crowley RK, et al. Therapy of endocrine disease: improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical cushing syndrome: a systematic review and meta-analysis. Eur J Endocrinol Eur Fed Endocr Soc. 2016;175(6):R283–R295.
5. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. Vasc Health Risk Manag. 2005;1(4):291–299.
6. Sala C, Ambrosi B, Morganti A. Blunted vascular and renal effects of exogenous atrial natriuretic peptide in patients with cushing disease. J Clin Endocrinol Metab. 2001;86(5):1957–1961.
7. Valassi E, Biller BM, Klibanski A, Misra M. Adipokines and cardiovascular risk in cushing syndrome. Neuroendocrinology. 2012;95(3):187–206.
8. Sugihara N, Shimizu M, Kita Y, et al. Cardiac characteristics and postoperative courses in cushing syndrome. Am J Cardiol. 1992;69(17):1475–1480.
9. Besemer F, Pereira AM, Smit JW. Alcohol-induced cushing syndrome. hypercortisolism caused by alcohol abuse. Netherl J Med. 2011;69(7):318–323.
10. Wannachalee T, Turcu AF, Bancos I, et al. The Clinical Impact of [(68) Ga]-DOTATATE PET/CT for the diagnosis and management of ectopic adrenocorticotropic hormone - secreting tumours. Clin Endocrinol. 2019;91(2):288–294.
11. Baid S, Nieman LK. Glucocorticoid excess and hypertension. Curr Hyper Rep. 2004;6(6):493–499.
12. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–1942.
13. Lloyd RVOR, Kloppel G, Rosai J. WHO classification of tumours: pathology and genetics of tumours of endocrine organs. 4th ed. Lyon: IARC; 2017.
14. Nieman LK. Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab. 2010;95(9):4106–4113.
15. Fishbein L. Pheochromocytoma and Paraganglioma: genetics, diagnosis, and treatment. Hematol Oncol Clin North Am. 2016;30(1):135–150.
16. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005;366(9486):665–675.
17. van Hulsteijn LT, Dekkers OM, Hes FJ, Smit JW, Corssmit EP. Risk of malignant paraganglioma in SDHB-mutation and SDHD-mutation carriers: a systematic review and meta-analysis. J Med Genet. 2012;49(12):768–776.
18. Bayley JP, Oldenburg RA, Nuk J, et al. Paraganglioma and pheochromocytoma upon maternal transmission of SDHD mutations. BMC Med Genet. 2014;15:111.
19. Rednam SP, Erez A, Druker H, et al. Von hippel-lindau and hereditary pheochromocytoma/Paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res. 2017;23(12):e68–e75.
20. Cohen DL, Fraker D, Townsend RR. Lack of symptoms in patients with histologic evidence of pheochromocytoma: a diagnostic challenge. Ann New York Acad Sci. 2006;1073:47–51.
21. Eisenhofer G, Huysmans F, Pacak K, Walther MM, Sweep FC, Lenders JW. Plasma metanephrines in renal failure. Kidney Int. 2005;67(2):668–677.
22. Neumann J, Ligtenberg G, Klein II , Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int. 2004;65(5):1568–1576.
23. Pamporaki C, Prejbisz A, Malecki R, et al. Optimized Reference Intervals

for Plasma Free Metanephrines in Patients With CKD. Am J Kidney Dis. 2018;72(6):907–909.

24. Kline GA, Boyd J, Leung AA, Tang A, Sadrzadeh HM. Moderate renal impairment does not preclude the accuracy of 24-hour urine normetanephrine measurements for suspected pheochromoctyoma. Clin Endocrinol. 2020;92(6):518–524.
25. Janssen I, Blanchet EM, Adams K, et al. Superiority of [68Ga]DOTATATE PET/CT to Other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. Clin Cancer Res. 2015;21(17):3888–3895.
26. Chang CA, Pattison DA, Tothill RW, et al. (68)Ga-DOTATATE and (18) F-FDG PET/CT in paraganglioma and pheochromocytoma: utility, patterns and heterogeneity. Cancer Imaging. 2016;16(1):22.
27. Janssen I, Chen CC, Millo CM, et al. PET/CT comparing (68)GaDOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2016;43(10):1784–1791.
28. Jha A, Ling A, Millo C, et al. Superiority of (68)Ga-DOTATATE over (18) F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. Eur J Nucl Med Mol Imaging. 2018;45(5):787–797.
29. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. J Clin Endocrinol Metab. 2010;95(2):678–685.
30. Buitenwerf E, Osinga TE, Timmers H, et al. Efficacy of alpha-blockers on hemodynamic control during pheochromocytoma resection - a randomized controlled trial. J Clin Endocrinol Metab. 2019.
31. Dickson PV, Alex GC, Grubbs EG, et al. Posterior retroperitoneoscopic adrenalectomy is a safe and effective alternative to transabdominal laparoscopic adrenalectomy for pheochromocytoma. Surgery. 2011;150(3):452–458.
32. Bancos I, Atkinson E, Eng C, et al. Maternal and fetal outcomes in phaeochromocytoma and pregnancy: a multicentre retrospective cohort study and systematic review of literature. Lancet Diabet Endocrinol. 2021;9(1):13–21.
33. Ayala-Ramirez M, Feng L, Johnson MM, et al. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. J Clin Endocrinol Metab. 2011;96(3):717–725.
34. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European society of endocrinology clinical practice guideline in collaboration with the european network for the study of adrenal tumors. Eur J Endocrinol Eur Feder Endocr Soc. 2016;175(2):G1–G34.
35. Zeiger MA, Thompson GB, Duh QY, et al. The American association of clinical endocrinologists and American association of endocrine surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15(suppl 1):1–20.
36. Di Dalmazi G, Pasquali R, Beuschlein F, Reincke M. Subclinical hypercortisolism: a state, a syndrome, or a disease? Eur J Endocrinol Eur Fed Endocr Soc. 2015;173(4):M61–71.
37. Morelli V, Eller-Vainicher C, Salcuni AS, et al. Risk of new vertebral fractures in patients with adrenal incidentaloma with and without subclinical hypercortisolism: a multicenter longitudinal study. J Bone Miner Res. 2011;26(8):1816–1821.
38. Di Dalmazi G, Vicennati V, Pizzi C, et al. Prevalence and incidence of atrial fibrillation in a large cohort of adrenal incidentalomas: a long-term study. J Clin Endocrinol Metab. 2020;105(8).
39. Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. Endocr Rev. 2014;35(2):282–326.
40. Robertson PW, Klidjian A, Harding LK, Walters G, Lee MR, Robb-Smith AH. Hypertension due to a renin-secreting renal tumour. Am J Med.

1967;43(6):963–976.
41. Lindop GBM, Leckie BJ, Mimran A. Renin-secreting tumors. In: Robertson JIS, Nicholls MG, eds. The Renin-Angiotensin System. 54. London: Gower Medical; 1993:51–54. 12.
42. Lam AS, Bedard YC, Buckspan MB, Logan AG, Steinhardt MI. Surgically curable hypertension associated with reninoma. J Urol. 1982;128(3):572–575.

References

43. Capatina C, Wass JA. 60 years of neuroendocrinology: acromegaly. J Endocrinol. 2015;226(2):T141–T160.
44. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol. 2010;72(3):377–382.
45. Vitale G, Pivonello R, Auriemma RS, et al. Hypertension in acromegaly and in the normal population: prevalence and determinants. Clin Endocrinol. 2005;63(4):470–476.
46. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004;25(1):102–152.
47. van der Lely AJ, Biller BM, Brue T, et al. Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab. 2012;97(5):1589–1597.
48. Jenkins PJ, Bates P, Carson MN, Stewart PM, Wass JA. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab. 2006;91(4):1239–1245.
49. Gumieniak O, Perlstein TS, Hopkins PN, et al. Thyroid function and blood pressure homeostasis in euthyroid subjects. J Clin Endocrinol Metab. 2004;89(7):3455–3461.
50. Vargas F, Moreno JM, Rodriguez-Gomez I, et al. Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol Eur Fed Endocr Soc. 2006;154(2):197–212.

51. Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J. 2002;143(4):718–724.
52. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab. 2002;87(5):1996–2000.
53. Richards AM, Nicholls MG, Espiner EA, Ikram H, Turner JG, Brownlie BE. Hypertension in hypothyroidism: arterial pressure and hormone relationships. Clin Exp Hypertens A. 1985;7(11):1499–1514.
54. Iglesias P, Acosta M, Sanchez R, Fernandez-Reyes MJ, Mon C, Diez JJ. Ambulatory blood pressure monitoring in patients with hyperthyroidism before and after control of thyroid function. Clin Endocrinol. 2005;63(1):66–72.
55. Agarwal G, Nanda G, Kapoor A, et al. Cardiovascular dysfunction in symptomatic primary hyperparathyroidism and its reversal after curative parathyroidectomy: results of a prospective case control study. Surgery. 2013;154(6):1394–1403. discussion 1403-1394.
56. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561–3569.

41

Neurogenic Hypertension, Including Hypertension Associated With Stroke or Spinal Cord Injury

Venkatesh Aiyagari, Philip B. Gorelick

An intimate relationship exists between the nervous system and blood pressure (BP).[1] It is well recognized that the elevated BP response to stressors is mediated by the sympathetic nervous system (SNS). However, the role of the SNS in long-term regulation of BP and the initiation and maintenance of hypertension is now better delineated. Several studies of serum catecholamine levels, renal norepinephrine spillover, microneurography, and heart rate variability suggest that sympathetic activation plays a major role in hypertensive patients.[2] The SNS also has an important role in hypertension after neurologic injury. This chapter discusses the physiology and management of hypertension in such injury.

a dysfunction of the neural-immune-vascular triad leading to an increase in central oxidative stress may drive sympathetic activation, which then increases Ang II and promotes further inflammation and vascular dysfunction.[6] Another matter for debate is whether the kidney or the central nervous system (CNS) is the main driver for increased sympathetic tone in patients with neurogenic hypertension. The role of the afferent and efferent renal nerves in mediating neurogenic hypertension is being researched, and renal denervation procedures are being explored as possible therapeutic options to treat hypertension.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Under normal conditions, cerebral blood flow (CBF) of the adult brain is approximately 50 mL/100 g/min. CBF is regulated by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR):

Neural Control of Blood Pressure

The brainstem, especially the ventral medulla, has a key role in the maintenance of BP (Fig. 41.1). BP is controlled by the nucleus tractus solitarius, which receives inhibitory baroreceptor afferents, and the rostral ventrolateral medulla and rostral ventromedial medulla, which are the source of excitatory descending bulbospinal pressor pathways. In addition, a depressor center in the caudal ventrolateral medulla composed of γ-aminobutyric acid (GABA)-containing neurons receives afferents from the nucleus tractus solitarius and projects to the rostral ventral medulla. These inhibitory GABA-containing neurons are tonically active, and reduced activity of these neurons leads to hypertension.[3–5]

The ultimate effector units are the sympathetic neurons located in the intermediolateral cell column of the spinal cord and the parasympathetic neurons found in the dorsal motor nucleus of the vagus and nucleus ambiguus located in the medulla. In addition, impulses from the limbic system, cerebral cortex, and hypothalamus directly or indirectly project to the intermediolateral cell column of the spinal cord and influence BP regulation.

The factors that lead to increased sympathetic activation in hypertension are poorly understood. However, there is strong evidence linking hypertension with increased levels of circulating inflammatory markers, such as tumor necrosis factor-α, interleukin-6, C-reactive protein, monocyte chemoattractant protein 1, and adhesion molecules such as P-selectin and intercellular adhesion molecule 1. Angiotensin II (Ang II) and aldosterone also play a crucial role in vascular inflammation, and treatment with both candesartan and mineralocorticoid antagonists decrease the levels of inflammatory markers. In addition, Ang II–mediated hypertension is associated with brain microglial activation and increased brain levels of inflammatory cytokines and reactive oxygen species. An increase in reactive oxygen species may directly activate or sensitize sympathetic neurons and scavenge nitric oxide, the latter of which tonically inhibits sympathetic outflow. Thus,

Cerebrovascular Autoregulation

CBF = CPP/CVR

CPP is the difference between the mean arterial blood pressure (MAP) and the intracranial pressure (ICP). If ICP is increased, systemic BP must also increase to maintain CPP and CBF.

Cerebrovascular autoregulation maintains a constant blood flow over a wide range of CPP. Normally, changes in CPP have little effect on CBF because of compensatory changes in CVR. An increase in CPP produces vasoconstriction and a decrease produces vasodilation, thus keeping the CBF constant (Fig. 41.2). Autoregulation is effective for a range of CPP from about 60 to 150 mm Hg. In chronically hypertensive individuals, the cerebral arterioles develop medial hypertrophy and lose the ability to dilate effectively at lower pressures. This leads to a shift of the autoregulatory curve to the right.7 In these individuals, a rapid reduction of BP may lead to a drop in CBF even though the BP might still be “normal.” With effective control of hypertension for several months, the normal range for autoregulation can be reestablished.8

Above the upper limit of autoregulation, there is breakthrough vasodilation leading to damage of the blood-brain barrier, cerebral edema, and possibly cerebral hemorrhage. Below the lower limit of autoregulation, decreases in CPP lead to a decrease in CBF. Under these circumstances, increased extraction of oxygen and glucose maintains normal cerebral metabolism and brain function. When the CBF decreases to less than 20 mL/100 g/min, increases in oxygen extraction are no longer able to supply the metabolic needs of the brain, leading to impairment of brain function.

NEUROGENIC HYPERTENSION

It is challenging to identify patients in whom neurogenic mechanisms are the main driver of hypertension. There are no readily available

Neural Pathways Involved in the
Control of Blood Pressure

Cerebral Autoregulation Curve
150
CPP
CVR

DMV
NA
RVLM
Baroreceptors
Ventral medulla

Heart

IMLC
Spinal cord

Fig. 41.1 Neural Pathways Involved in the Control of Blood Pressure. The ventral medulla has a key role in generating both excitatory (solid line) and inhibitory (dotted line) pathways, largely through the rostral ventrolateral medullary neurons (RVLM) and nucleus tractus solitarius (NTS), respectively. Ultimate effector control is provided by sympathetic activation originating in the intermediolateral cell column (IMLC) and parasympathetic action through the nucleus ambiguus (NA) and dorsal motor nucleus of the vagus nerve (DMV). CVLM, Caudal ventrolateral medullary neurons.

clinical tests to evaluate increased sympathetic activity and differentiate neurogenic hypertension from nonneurogenic hypertension.
Nonetheless, some clinical clues may suggest the presence of neurogenic hypertension. These include paroxysmal or labile hypertension, young age of onset, severe hypertension that is resistant to angiotensinconverting enzyme (ACE) or diuretic therapy and hypertension associated with ingestion of sympathomimetic agent.9

SPECIFIC SYNDROMES

Hypertension After Stroke

Epidemiology

BP is commonly elevated in patients with stroke. The reason for this acute hypertensive response after stroke remains a matter of conjecture. In a large retrospective analysis that examined 276,734 patients presenting to the emergency department (ED) with acute ischemic stroke, the incidence of elevated BP was 76.5%.10 The Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST), each enrolling approximately 20,000 patients with ischemic stroke, reported systolic BP (SBP) above 140 mm Hg in 75% and 80% of patients and severely elevated SBP of greater than 180 mm Hg in 25% and 28%, respectively.11 12

Hypertension is the most important modifiable risk factor for stroke, and reduction in BP is effective in the primary prevention of both ischemic and hemorrhagic stroke; BP reduction also decreases the risk for a recurrent ischemic or hemorrhagic stroke.13 Combined

MAP–ICP
MAP–JVP
or
CVR
CVR

Decreasing vessel diameter

100

50

0

CVLM

Blood vessel

CBF (mL .mg–1.min–1)

NTS

0

50

100

150

200

250

CPP (mm Hg)
Fig. 41.2 Cerebral Autoregulation Curve. In the normal state (solid line), the cerebral blood flow (CBF) is held constant across a wide range of cerebral perfusion pressure (CPP) (60–150 mm Hg). In chronic hypertension (dashed line), the autoregulation curve shifts to the right. In the presence of acute cerebral ischemia (dotted line), cerebral autoregulation may be impaired, and the CBF becomes dependent on the CPP. CVR, Cerebral venous resistance; ICP, intracranial pressure; JVP, jugular venous pressure; MAP, mean arterial pressure. (From Testai FD, Aiyagari V. Acute hemorrhagic stroke pathophysiology and medical interventions: blood pressure control, management of anticoagulantassociated brain hemorrhage and general management principles. Neurol Clin. 2008;26:963–985.)

data from 40 trials show that a 10% reduction in SBP lowers stroke risk by one-third.14 A 5-mm reduction in diastolic pressure together with a 9-mm lower SBP confers a 33% lower risk for stroke, and a 10mm lower diastolic BP (DBP) together with an 18- to 19-mm lower SBP confers more than a 50% reduction in stroke risk.15 In patients who have had a stroke, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that BP reduction was associated with reductions of 28% in stroke recurrence and 26% in major coronary and vascular events, even in normotensive subjects. This study also demonstrated a reduction of absolute rates of hemorrhagic stroke from 2% to 1% over a mean of 3.9 years of follow-up.16
However, the management of BP in the immediate aftermath of a stroke is controversial.17 A high proportion of patients have elevated BP immediately after a stroke, but BP spontaneously decreases over 1 to 2 weeks to the prestroke baseline in most patients. Some of the postulated causes of elevated BP are listed in Box 41.1. An increased BP after stroke is associated with a higher mortality. Nonetheless, it is uncertain whether this increase directly contributes to poor outcome and whether immediate lowering of BP will lead to better outcomes.
SBP variability may be associated with the risk for cerebrovascular events independent of the mean BP. Home BP monitoring and

ambulatory BP monitoring are useful in monitoring BP variability.

Normally, BP is highest in the morning and gradually falls to reach its lowest level during sleep. Several alterations in this pattern, including a lack of nighttime decline in BP (nondippers), a rise in nighttime BP (reverse dippers), and a more than 20% fall in nighttime BP (extreme dippers), are associated with increased risk for vascular complications, including stroke. These findings also have a bearing on the choice of the antihypertensive agent for stroke prevention. Calcium channel blockers (CCBs) and nonloop diuretics appear to decrease SBP variability,

Postulated Causes of Hypertension After Stroke

BOX 41.1

- Preexisting hypertension
- “White coat” effect
- Stress of hospitalization
- Cushing reflex[a]
- Catecholamine and cortisol release
- Lesion of brainstem or hypothalamus
- Nonspecific response to brain damage

[a] Hypothalamic response to raised intracranial pressure or ischemia consisting of hypertension with bradycardia.

whereas β-blockers, angiotensin receptor blockers (ARBs), and ACE inhibitors do not appear to decrease BP variability.

Pathophysiology

An understanding of cerebrovascular pathophysiology is essential to understand the pros and cons of treating hypertension in these patients (Table 41.1).

In patients with an ischemic stroke, vascular occlusion leads to a central region of irreversibly ischemic brain surrounded by an ischemic zone where blood flow is reduced but brain tissue is still viable (the so-called penumbra zone). After 2 or 3 days, the ischemic areas either recover or undergo infarction. In the first few days, perfusion of the area surrounding that destined to infarction is marginal and a further decrease in blood flow might lead to infarction there as well. Because cerebral autoregulation is impaired with acute ischemic stroke, a fall in BP could lower blood flow and extend infarction. On the other hand, a very high BP could exacerbate cerebral edema or lead to hemorrhagic transformation, especially if thrombolytic agents have been given.

In patients with intracerebral hemorrhage (ICH), the considerations are different.[18] Hematoma expansion occurs in 73% of patients within 24 hours, and significant expansion (>33% increase in volume) occurs in nearly 40% of patients.[19] Hematoma expansion is frequently associated with decline in neurologic status and is an independent predictor of mortality and poor functional outcome. Therefore, BP is often lowered in these patients in the hope that this might decrease hematoma expansion. However, it is not often clear if the elevation in BP is the cause or the consequence of hematoma expansion. The suggestion that there may be perihematomal ischemia around an ICH has not been supported by recent studies.[20] Furthermore, some patients with ICH might have increased ICP because of the hematoma volume or associated hydrocephalus. In such a situation, lowering of BP is not warranted because it might critically lower CPP. Monitoring of ICP and CPP may be helpful in choosing the appropriate BP target in these circumstances.

In patients with aneurysmal subarachnoid hemorrhage (SAH), there is a significant risk for rebleeding from aneurysmal rerupture, and therefore early BP control is recommended to decrease the rebleeding risk. Some patients with SAH have associated myocardial dysfunction (stunned myocardium), in which case high BP might worsen myocardial function. Like patients with ICH, in patients with hydrocephalus or an associated ICH, ICP and CPP monitoring can help guide BP management. However, many patients develop vasospasm of the intracranial arteries at 4 to 12 days after SAH, and reduction of BP may lead to worsening of cerebral ischemia in this situation. Therefore, once the aneurysmal rupture has been adequately treated with surgical clipping or coiling, BP is usually maintained at a normal or slightly elevated level in these patients.

Acute Treatment of
Hypertension in Stroke: Advantages and
Disadvantages

TABLE 41.1

Advantages
Acute Ischemic Stroke
Might lower mortality
Might decrease stroke progression
Might decrease hemorrhagic
transformation (especially after
tPA)
Might decrease cerebral edema
formation
Might be helpful for systemic
reasons (e.g., associated
myocardial ischemia)
Patients likely to be more compliant
with antihypertensive use if
treatment initiated in hospital

Disadvantages
BP decreases on its own
No proven benefit
Ongoing ischemia around infarct
(ischemic penumbra)
Altered autoregulation from chronic
hypertension, ischemia
Large-vessel stenosis might have
resulted in reduction of perfusion
Chance of propagating thrombus
Anecdotal case reports and trial
results demonstrating deterioration
with BP decrease
Principle of “do no harm” (primum non
nocere)

Acute Intracerebral Hemorrhage
Might lower mortality
BP decreases on its own
Might decrease hematoma
No proven benefit
expansion
Possible zone of ischemia around
Might decrease cerebral edema
intracerebral hematoma
formation
Chronically hypertensive patients
Might be helpful for systemic

require higher CPP because of shift
reasons (e.g., associated
in autoregulatory curve
myocardial ischemia)
ICP may be elevated, and lowering BP
Patients likely to be more compliant
reduces what could be marginal CPP
with antihypertensive use if
Principle of “do no harm” (primum non
treatment initiated in hospital
nocere)
Aneurysmal Subarachnoid Hemorrhage
Might decrease rebleeding rate
No proven benefit
Might help if there is cardiac
ICP may be elevated, and lowering BP
ischemia (stunned myocardium)
reduces what could be marginal CPP
Might lead to cerebral ischemia in
presence of vasospasm

BP, Blood pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; tPA, tissue plasminogen activator.

Diagnosis and Treatment

Acute management of hypertension in stroke is highly dependent on the type of stroke (ischemic vs. hemorrhagic) and, for ischemic stroke, the use of thrombolysis. The benefits of lowering BP to prevent hematoma expansion in the setting of ICH or hemorrhagic transformations of ischemic stroke should be balanced with the risk for abrupt reduction of CBF in chronically hypertensive patients with shifted cerebrovascular autoregulation, especially if increased ICP and cerebral edema are present.

It is important to distinguish between hypertensive encephalopathy, in which lowering of BP is clearly indicated, and ischemic stroke with hypertension, in which urgent lowering of BP may not be warranted. The level of consciousness, the presence of focal neurologic deficits, and the funduscopic examination can help in making this distinction. Hypertensive encephalopathy is a syndrome of global neurologic dysfunction, usually with papilledema. Focal neurologic deficits are usually less prominent. In acute ischemic stroke, the focal neurologic deficit is prominent, and the symptoms and neurologic signs

Management of Hypertension
Following Acute Stroke
Acute stroke with hypertension

Ischemic
stroke

Intracerebral
hemorrhage

Subarachnoid
hemorrhage

Aneurysm
secured

IV thrombolysis
candidate
No

No

Yes

Tight BP
control

Follow tPA
guidelines
(see text)
Lower BP by
~15% in first
day

Yes

Indication to
lower BP*
(see text)
No

Monitor BP
over next
1-2 weeks

Initiate oral
antihypertensives

Yes

Consider
raising
BP
Initiate
BP lowering
therapy

Yes

No BP lowering

unless otherwise
indicated
(see text)

Vasospasm
No

Yes
BP elevated
after 3 weeks
No

Yes
BP elevated
No

No treatment

Consider BP
reduction
even if BP is
normal

Fig. 41.3 Management of Hypertension After Acute Stroke. *Indication for treatment includes systolic blood pressure (BP) >220 mm Hg or diastolic BP >120 mm Hg for ischemic stroke, the presence of associated conditions such as aortic dissection or myocardial infarction, and, in cases of cerebral hemorrhage, systolic BP >180 mm Hg or mean arterial pressure >130 mm Hg. IV, Intravenous; tPA, tissue plasminogen activator.

often can be mapped to the vascular territory supplied by a specific cerebral blood vessel. Early alterations of consciousness are less common, except with brainstem strokes or when there is “malignant” brain edema secondary to a massive hemispheric infarction.

Several recent studies assess the benefits and risks of BP lowering after ischemic and hemorrhagic stroke. A Cochrane review on this topic concluded that more research is needed to evaluate and identify the candidates most likely to benefit from management of BP in the acute phase of stroke and the timeframe for such intervention.21

An overview of recommendations for treating BP in different clinical situations is outlined in Fig. 41.3

Acute ischemic stroke. Several large prospective trials of BP lowering in acute ischemic stroke have been completed and are summarized in Table 41.2 22–32

The current guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organisation (ESO) for BP management in acute ischemic stroke recommend a cautious approach to lowering BP in acute ischemic stroke.

Patients receiving thrombolytic therapy should have their BP lowered to less than 185/110 mm Hg before the administration of the thrombolytic agent and maintained at a level of less than 180/105 mm Hg for at least the first 24 hours after thrombolytic treatment. Patients not receiving thrombolytic agents should have antihypertensive medications withheld unless the SBP is greater than 220 mm Hg or the DBP is greater than 120 mm Hg, in which case a 15% reduction in BP in the first 24 hours appears reasonable. Recommendations are summarized in Table 41.3 33 34

Thus, available evidence does not support immediate BP reduction after an acute ischemic stroke. Based on the limited data and natural history of BP after ischemic stroke, treatment of newly diagnosed previously untreated hypertension or resumption of long-term antihypertensive medication can be initiated or resumed gradually after the first 24 hours. Reduced dosage and/or number of agents from the prestroke regimen should be used to avoid rapid reduction of BP in the case of prior outpatient noncompliance. It may be advisable to administer BP-lowering agents when the patient's neurologic status is stable.35

Intracerebral hemorrhage. Hypertension is the most important modifiable risk factor for ICH. Although long-term benefit in lowering BP in patients with ICH is widely accepted, it remains unclear if elevated BP should be lowered in the acute phase. In recent years, a few randomized trials have attempted to address the issue of acute BP lowering in ICH and are summarized in Table 41.4 27 36–39

The currently recommended guidelines of the AHA/ASA and the European Stroke Initiative (ESI) for BP management in acute ICH are summarized in Table 41.5 40 41 The AHA/ASA guidelines also recommend avoiding peaks and large variability in SBP and initiating BP-lowering treatment within 2 hours of ICH onset and reaching target within 1 hour. If elevated ICP is of concern, such as in patients with large hemorrhages or with hydrocephalus, ICP should be monitored to ensure that the CPP is appropriate before significant BP reduction.

Subarachnoid hemorrhage. Before definitive treatment of the ruptured aneurysm, SBP is usually kept below 160 mm Hg, although there is no conclusive evidence that higher BPs increase rebleeding rates. In patients with suspected elevation of ICP, it is important to monitor ICP and keep the CPP greater than 70 mm Hg. The AHA/ ASA guidelines recommend monitoring and control of BP to balance the risk for stroke, hypertension-related bleeding, and maintenance of CPP. An SBP goal of less than 160 mm Hg is considered reasonable.42 The ESO recommends keeping the SBP at less than 180 mm Hg but keeping the MAP at greater than 90 mm Hg.43 After the ruptured aneurysm has been secured, aggressive treatment of BP should be avoided, and in the setting of cerebral vasospasm, BP is usually elevated using vasopressors until the neurologic deficits resolve, often as high as an SBP of 200 to 220 mm Hg.

Hypertension After Carotid Endarterectomy and Endovascular Procedures

Definition, Incidence, and Clinical Features

Hemodynamic disturbances such as hypotension, bradycardia, and hypertension are common (10%–40%) after carotid endarterectomy and endovascular procedures such as angioplasty and stenting. A small percentage of these patients develop carotid hyperperfusion (or reperfusion) syndrome. This syndrome occurs in the first week after surgery or angioplasty-stenting and manifests as ipsilateral pulsatile headache, seizures, ICH, transient or permanent contralateral neurologic signs, encephalopathy, or reversible cerebral edema.44-46 Recently, this syndrome has also been reported after treatment of acute ischemic stroke with intravenous thrombolysis and endovascular treatment. Some subjects with cerebral hyperperfusion after revascularization may not manifest clinical signs acutely but may later develop cortical neuronal loss and cognitive impairment.47

TABLE 41.2

Major Trials of Acute Blood Pressure Reduction in Ischemic Stroke

Trial	Study Design	Study Arms	No. of Patients	Results
Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS)[32]	Prospective, double-blind, placebo-controlled, randomized, multicenter, phase II	Candesartan vs. placebo	342	Lower 12-month mortality and vascular events in the candesartan group, but no significant difference in BP between the two arms.
Scandinavian Candesartan Acute Stroke Trial (SCAST)[31]	Prospective, double-blind, placebo-controlled, randomized, multicenter	Candesartan vs. placebo	2029 (274 had cerebral hemorrhage)	During 6 months of follow-up, the risk of the composite vascular endpoint did not differ between treatment groups. Analysis of functional outcome suggested a higher risk for poor outcome in the candesartan group.
Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS)[29]	Prospective, double-blind, placebo-controlled, randomized, multicenter			

Labetalol vs. lisinopril vs.
placebo

179 (25 had
cerebral
hemorrhage)

No difference in death or dependency at 2 weeks, early neurologic deterioration, or serious adverse event.

Continue or Stop Poststroke Antihypertensive Collaborative Study
(COSSACS)30

Prospective, open, multicenter, randomized, blindedendpoint trial

Continue vs. stop
preexisting
antihypertensive drugs

763 (38 had
cerebral
hemorrhage)

Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months.

Glycine Antagonist in
Neuroprotection (GAIN
International)24

Prospective, double-blind,
placebo-controlled,
randomized, multicenter

Gavestinel vs. placebo

1445

A 30% drop in mean arterial pressure from baseline was not associated with poor outcome.

Intravenous Nimodipine
West European Stroke
Trial (INWEST)22

Prospective, double-blind,
placebo-controlled,
randomized, multicenter

Placebo vs. low-dose vs.
high-dose nimodipine

265

Patients with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted odds ratio for the compound outcome variable of death or dependency.

Chinese Antihypertensive Trial in Acute Ischemic Stroke (CATIS)25

Prospective, single-blind, randomized, blinded endpoint, multicenter

Antihypertensive treatment vs. discontinuing all antihypertensives

4071

BP reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 days or hospital discharge.

Efficacy of Nitric Acid in Stroke (ENOS)26

Prospective, multicenter, randomized, placebocontrolled, patient-masked, outcome-assessor-masked, parallel-group trial

Glyceryl trinitrate vs. no treatment; subset taking antihypertensive medications on admission randomized to taking vs. stopping them

4011 (629 had cerebral hemorrhage)

Transdermal glyceryl trinitrate lowered BP and had acceptable safety but did not improve functional outcome. There was no evidence to support continuing prestroke antihypertensive drugs in patients in the first few days after acute stroke.

Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke (VENTURE)28

Prospective, multicenter, randomized, open-label, blinded-endpoint trial

Valsartan vs. no treatment

393

Early reduction of BP with valsartan did not reduce death or dependency and major vascular events at 90 days but increased the risk for early neurologic deterioration.

Intensive BP reduction with intravenous thrombolysis therapy for acute ischemic stroke (ENCHANTED)23

International, partial-factorial, open-label, blinded-endpoint

Intensive (systolic BP 130–140 mm Hg) or guideline (systolic BP < 180 mm Hg) antihypertensive treatment for 72 hours in patients within 6 hours of stroke onset and treated with intravenous alteplase

2227

Fewer patients in the intensive group had intracranial hemorrhage, but there was no difference in clinical outcome between the two groups.

Prehospital transdermal glyceryl trinitrate in patients with ultraacute presumed stroke (RIGHT-2)27

Prospective, multicentric, paramedic-delivered, ambulance-based, randomized, shamcontrolled, blinded endpoint

Transdermal nitroglycerin vs. sham dressing

1149 (597 with ischemic stroke, 145 with cerebral hemorrhage, 109 with transient ischemic attack, 297 with a nonstroke mimic)

Nitroglycerin did not lead to an improved outcome at 90 days.

BP, Blood pressure; DBP, diastolic blood pressure.

Guidelines for Blood Pressure Management After Acute Ischemic Stroke

TABLE 41.3

AHA/ASA

ESO

Patients Eligible for Thrombolytic Therapy or Mechanical Thrombectomy

Before Thrombolytic Therapy

- Lower SBP to <185 and DBP to <110 mm Hg.

- Routine BP lowering is not recommended.
- Cautious BP lowering is recommended in patients with extremely high BP (>220/120 mm Hg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy.
- Abrupt BP lowering should be avoided.
- BP must be <185/110 mm Hg before, and for the first 24 hours after, thrombolysis.

During and After Thrombolytic Therapy or Mechanical Thrombectomy

- Lower SBP to <180 and DBP to <105 mm Hg.

Patients Not Eligible for Thrombolytic Therapy

- Patients with markedly elevated BP may have their BP lowered.
- Lowering BP by ~15% in these patients is reasonable.
- Antihypertensive drugs should be withheld unless SBP >220 or DBP >120 mm Hg.

Trial

Pathophysiology

Preexisting hypertension, baroreceptor impairment after surgical manipulation, and elevated catecholamine levels after cerebral hypoperfusion during intraoperative cross-clamping may contribute to postoperative hypertension that contributes to cerebral hyperperfusion, which may in turn lead to cerebral hemorrhage. The hyperperfusion syndrome may be due, in part, to impaired autoregulation from chronic vasodilation of the distal vascular bed ipsilateral to a hemodynamically significant internal carotid artery stenosis.49 Other postulated mechanisms include activation of the trigeminovascular axon reflex and derangement of the carotid baroreceptors.50 Subjects at risk for development of this syndrome are those with extensive microvascular disease, preoperative hypoperfusion and impaired autoregulation, or postoperative hyperperfusion.

AHA/ASA, American Heart Association/American Stroke Association;
BP, blood pressure; DBP, diastolic blood pressure; ESO, European
Stroke Organisation; SBP, systolic blood pressure.

After carotid endarterectomy, the incidence of postoperative severe hypertension is reported as 19% and that of carotid hyperperfusion syndrome as 1%. Most cases occurred in the first week and the average time to symptoms was the fifth postoperative day. Seizures (36%), hemiparesis (31%), or both (33%) were common presenting features, and 59% of patients had headache.48

Cerebral hyperperfusion represents a postoperative increase in CBF of more than 100% compared with preoperative flow. However, this increase in blood flow may be only approximately 20% compared with the contralateral side.51 Making a diagnosis based on CBF doubling alone may lead to a significant overestimation of the incidence, and the following four criteria have been suggested: (1) occurrence within 30

TABLE 41.4

Major Trials of Acute Blood Pressure Reduction in Cerebral Hemorrhage

	Study Design	Study Arms	No. of Patients	Results
et al.38	Prospective, randomized	Target MBP <110 or 110–130 mm Hg	42	No significant differences in early neurologic deterioration, hematoma and edema growth, and clinical outcome.
INTERACT36	Prospective, randomized, blinded endpoint assessment	Target SBP <140 or <180 mm Hg	404	No significant difference in hematoma growth between the two tiers after adjustment for baseline hematoma volume and time to CT scan.
INTERACT 263	Prospective, randomized, blinded endpoint			

assessment

Target SBP <140 or <180 mm Hg

2839

No significant reduction in the rate of primary outcome of death or severe disability with intensive lowering of BP. Improved functional outcomes with lower BP target on ordinal analysis of modified Rankin Scale score.

ATACH37

Prospective, Phase I doseeescalation

Target SBP 110–140 or 140–170 or 170–200 mm Hg

60

Observed proportions of neurologic deterioration and serious adverse events below the prespecified safety thresholds; 3-month mortality rate lower than expected in all tiers.

ATACH 239

Prospective, randomized, multicenter, open-label trial

Target SBP 110–140 or 140–179 mm Hg

1000

BP reduction to a target SBP of 110–139 mm Hg did not result in a lower rate of death or disability than a target of 140–179 mm Hg. The rate of renal adverse events within 7 days after randomization was significantly higher in the group with the lower BP target.

Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2)27

Prospective, multicentric, paramedic-delivered, ambulance-based, randomized, shamcontrolled, blinded end-point

Transdermal nitroglycerin versus sham dressing

1149 (597 with ischemic stroke, 145 with cerebral

hemorrhage, 109 with
transient ischemic attack,
297 with a nonstroke mimic)

Nitroglycerin did not lead to an improved outcome
at 90 days.

Koch

BP, Blood pressure; CT, computed tomography; MAP, mean arterial blood pressure;
SBP, systolic BP.

Guidelines for Blood Pressure Management After Acute Cerebral Hemorrhage

TABLE 41.5

AHA/ASA	ESO
For patients with mild to moderate severity ICH presenting with SBP between 150 and 200 mm Hg, acute lowering of SBP to a goal of 140 mm Hg is safe and may be reasonable for improving functional outcomes (Class 2b; Level of Evidence B-R). In patients with large or severe ICH and in those requiring surgical decompression, the safety and efficacy of intensive BP lowering are not well established (Class 2b, Level of Evidence C-LD). In patients with mild to moderate severity ICH presenting with SBP >150 mm Hg, acute lowering of SBP to <130 mm Hg is probably harmful (Class 3, Level of Evidence B-R).	In acute ICH within 6 hours of onset, intensive BP reduction (SBP target <140 mm Hg in <1 hour) is safe and may be superior to SBP target of <180 mm Hg. No specific agent can be recommended. (quality of evidence: moderate; strength of recommendation: weak).

AHA/ASA, American Heart Association/American Stroke Association; BP, blood pressure; ESO, European Stroke Organisation; ICH, intracerebral hemorrhage; SBP, systolic BP.

days post–carotid endarterectomy; (2) evidence of hyperperfusion (on transcranial Doppler, single-photon emission computed tomography, or computed tomography [CT]/magnetic resonance [MR] perfusion imaging) or SBP greater than 180 mm Hg; (3) clinical features such as new headache, seizures, hemiparesis, and Glasgow Coma Scale score less than 15 or radiologic features such as cerebral edema or ICH; and (4) no evidence of new cerebral ischemia, postoperative carotid occlusion, or metabolic or pharmacologic cause to explain the findings.[48]

Because of the risk for development of carotid hyperperfusion syndrome after carotid endarterectomy or stenting, all patients should have continuous intraoperative and postoperative BP monitoring. Most authors advocate strict BP control (SBP <120 mm Hg) from the time of intraoperative internal carotid artery unclamping or angioplasty, particularly in high-risk patients.[52] If high-risk features are absent, aiming for SBP of 140 to 160 mm Hg or preoperative SBP (if lower) in the postoperative period is reasonable. Elevated BP should be treated with intravenous (IV) labetalol or clonidine. Vasodilators such as nitroglycerin, hydralazine, and sodium nitroprusside should be avoided. Because this syndrome may occur after patients have been discharged from the hospital, it is important for physicians to ensure that BP is appropriately controlled even after the immediate postoperative period.

Hypertension After Spinal Cord Injury

Definition and Epidemiology

Hypertension is quite prevalent in patients with spinal cord injury (SCI), with a reported prevalence of 14% to 61%. The prevalence is higher in patients with paraplegia compared with tetraplegia and in those with nontraumatic SCI compared with those with traumatic SCI.53

In addition, autonomic dysreflexia occurs in up to 70% of persons after SCI, most often during the first 2 to 4 months after injury.

It is defined as an increase in SBP by at least 20%, associated with a change in heart rate, and accompanied by at least one sign (sweating, piloerection, facial flushing) or symptom (headache, blurred vision, stuffy nose).54 If autonomic dysreflexia is unrecognized, it can result

in serious sequelae, such as posterior leukoencephalopathy, ICH, SAH, seizures, arrhythmia, pulmonary edema, retinal hemorrhage, and, rarely, coma or death.55

Pathophysiology and Diagnosis of Autonomic Dysreflexia

Autonomic dysreflexia is most commonly seen in patients with complete SCI in which there is loss of all neurologic function below the level of the lesion. The spinal cord lesion is typically at or above the sixth thoracic spinal level. Immediately after the injury, there is initial loss of supraspinal sympathetic control similar to the initial period of muscle flaccidity. This often leads to hypotension and bradycardia (spinal shock). After a few weeks to months, there is extrajunctional sprouting of the α-receptors, denervation hypersensitivity, and impaired presynaptic uptake of norepinephrine. In addition, there may be derangement of spinal glutaminergic interneurons. Noxious stimuli below the neurologic level of the lesion trigger a spinal reflex arc that results in increased sympathetic tone and hypertension.56 The most common inciting events are an overdistended urinary bladder and fecal impaction. However, it may be secondary to other precipitants, including infections, pressure ulcers, urologic and endoscopic procedures, sympathomimetic medications, and sildenafil citrate used for sperm retrieval.57

Clinical symptoms include pulsatile headache, blurred vision, anxiety, nasal congestion, nausea, and sweating above the involved spinal level. The flushed, sweaty skin above the lesion level is because of brainstem parasympathetic activation. At and below the lesion, the skin remains pale, cool, and dry. Heart rate can be quite variable from bradycardia to tachycardia. The hallmark physical finding is elevated BP. However, because BP may normally be quite low after SCI, baseline BP readings may be within the normal range but elevated for a given individual, making clinical suspicion and reliance on other clinical signs and symptoms paramount in the diagnosis if baseline BP is not known.56

Treatment

Although it is recognized that BP is often lower in patients with tetraplegia and high paraplegia, current guidelines suggest applying evidence-based guidelines for treating hypertension in the general population to SCI patients as well. However, SCI may affect the choice of the antihypertensive agent. Thiazide diuretics are not preferred in patients who perform intermittent bladder catheterization because they increase urine volume. In addition, SCI patients may experience electrolyte abnormalities or decline in renal function during thiazide use. Some patients with SCI may experience supine hypertension with coexisting orthostatic hypotension, which requires cautious trial and titration of antihypertensive agents.53

Vigilant preventive measures for autonomic dysreflexia include proper bowel, bladder, and skin care. However, expeditious treatment of elevated BP is critical to avoid the potentially life-threatening consequences. Placement of the patient upright with the legs lowered to reduce BP and removal of any possible noxious stimuli (such as binding clothing and devices) are the initial treatments. It is also important to look for and appropriately treat other common triggers such as urinary retention or constipation.

Pharmacologic treatment with rapid-acting, short-lived agents may be indicated for SBP elevation of 150 mm Hg or greater that persists after the preceding interventions. Nitroglycerin is often used to treat hypertension associated with autonomic dysreflexia. However, to avoid precipitating hypotension, nitrate-containing agents should not be given for 24 hours before the use of sildenafil or similar agents to facilitate sperm retrieval or treat erectile dysfunction in SCI. CCBs and ACE inhibitors

TABLE 41.6

Hypertension

Preferred Antihypertensive Agents in the Treatment of Stroke-Associated

Drug	Mechanism of Action	Intravenous Dose	Advantages	Disadvantages
Labetalola	α1-, β1-, and β2-receptor antagonist	10 mg IV over 1–2 min, may repeat once; IV infusion 2–8 mg/min	Does not lower CBF Does not increase ICP	May exacerbate bradycardia
Nicardipinea	L-type CCB	5–15 mg/hr	Does not decrease CBF	May increase ICP Long duration of action
Clevidipinea	L-type CCB	Starting dose 1–2 mg/hr; dose can be doubled every 2–5 min up to a maximum dose of 21 mg/hr	Does not decrease CBF	Should be avoided in patients with egg/soy allergy
Esmolol	β1-receptor antagonist	500-µg/kg bolus, then 50–300µg/kg/min		

Does not lower CBF
Does not increase ICP

May exacerbate bradycardia

Sodium nitroprusside

Vasodilator

0.25–10μg/kg/min

Potent antihypertensive

May increase ICP
Can cause cerebral steal
Potential for cyanide toxicity

Nitroglycerin

Vasodilator

5–200μg/min

Can be helpful for concomitant
cardiac ischemia

May increase ICP
Can cause cerebral steal

Hydralazine

Vasodilator

2.5- to 10-mg bolus

Can be given as IV bolus when
labetalol is contraindicated
because of bradycardia

May increase ICP
Can cause cerebral steal

Enalaprilat

ACE inhibitor

0.625–1.25 mg every 6 hr

Does not decrease CBF

Variable response
Long duration of action

[a]Preferred

agents listed in 2018 American Heart Association/American Stroke Association guidelines.
ACE, Angiotensin-converting enzyme; CBF, cerebral blood flow; CCB, calcium channel blocker; ICP, intracranial pressure; IV, intravenous.

also have been reported to be effective.58 However, these agents might exacerbate resting hypotension and therefore should be used with caution. Prazosin has been reported to be effective in reducing the severity of autonomic dysreflexia without significantly lowering the resting

BP. If the bladder is empty and the BP is less than 150 mm Hg, fecal disimpaction with topical anesthetic should be attempted. If dysreflexia is refractory or associated with severe clinical presentation, other precipitants should be sought, and hospitalization may be indicated.59

Up to 90% of pregnant women with upper SCI experience autonomic dysreflexia during labor and delivery. Appropriate epidural or spinal anesthesia techniques can ameliorate the risk.60

Cerebrovascular Effects of Antihypertensive Agents

Different classes of antihypertensive agents have different direct effects on the CBF, ICP, and autoregulation. The ideal drug would not increase ICP or decrease blood flow to ischemic regions. In addition, in treatment of hypertension in the acute setting, drugs that can be given by IV, have a short half-life, and do not cause sedation are preferable.

In the chronic phase after a stroke, adequate BP lowering is key, and there is no clear evidence favoring one class of antihypertensive agent over another; however, one may consider avoiding the use of nonselective β-blockers that may increase SBP variability.

The advantages and disadvantages of various classes of antihypertensive agents after acute stroke are summarized in Table 41.6

β-Adrenergic antagonists (e.g., esmolol) and combined α- and β adrenergic receptor antagonists (e.g., labetalol) do not increase ICP or affect cerebral autoregulation. They are suitable for treatment of hypertension in the setting of acute cerebral ischemia or increased ICP. However, bradycardia secondary to increased ICP is a relative contraindication.

Vasodilators (e.g., sodium nitroprusside, nitroglycerin) cause cerebral arterial dilation and venodilation and can theoretically increase ICP and cause a cerebral steal phenomenon in patients with acute cerebral ischemia. Other disadvantages of sodium nitroprusside are tachyphylaxis, the need to shield the medication from light because of its photosensitivity, and the danger of cyanide and thiocyanate toxicity that may be difficult to detect in patients with brain injury. However, they may be used in patients with small and moderate-sized ICH and in patients with SAH if increased ICP is not a concern.

CCBs have varying effects on cerebral autoregulation. Nifedipine can lead to severe reduction in BP and is not recommended. Nimodipine is used routinely in patients with SAH because it has been shown to improve outcome, possibly because of a neuroprotective effect. Nicardipine has been used in patients with acute ICH without any change in CBF and is often used in patients with SAH. It is becoming quite popular in neurocritical care units because of its efficacy, ease of titration, predictable response, and favorable cerebral hemodynamic effects. Clevidipine has been used to lower BP in patients with ischemic and hemorrhagic stroke with a similar safety and efficacy profile as nicardipine.

ACE inhibitors and the ARB candesartan have been used in patients with acute cerebral ischemia and have no effect on CBF. However, shortacting parenteral forms of these drugs are not available. ACE inhibitors and ARBs shift the lower limit of cerebral autoregulation toward lower BP in rats and humans. However, these agents have a long half-life, which is not desirable in treatment of hypertension in the acute phase.

Similarly, because of its long half-life and sedative effect, the α2 adrenergic agonist clonidine is not preferred.

The cerebrovascular effects of the newer parenteral antihypertensives such as fenoldopam, a peripheral dopamine-1 receptor agonist, and clevidipine, a CCB, have not been extensively studied. However, in small studies, fenoldopam has been shown to decrease global CBF and increase ICP in patients with impaired intracranial compliance.61

In a small single-center study, clevedipine was found to be safe and effective in perioperative neurosurgical patients with hypertension.62

In practice, we prefer IV boluses of labetalol and hydralazine to treat elevated BP in the setting of an acute stroke. If frequent doses are required, or the BP is extremely elevated, an IV infusion of nicardipine or clevidipine is used.

CHAPTER 41 Neurogenic Hypertension

SUMMARY

This chapter provides a summary of neurologic pathways that may be responsible for mediating systemic BP control and emphasizes management of BP in acute ischemic and hemorrhagic stroke subtypes.

For supplemental information on the topical matter emphasized in this chapter and for discussion of first and recurrent stroke prevention and prevention of cognitive impairment and dementia in relation to BP management, readers are referred to a publication by Gorelick et al.35

SELF-ASSESSMENT QUESTIONS

1. A 55-year-old man with longstanding hypertension presents with acute right hemiplegia. The onset of symptoms was 45 minutes before presentation. His BP on presentation is 200/110 mm Hg and his noncontrast head CT scan is normal. He is given 10 mg labetalol and his BP is now 175/105 mm Hg. IV tissue plasminogen activator (tPA) is administered for acute ischemic stroke. An hour later, his BP is 170/110 mm Hg. Which of the following statements best characterizes BP management in this case?

A. The patient should not have been given IV tPA because his BP (175/105 mm Hg) was too high.

B. The patient’s current BP of 170/110 mm Hg needs to be lowered with IV labetalol or nicardipine.

C. Sublingual nifedipine is the drug of choice in the acute management of elevated BP in the setting of an acute stroke.

D. BP should be increased using vasopressors to augment cerebral perfusion.

E. None of the above.

2. A 60-year-old man with poorly controlled BP presents to the emergency department with left hemiparesis that was first noticed 2 days ago. He is awake, fully alert, and oriented. His strength on the right side is normal. His head CT scan shows a 2 × 2 cm right putaminal hemorrhage with no hydrocephalus or intraventricular extension. His BP is 150/85 mm Hg. Which of the following statements best characterizes BP management in this case?

A. This patient has a greater than 50% chance of clinically significant expansion of his ICH over the next 48 hours if his BP is not lowered acutely.

B. BP should be lowered immediately to less than 120/80 mm Hg with intravenous nicardipine to prevent hematoma expansion.

C. He should have an intracranial pressure monitor inserted to measure intracranial pressure.

D. There is an area of ischemia surrounding an ICH that may increase in size with additional BP lowering.

E. None of the above.

3. Which of the following features best characterizes carotid hyperperfusion syndrome after a carotid endarterectomy?

A. Headache

B. Intracerebral hemorrhage

C. Increase in cerebral blood flow ipsilateral to the endarterectomy

D. Seizures

E. All of the above

REFERENCES

1. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. Circulation. 2008;118:176–187.
2. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. Euro Heart J. 2012;33:1058–1066.
3. Chalmers J. Volhard lecture. Brain, blood pressure and stroke. J Hypertens. 1998;16:1849–1858.
4. Colombari E, Sato MA, Cravo SL, Bergamaschi CT, Campos Jr RR, Lopes OU. Role of the medulla oblongata in hypertension. Hypertension. 2001;38:549–554.
5. Talman WT. Cardiovascular regulation and lesions of the central nervous system. Ann Neurol. 1985;18:1–13.
6. Fisher JP, Paton JF. The sympathetic nervous system and blood pressure in humans: implications for hypertension. J Hum Hypertens. 2012;26:463–475.
7. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. Br Med J. 1973;1:507–510.
8. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation. 1976;53:720–727.
9. Mann SJ. Neurogenic hypertension: pathophysiology, diagnosis and management. Clin Auton Res. 2018;28:363–374.
10. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emergen Med. 2007;25:32–38.
11. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997;349:1641–1649.
12. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349:1569–1581.
13. Pedelty L, Gorelick PB. Chronic management of blood pressure after stroke. Hypertension. 2004;44:1–5.
14. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35:776–785.
15. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet. 1990;335:765–774.
16. Group PC. Randomised trial of a perindopril-based blood-pressurelowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033–1041.
17. Aiyagari V, Gorelick PB. Management of blood pressure for acute and recurrent stroke. Stroke. 2009;40:2251–2256.
18. Testai FD, Aiyagari V. Acute hemorrhagic stroke pathophysiology and medical interventions: blood pressure control, management of anticoagulant-associated brain hemorrhage and general management principles. Neurol Clin. 2008;26:963–985.
19. Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006;66:1175–1181.
20. Butcher KS, Jeerakathil T, Hill M, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. Stroke. 2013;44:620–626.
21. Geeganage C, Bath PM. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2008:CD000039.
22. Ahmed N, Nasman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke. 2000;31:1250–1255.
23. Anderson CS, Huang Y, Lindley RI, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet. 2019;393:877–888.
24. Aslanyan S, Fazekas F, Weir CJ, et al. Effect of blood pressure during the

acute period of ischemic stroke on stroke outcome: a tertiary analysis of the GAIN international trial. Stroke. 2003;34:2420–2425.

25. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. J Am Med Assoc. 2014;311:479–489.
26. Investigators ET. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet. 2015;385:617–628.
27. Investigators R-. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulancebased, randomised, sham-controlled, blinded, phase 3 trial. Lancet. 2019;393:1009–1020.
28. Oh MS, Yu KH, Hong KS, et al. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. Int J Stroke. 2015;10:745–751.
29. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebocontrolled, double-blind pilot trial. Lancet Neurol. 2009;8:48–56.
30. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol. 2010;9:767–775.
31. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet. 2011;377:741–750.
32. Schrader J, Luders S, Kulschewski A, et al. The ACCESS study: evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke. 2003;34:1699–1703.
33. Ahmed N, Audebert H, Turc G, et al. Consensus statements and recommendations from the ESO-karolinska stroke update conference, Stockholm 11-13 November 2018. Eur Stroke J. 2019;4:307–317.
34. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:e46–e110.
35. Gorelick PB, Whelton PK, Sorond F, Carey RM. Blood pressure management in stroke. Hypertension. 2020;76:1688–1695.
36. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008;7:391–399.
37. Antihypertensive Treatment of Acute Cerebral Hemorrhage. Antihypertensive treatment of acute cerebral hemorrhage. Critical Care Med. 2010;38:637–648.
38. Koch S, Romano JG, Forteza AM, Otero CM, Rabinstein AA. Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. Neurocrit Care. 2008;8:316–321.
39. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. New Engl J Med. 2016;375:1033–1043.
40. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke. 2022;53:e282–e361.
41. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014;9:840–855.
42. Connolly Jr ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the american heart association/American stroke association. Stroke. 2012;43:1711–1737.
43. Steiner T, Juvela S, Unterberg A, et al. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35:93–112.

44. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke. 1999;30:2086–2093.
45. Wade JG, Larson Jr CP, Hickey RF, Ehrenfeld WK, Severinghaus JW. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N Engl J Med. 1970;282:823–829.

References

46. Wong JH, Findlay JM, Suarez-Almazor ME. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. Neurosurgery. 1997;41:35–41.
47. Chida K, Ogasawara K, Suga Y, et al. Postoperative cortical neural loss associated with cerebral hyperperfusion and cognitive impairment after carotid endarterectomy: 123I-iomazenil SPECT study. Stroke. 2009;40:448–453.
48. Bouri S, Thapar A, Shalhoub J, et al. Hypertension and the post-carotid endarterectomy cerebral hyperperfusion syndrome. Eur J Vasc Endovasc Surg. 2011;41:229–237.
49. Yoshimoto T, Houkin K, Kuroda S, Abe H, Kashiwaba T. Low cerebral blood flow and perfusion reserve induce hyperperfusion after surgical revascularization: case reports and analysis of cerebral hemodynamics. Surg Neurol. 1997;48:132–138.
50. van Mook WN, Rennenberg RJ, Schurink GW, et al. Cerebral hyperperfusion syndrome. Lancet Neurol. 2005;4:877–888.
51. Karapanayiotides T, Meuli R, Devuyst G, et al. Postcarotid endarterectomy hyperperfusion or reperfusion syndrome. Stroke. 2005;36:21–26.
52. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. Catheter Cardiovasc Interv. 2007;69:690–696.
53. Nash MS, Groah SL, Gater Jr DR, et al. Identification and management of cardiometabolic risk after spinal cord injury: clinical practice guideline for health care providers. Top Spinal Cord Inj Rehabil. 2018;24:379–423.
54. Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: pathophysiology, diagnosis, and management. Neurosurg Focus. 2008;25:E13.

55. Valles M, Benito J, Portell E, Vidal J. Cerebral hemorrhage due to autonomic dysreflexia in a spinal cord injury patient. Spinal Cord. 2005;43:738–740.
56. Blackmer J. Rehabilitation medicine: 1. Autonomic dysreflexia. CMAJ. 2003;169:931–935.
57. Sheel AW, Krassioukov AV, Inglis JT, Elliott SL. Autonomic dysreflexia during sperm retrieval in spinal cord injury: influence of lesion level and sildenafil citrate. J Appl Physiol (1985). 2005;99:53–58.
58. Hagen EM, Rekand T, Gronning M, Faerestrand S. Cardiovascular complications of spinal cord injury. Tidsskr Nor Laegeforen. 2012;132:1115–1120.
59. Consortium for Spinal Cord M. Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities. J Spinal Cord Med. 2002;25(suppl 1):S67–S88.
60. Ribes Pastor MP, Vanarase M. Peripartum anaesthetic management of a parturient with spinal cord injury and autonomic hyperreflexia. Anaesthesia. 2004;59:94.
61. Rhoney DH, Liu-DeRyke X. Effect of vasoactive therapy on cerebral circulation. Critical care clinics. 2006;22:221–243, vi.
62. Bekker A, Didehvar S, Kim S, et al. Efficacy of clevidipine in controlling perioperative hypertension in neurosurgical patients: initial single-center experience. J Neurosurg Anesthesiol. 2010;22:330–335.
63. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355–2365.

42

Blood Pressure Management in the Dialysis Patient

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Hypertension in dialysis patients is common, remains often uncontrolled, and, when diagnosed objectively with out-of-dialysis blood pressure (BP) monitoring, is directly associated with excess risk for mortality. The pathogenesis of hypertension is multifactorial, but volume overload is the most important cause of hypertension in these patients. Accordingly, the initial management relies on nonpharmacologic strategies, such as dry weight adjustment, sodium restriction, and adequate delivery of dialysis time. When BP remains uncontrolled despite aggressive volume management, non–volume-dependent mechanisms are involved as mediators of sustained hypertension (Box 42.1). In such patients, antihypertensive therapy is the next step to achieve BP control.1 2 This chapter describes the diagnosis, epidemiology, and management of hypertension among patients on dialysis.

DIAGNOSIS

Peridialytic Blood Pressure Recordings

BP recordings taken shortly before (predialysis) or after dialysis (postdialysis) are the basis for the diagnosis of hypertension among dialysis patients, mainly because these measurements are readily available.3 4 However, routine pre- or postdialysis BP recordings provide imprecise estimates of interdialytic ambulatory BP.5 Peridialytic BP remains insufficiently accurate, even when a greater number of recordings are averaged over six dialysis sessions.6 Thus, BP variability is not the sole factor that accounts for poor diagnostic performance of peridialysis BP recordings.7 A potential source of bias could be the lack of attention to proper BP measurement technique. However, even when these measurements are obtained under standardized conditions, peridialytic BP is still inadequate for diagnosing hypertension8 9 (Box 42.2).

Intradialytic (During Dialysis) BP Recordings

The diagnostic accuracy of peridialytic BP is improved when these recordings are considered jointly with BP measurements during the entire dialysis procedure10; the average of intradialytic and peridialytic BP over six consecutive dialysis sessions was superior to predialysis or postdialysis BP alone in predicting interdialytic ambulatory BP.10 Because calculating an average is impractical at the bedside, this study explored the diagnostic performance of median intradialytic BP from a single midweek dialysis session. A midweek median cut-off systolic BP (SBP) of 140 mm Hg provided 80% sensitivity and 80% specificity in diagnosing hypertension.10 Therefore, median intradialytic BP can be used to quickly screen for hypertension at the bedside, but this is a method of last resort. Interdialytic BP recordings, though less convenient, may be better for the long-term management of hypertension.

assessment and management of hypertension. This technique improves the diagnosis of hypertension among patients on dialysis.14 A 1-week average home SBP of 150 mm Hg or above provided 80% sensitivity and 84.1% specificity in diagnosing hypertension. In contrast, no cutpoint for routine or standardized peridialytic BP provided a satisfactory combination of sensitivity and specificity for diagnosing hypertension.8 Additional advantages of HBPM also exist. In the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, home BP could track changes in interdialytic ambulatory BP (see later) provoked by probing of dry weight.15 Contrary to the poor reproducibility of pre- and postdialysis BP, home BP had even greater test-retest reliability than interdialytic ambulatory BP.15 HBPM also serves as a useful tool to guide therapeutic decisions and facilitate the achievement of adequate BP control. In a randomized trial enrolling 65 hypertensive dialysis patients,16 compared with predialysis BP-guided management of hypertension, a home BP-guided strategy provoked a reduction of approximately 9/7 mm Hg in interdialytic ambulatory BP.16 Furthermore, home BP is superior to peridialytic BP in detecting echocardiographic left ventricular hypertrophy (LVH) and in predicting the risk of mortality.17-19 For the long-term management of dialysis patients, we recommend twice daily home BP recordings after a midweek dialysis session for 4 days. We tell our patients to keep their home BP monitors in their bedroom and measure BP first thing after they wake up and last thing before going to bed. Monthly monitoring is sufficient for most clinical purposes.

Interdialytic ambulatory BP monitoring (ABPM) is the gold standard technique for diagnosing hypertension.3,4 ABPM uses an automated device programmed to record BP 2 to 3 times an hour over the entire interdialytic interval. This method is valid,20 reproducible,21 and is superior to peridialytic BP recordings in predicting the presence of LVH or long-term outcomes.17-19 A unique advantage of ABPM is that BP can be recorded during sleep, enabling the diagnosis of nocturnal hypertension and nondipping BP patterns.22 ABPM also has some weaknesses (i.e., limited availability and costs of equipment, need for training, patient discomfort) that limit the wide adoption of this technique in practice.3,4,22

Because the implementation of ABPM in the long-term management of hypertension is often impractical, we recommend the use of HBPM as a simple and reliable approach to diagnose hypertension and guide therapeutic decisions from month to month.1,2 In patients who are nonadherent to HBPM, we use midweek median intradialytic BP to make therapeutic decisions.1,2 We do not use peridialytic BP recordings for managing hypertension.

EPIDEMIOLOGY

Interdialytic (Between Dialysis) Recordings

Prevalence, Treatment, and Control of Hypertension

Home BP monitoring (HBPM) is an established technique4 recommended by guidelines11–13 and widely adopted in clinical practice for the

Epidemiology of hypertension among patients on dialysis differs depending on the method of BP measurement (Table 42.1). Studies

BOX 42.1

Non–Volume-Dependent Causes of Hypertension Among Patients on Dialysis

- Increased arterial stiffness
- Sympathetic overactivity
- Activation of the renin-angiotensin-aldosterone system
- Endothelial dysfunction
- Erythropoietin therapy
- Sleep apnea

BOX 42.2

- Predialysis or postdialysis (peridialysis) BP: do not reflect the usual level of BP in the interdialytic period and therefore not useful for management of hypertension.
- Median intradialytic BP: systolic BP ≥140 mm Hg on a midweek dialysis session in a patient being dialyzed 3 times weekly suggests poorly controlled hypertension.
- Home BP monitoring: measurements done twice daily (morning and evening) after 5 min of seated rest in duplicate, after a midweek dialysis session for 4 days on a monthly basis, is the most practical way to manage hypertension in long-term hemodialysis patients.
- Interdialytic ambulatory BP monitoring: measurements after dialysis 2–3 times/hr over the entire 44-hr interdialytic period is the gold standard of diagnosing hypertension in hemodialysis patients.

that were based on conventional predialysis BP recordings used different definitions and provided variable estimates of the prevalence and control of hypertension.23-26 A more precise description of the epidemiology was provided by a few studies using ABPM. For example, in a cross-sectional study of 369 patients,27 the prevalence of hypertension (defined as interdialytic BP ≥135/85 mm Hg or antihypertensive drug use) was 82%. Although 89% of hypertensive dialysis patients were being treated, adequate ambulatory BP control was achieved in only 38%.27 Subsequent studies using HBPM or ABPM confirmed that the burden of hypertension in the dialysis population is high and its control poor.28 29

Among patients on peritoneal dialysis, the absence of acute shifts in pressure and volume parameters is thought to mitigate hypertension. However, the burden of hypertension and prognostic association of BP with mortality follows a pattern similar to that seen among hemodialysis.30

Prognosis

In sharp contrast with the direct and linear association between BP and outcome in the general population, large-scale cohort studies conducted in dialysis patients showed a U-shaped or J-shaped association of peridialytic BP with mortality.31-34 The phenomenon of reverse epidemiology has raised concerns on whether hypertension in dialysis patients is an independent risk factor that should be adequately controlled.35 However, two separate cohort studies showed that BP measurement technique strongly confounds the relation of BP with mortality.18 19 In these studies, increasing interdialytic SBP assessed either with HBPM or with ABPM was directly associated with higher mortality risk. In contrast, neither routine nor standardized peridialytic BP recordings were prognostically informative. Home SBP between 120 to 130 mm Hg and 44-hour ambulatory SBP ranging from 110 to 120 mm Hg were associated with the best prognosis.18

The reverse epidemiology of hypertension seen in observational studies contrasts with two meta-analyses of randomized trials among dialysis patients showing cardiovascular protection with antihypertensive therapy.36 37 In the first meta-analysis (eight trials, N = 1679), BP-lowering treatment was associated with a 29% reduced risk for cardiovascular events and a 20% reduction in all-cause mortality.37 In the second meta-analysis (five trials, N = 1212), compared with placebo, antihypertensive therapy lowered the risk for cardiovascular events and all-cause mortality by 31%.36 The cardiovascular benefit of antihypertensive therapy was greater when trials with hypertensive patients were combined separately from trials that included normotensives.36 Therefore, deliberate BP lowering with antihypertensive therapy has proven cardioprotective benefits for dialysis patients, particularly when they are hypertensive.

THERAPEUTIC TARGETS

The optimal BP threshold for the diagnosis and management of hypertension in the dialysis population is unknown.12 38 The only trial to compare two different BP targets was the Blood Pressure in Dialysis (BID) trial.39 In BID, 126 hypertensive dialysis patients were randomized to a tighter (110–140 mm Hg) versus a standard (155–165 mm Hg) control of predialysis SBP over 12 months of follow-up. BID reported a possible safety signal, but on closer examination intensive BP lowering was associated with 1.3-fold higher risk for recurrent intradialytic hypotension, 1.66-fold higher risk for recurrent hospitalization, and 2.8fold higher risk for recurrent vascular access thrombosis.39 Regression of LVH, a secondary efficacy endpoint, did not differ between arms.

Blood Pressure Measurement
Techniques in Dialysis Patients

BP, Blood pressure.

BID was a feasibility trial aiming to inform the design of a full-scale trial.39 Although a full-scale trial is warranted to define the optimal BP goals, we do not believe that peridialytic BP recordings are appropriate targets for managing hypertension. Given the evidence supporting the superiority of home over predialysis BP-guided therapy,14 16 we believe that a future full-scale trial should ideally compare the benefits of tighter versus standard home SBP targets for clinical outcomes. In the meantime, we recommend that controlling home SBP to levels below 140 mm Hg is a reasonable target in dialysis patients.1 2 If a home BP-guided strategy is not feasible, lowering midweek median intradialytic SBP below 140 mm Hg is an alternative strategy.1 2 In our practice, we prefer to treat hypertension in dialysis patients than maintain the status quo.

VOLUME MANAGEMENT STRATEGIES

Once an accurate diagnosis is made, the initial management of hypertension is based on nonpharmacologic strategies that target and maintain euvolemia.1 2 The four basic principles of nonpharmacologic treatment are summarized in Fig. 42.1 and are discussed in detail later.

Probing of Dry Weight

The assessment and management of dry weight is challenging. There is no consensus on the optimal definition of dry weight. In 2009 Sinha and Agarwal stated that dry weight reflects the lowest tolerated postdialysis weight at which the patient experiences minimal signs and symptoms of either hypovolemia or hypervolemia.40 According to this definition, the management of dry weight is based on an iterative process of gentle and gradual intensification of ultrafiltration guided by the patient’s symptoms.40

Benefits of Probing Dry Weight

Dry weight was probed without increasing the dialysis duration in the DRIP trial.41 In DRIP, 150 dialysis patients who had uncontrolled hypertension despite stable background treatment with 2.7 antihypertensive

TABLE 42.1

Prevalence, Treatment and Control of Hypertension Among Patients on Dialysis

Study	Region	N	Definition of Hypertension	Prevalence	Hypertensive Patients on Treatment	Control
Studies Using Dialysis Unit BP Recordings						
Salem,26 1995	US	649	Predialysis mean BP ≥114 mm Hg or antihypertensive drug use	71.9%	81.5%	48.6%
Rahman et al.,25 1999	US	489	Predialysis BP ≥160/90 mm Hg or antihypertensive drug use	87.7%	92.3%	28.9%
Agarwal et al.,23 2003	US	2535	Predialysis BP ≥150/85 mm Hg or antihypertensive drug use	85.7%	88.4%	30.3%

Del Vecchio et al.,24 2013

Italy

4022

Predialysis BP ≥140/90 mm Hg or
antihypertensive drug use

70.3%

57.7%

40.0%

82.0%

89.0%

38.0%

Studies Using Home or Ambulatory BP Monitoring
US
369
44-hour interdialytic BP ≥135/85 mm Hg or
Agarwal,27 2011
antihypertensive drug use
Sarafidis et al.,28 2019

Italy, Greece,
Slovenia

396

48-hour intra- and interdialytic BP ≥130/80
mm Hg or antihypertensive drug use

84.3%

86.8%

28.7%

Tsikliras et al.,29 2020

Greece

116

1-week averaged home BP ≥135/85 mm Hg
or antihypertensive drug use

88.8%

95.0%

32.6%

BP, Blood pressure.

Management of Hypertension Among Patients on Dialysis

Hypertension diagnosed
by out-of-dialysis BP

monitoring
(HBPM or ABPM)

- Dietary Na restriction
- Individualized dialysate Na

Gentle and gradual
dry weight reduction with the
guidance of symptoms

Adequate delivery of
dialysis time
(3 sessions per week of
at least 12 hours)

BP unresponsive to volume management strategies

Individualized pharmacologic management of BP:
- Atenolol 3 times a week immediately postdialysis
- Long-acting CCBs, such as amlodipine or felodipine
- ACE inhibitor or ARB

Fig. 42.1 Algorithm for the Management of Hypertension Among Patients on Dialysis. The diagnosis of hypertension among patients on dialysis should be based on blood pressure (BP) recordings taken outside of dialysis. Predialysis and postdialysis BP recordings are not suitable for diagnosing and managing hypertension. Once an accurate diagnosis is made, first-line management of hypertension among patients on dialysis relies on nonpharmacologic strategies that target the achievement and maintenance of euvolemia. The adequate management of volume follows four principles: probing of dry weight, dietary sodium restriction, individualized prescription of the dialysate sodium concentrations, and adequate delivery of dialysis time. If hypertension remains uncontrolled despite adequate volume management, pharmacologic treatment is the next step to achieve an adequate control of BP. The selection of an appropriate antihypertensive regimen should be individualized, taking into consideration the efficacy, safety, and pharmacokinetic properties of the antihypertensive medications in the dialysis population. We use β-blockers, particularly atenolol administered 3 times per week immediately postdialysis, as first-line therapy. We use long-acting calcium channel blockers (CCBs), such as amlodipine or felodipine, as second-line therapy in patients with uncontrolled BP despite the adequate management of dry weight and the administration of atenolol. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are our third-line option. Because of concerns related to hyperkalemia and in anticipation of stronger safety and efficacy data from ongoing randomized trials, we do not recommend the wide use of mineralocorticoid receptor antagonists for the management of hypertension among patients on dialysis. ABPM, Ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; Na, sodium.

Clinical Signs Indicating Volume
Excess in a Dialysis Patient

BOX 42.3

Ambulatory BP Reduction Over 4 and 8
Weeks of Dry Weight Probing

Systolic blood pressure (mm Hg)

150

140

Diastolic blood pressure (mm Hg)

A

–3.8
(0.7 to –8.4)

–10.7‡
(–7.4 to –13.9)

–7.4†
(–2.1 to –12.7)

Ultrafiltration

0

4

8

Control
–0.5
(–4.4 to 3.4)

–3.0*
(–0.5 to –5.5)
–0.9
(1.7 to –3.5)
–3.6
(0.4 to –7.7)
–6.1‡
(–4.3 to –7.9)

80

–3.8
(0.2 to –7.9)
–1.1
(0.7 to –3.0)

Ultrafiltration
75
4

Overt symptoms of congestive heart failure (e.g., shortness of breath)
Uncontrolled hypertension confirmed by home or ambulatory BP monitoring
The use of multiple antihypertensive medications

Low interdialytic weight gain
Persistent BP elevation during dialysis (intradialytic hypertension)

BP, Blood pressure.

–2.8
(–0.5 to –6.1)

130

85

–3.1
(1.6 to –7.8)

–7.1†
(–1.8 to –12.5)

0

B

-
-
-
-
-

Control
–0.5
(–5.6 to 4.5)

495

8

Weeks

Fig. 42.2 Ambulatory Blood Pressure (BP) Reduction Over 4 and 8 Weeks of Dry Weight Probing in Hypertensive Dialysis Patients. The mean 44-hour ambulatory systolic and diastolic BPs are shown for the control (blue lines) and ultrafiltration (teal lines) groups. The mean changes in BP are shown for weeks 4 and 8 after randomization (teal squares and arrows), as well as the mean differences in BPs (black arrows) between the two groups at each 4-week interval. The numbers next to the blue diamonds and arrows connecting the data points are the mean changes in BP between groups at 4 and 8 weeks after randomization. The 95% confidence intervals (CIs) are given in parentheses. *P < .05, †P < .01, and ‡P < .001 indicate significant differences between groups or within groups. The placebo-subtracted change in 44-hour systolic BP provoked by probing of dry weight was −6.9 mm Hg (95% CI, −12.4 to −1.3 mm Hg; P = .016) at 4 weeks and −6.6 mm Hg (95% CI, −12.2 to −1.0 mm Hg; P = .021) at 8 weeks. The placebo-subtracted change in 44-hour diastolic BP was −3.1 mm Hg (95% CI, −6.2 to −0.02 mm Hg; P = .048) at 4 weeks and −3.3 mm Hg (95% CI, −6.4 to −0.2 mm Hg; P = .037) at 8 weeks.

medications daily were randomized in a 2:1 ratio to ultrafiltration and control groups. In the ultrafiltration group, postdialysis weight was gradually reduced until the development of symptoms indicating dry weight achievement. In the control group, patients received only physician visits.41 A modest reduction in dry weight by 0.9 kg from baseline to 4 weeks provoked an average placebo-subtracted reduction of −6.9 mm Hg in 44hour SBP and a placebo-subtracted reduction of −3.1 mm Hg in 44-hour diastolic BP (DBP) (Fig. 42.2).41 This BP-lowering effect was sustained till study end at 8 weeks. Probing of dry weight also provoked a significant reduction in LV mass index (LVMI) over the first 4 weeks of follow-up.42

Assessment and Management of Dry Weight

The results of the DRIP trial41 have important implications for the assessment and management of dry weight (Box 42.3).

The DRIP trial explored the hypothesis that hypertension in dialysis is a clinical manifestation of volume excess. Accordingly, patients with clinically overt hypervolemia were a priori excluded from this trial.40 Despite the fact that DRIP participants were euvolemic based on clinical judgment, probing of dry weight provoked a clinically meaningful reduction of approximately 7/3 mm Hg in 44-hour BP.41 Thus, among hypertensive dialysis patients, the management of dry weight should not be based on the presence or absence of clinically overt hypervolemia. In such patients, volume excess is more often covert. The discriminatory power of physical examination in ruling in or out volume overload is low.43 44

An important sign that should raise the suspicion of volume excess is the use of multiple BP-lowering medications in a dialysis patient. DRIP participants had uncontrolled hypertension despite the administration of 2.7 BP-lowering medications daily.41 The mediator of sustained hypertension in these patients was subclinical volume excess. In DRIP, the magnitude of ambulatory BP reduction evoked by probing of dry weight was probably much larger than what would be expected by intensifying antihypertensive therapy with one additional drug. This is in line with several cross-sectional studies showing an increasing number of prescribed antihypertensive medications to be paradoxically associated with worse BP control.23 27 29 These observations suggest that intensification of antihypertensive therapy is likely to fail to control BP if volume excess is not primarily addressed, supporting a “volume-first” approach of hypertension.

A high interdialytic weight gain (IDWG) is often (but erroneously) considered as equivalent with hypervolemia. However, recent studies using more objective methods in the assessment of dry weight inform us that IDWG and volume overload are two discrete components of the dynamic fluid balance.44 These studies showed that dialysis patients with low IDWG were often volume overloaded.44 In DRIP,45 volume status was assessed using the method of relative plasma volume (RPV) monitoring. At baseline, patients with steeper RPV slopes and therefore most euvolemic had the highest IDWG. In contrast, patients with the greatest volume expansion based on RPV monitoring had the lowest IDWG.45 However, these patients tolerated the greatest dry weight reduction during follow-up (−1.5 kg). Most importantly, these patients experienced the greatest improvement in 44-hour SBP in response to dry weight reduction (−12.6 mm Hg).45 Therefore, a low IDWG may reflect volume excess, particularly when accompanied by other clinical indications, such as uncontrolled interdialytic hypertension.

Unlike the typical decline in BP with ultrafiltration, BP increases during dialysis in approximately 10% to 15% of patients. This paradoxical hemodynamic response is described as intradialytic hypertension 46 The precise definitions and pathophysiology of intradialytic hypertension is debated; earlier studies suggested that this phenomenon may be mediated through release of vasoconstrictors in response to ultrafiltration.46 On this basis, the management of intradialytic hypertension often relied on interruption of ultrafiltration and/or immediate administration of potent short-acting antihypertensive agents. However, more recent studies showed a close relation between

TABLE 42.2 Randomized Trials Comparing Management of Dry Weight Guided by Assistive Technologies Versus Usual Care on Clinical Outcomes

Study	Design	Patients	N	Intervention	Follow-up	Results
Reddan et al.[58]	Open-label RCT	Patients on dialysis (≥2 mo)	443	RPV monitoring using Crit-Line vs. conventional clinical monitoring	6 mo	Higher risk of hospitalization and all-cause mortality in the RPV monitoring group than in the control group
Onofriescu et al.[57]	Open-label RCT	Patients on dialysis (≥3 mo)	131	BIS every 3 mo to guide dry weight adjustment vs. clinical judgment	30 mo	One death in the BIS group vs. 8 deaths in the control group (HR, 0.112; 95% CI, 0.014–0.918)
Huan-Sheng et al.[55]	Open-label RCT					

		Patients on dialysis (≥3 mo)	298	BIS every month to guide dry weight adjustment vs. clinical judgment	12 mo	No between-group difference in all-cause hospitalizations (HR, 1.19; 95% CI, 0.79–1.80), cardiovascular events (HR, 0.57; 95% CI, 0.26–1.25), and all-cause mortality (HR, 0.85; 95% CI, 0.29–2.53)
Siriopol et al.59	Open-label RCT	Patients on dialysis (≥3 mo) at low cardiovascular risk	250	Lung ultrasound combined with BIS (in case of clinical symptoms of hypovolemia) vs. clinical judgment	Mean 21.3 ± 5.6 mo	No between-group difference in the composite outcome of all-cause death or first nonfatal cardiovascular event (HR, 1.09; 95% CI, 0.64–1.86)
Liu et al.56	Open-label RCT	Patients on dialysis (≥3 mo)	445	BIS every 2 months to guide dry weight adjustment vs. clinical judgment	Median 13.7 mo	No between-group difference in the composite outcome of all-cause death or nonfatal cardiovascular event (HR, 0.487; 95% CI, 0.217–1.091)

BIS, Bioimpedance spectroscopy; CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RPV, relative plasma volume.

intradialytic and interdialytic hypertension.47 In a post hoc analysis of the DRIP trial, probing of dry weight in patients with intradialytic hypertension was effective in normalizing both intradialytic and interdialytic BP profiles.48 Therefore, persistent BP elevation during dialysis may be another signal of volume excess.

Bioimpedance spectroscopy, RPV monitoring, and lung ultrasound, are under investigation and offer promise for more objective assessment of dry weight.45 49 50 Observational studies showed that hypervolemia, as assessed with these devices, is prognostically associated with higher mortality risk.51-54 Randomized trials have so far failed to prove that these technologies are superior to usual care in improving clinical outcomes (Table 42.2),55-59 although most of these trials had short follow-up and lacked statistical power.60 61 Therefore, these technologies require further study before being implemented in clinical practice.

Potential Hazards of Probing Dry Weight

Probing of dry weight may be associated with potential hazards, such as higher risk for intradialytic hypotension, vascular access thrombosis, and more rapid loss of residual renal function.1 2 However, none of these risks has been adequately studied. In DRIP, probing of dry weight provoked temporal intradialytic symptoms of hypotension, but these symptoms did not unduly affect any domain of health-related quality of life.41 Because DRIP only followed participants for 8 weeks, the benefits and risks of dry weight probing warrant examination in long-term trials.

Dietary Sodium Restriction

Dietary sodium restriction is an established nonpharmacologic approach to limit IDWG and facilitate the achievement of dry weight.1 2 International guidelines recommend that among patients on dialysis, dietary sodium intake should not exceed 80 to 100 mmol (1.8–2.3 g; equivalent to 4.5–5.8 g sodium chloride) daily.62 Observational studies support this guidance, showing that compared with pharmacologic management of hypertension, sodium restriction together with adequate adjustment in dry weight was associated with greater regression of LVH and reduced incidence of intradialytic hypotension.63 64

Individualized Dialysate Sodium Prescription

Sodium loading in hemodialysis patients occurs when the prescription of dialysate sodium concentration results in a positive sodium gradient during dialysis.65 This scenario is rather common in daily clinical practice.66 However, this therapeutic approach perpetuates a vicious cycle. Intradialytic sodium gain is directly associated with increased sense of thirst and greater IDWG, resulting in higher ultrafiltration requirements during the subsequent dialysis sessions. The higher ultrafiltration rates can aggravate the risk of intradialytic hypotension, which might result in the prescription of even higher dialysate sodium concentrations.1 2

Lowering the dialysate sodium concentration could possibly interrupt this vicious cycle. The benefit/risk ratio of this intervention was investigated in a meta-analysis of 12 trials involving 266 patients.67 Compared with neutral (138–140 mEq/L) or high (>140 mEq/L) dialysate sodium, a low sodium concentration (<138 mEq/L) was associated with reduced IDWG and improvement in BP. However, these benefits were accompanied by higher risk for intradialytic cramps and hypotension.67 These results should be carefully interpreted because all trials were small. Of the 12 trials included in this meta-analysis, 10 compared a fixed prescription of a lower versus a higher dialysate sodium concentration. Several trials performed large reductions in dialysate sodium concentration over a short-term follow-up.67 Therefore, an abrupt and fixed intervention may result in a steeply negative sodium gradient, raising the risk for adverse events.

We recommend that lowering of dialysate sodium concentration should be gradual and individualized.1 2 Observational studies and pilot trials suggest that this approach has the potential for short-term and long-term benefits without excess risk of intradialytic complications.68-70

Adequate Delivery of Dialysis Time

The prescription of dialysis duration varies considerably across countries. Approximately one-third of patients in the United States are prescribed hemodialysis with a duration of less than 200 minutes.71 Among several other risks, nonadherence to the dialysis regimen has been associated with worse BP control.72 This was also illustrated in a post hoc analysis of DRIP.73 Median intradialytic SBP followed a rising pattern in the control group. In contrast, probing of dry weight lowered median intradialytic SBP regardless of the duration of dialysis. However, patients with shorter dialysis duration required more dialysis sessions to achieve the BP-lowering benefit of probing dry weight.73 Therefore, shorter delivered dialysis is a barrier to dry weight achievement, limiting the opportunity for adequate BP control.

Management of Hypertension in Peritoneal Dialysis Patients

As in hemodialysis patients, volume management is of central importance for BP control among peritoneal dialysis (PD) patients.30 Two unique aspects in PD patients are long-term preservation of both residual diuresis and peritoneal membrane function. To achieve euvolemia, we adapt the PD regimen to the peritoneal transport characteristics. To protect the peritoneal membrane, we limit exposure of peritoneal membrane to bioincompatible solutions and use icodextrin judiciously30 (prescription of PD is discussed in Chapter 101).

PHARMACOTHERAPY OF HYPERTENSION (BASED ON INTERDIALYTIC MEASUREMENTS)

Despite assiduously adhering to the volume-first management strategies, a large fraction of dialysis patients remain hypertensive, and drug therapy is necessary to achieve an adequate control of BP. We believe that treatment should be guided by evidence from trials done in the dialysis population and not on extrapolation of evidence from trials conducted in earlier stages of kidney disease or in the general population.1 2 A summary of key randomized trials is provided in Table 42.3 74-82

β-Blockers

The safety and efficacy of β-blocker–based and angiotensin-converting enzyme (ACE) inhibitor–based regimens were compared in the Hypertension in Hemodialysis Patients Treated With Atenolol or Lisinopril (HDPAL) trial.73 In HDPAL, 200 hypertensive dialysis patients with echocardiographic LVH were randomized to atenolol or lisinopril, each administered 3 times per week immediately postdialysis. Contrary to the original hypothesis that a lisinopril-based regimen would be superior to atenolol in improving LVH, both drugs

Dialyzability and Dosing of Antihypertensive Agents 2,73,82,83

BOX 42.4

- β-blockers are a heterogeneous drug class with respect to their pharmacokinetic profiles. Recent studies showed substantial dialyzability of atenolol, metoprolol, and bisoprolol; in contrast, carvedilol and propranolol were found to be nondialyzable.
- With the exception of the nondialyzable fosinopril, most other ACE inhibitors are removed during dialysis; in contrast, ARBs are generally nondialyzable.
- Long-acting CCBs, such as amlodipine and felodipine, are also nondialyzable and can be dosed once daily.
- Based on the HDPAL trial, the optimal dosing regimen for long-acting agents with high dialyzability, such as atenolol and lisinopril, is the administration 3 times per week immediately postdialysis.

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HDPAL, Hypertension in Hemodialysis Patients Treated With Atenolol or Lisinopril.

provoked similar reductions in LVMI over 12 months.74 In addition, atenolol appeared to be more effective in controlling hypertension, because monthly monitored home BP was consistently lower in the atenolol group despite the need for a greater number of antihypertensive drugs and a greater dry weight reduction in the lisinopril group. Furthermore, compared with lisinopril, atenolol provoked a greater reduction in aortic pulse wave velocity over the first 6 months of follow-up.83 Because the incidence of serious adverse cardiovascular events was 2.36-fold higher in the lisinopril group than in the atenolol group, HPDAL was terminated early.74

Based on the results of the HDPAL trial, we use β-blockers as first-line pharmacotherapy for hypertension among dialysis patients (Fig. 42.1)1 2 and prefer to use atenolol administered 3 times per week immediately postdialysis based on the results of HDPAL. This dosing regimen overcomes the high dialyzability of atenolol and ensures a potent BP-lowering action of this agent over the entire interdialytic interval (Box 42.4).84

Calcium Channel Blockers

Long-acting dihydropyridine calcium channel blockers (CCBs) such as amlodipine or felodipine are useful in combination with other agents, such as atenolol, and represent our second-line choice for the pharmacotherapy of hypertension in dialysis patients. The efficacy of this drug class is supported by a double-blind trial in which 251 hypertensive dialysis patients were randomized to amlodipine or placebo.80 Whereas BP remained constant with placebo, amlodipine provoked a significant reduction of ~10 mm Hg in SBP over 30 months of follow-up.

Although amlodipine did not reduce all-cause mortality relative to placebo, there was a significant reduction by 47% in the composite secondary outcome of cardiovascular events and all-cause mortality.80

ACE Inhibitors/Angiotensin Receptor Blockers

In the Fosinopril in Dialysis (FOSIDIAL) trial,81 397 French dialysis patients who had echocardiographic LVH with or without hypertension were randomized to the ACE inhibitor fosinopril or placebo for 48 months. Compared with placebo, fosinopril had no benefit on cardiovascular outcomes.81 In contrast, two smaller trials from Japan showed cardioprotective benefit when an angiotensin receptor blocker (ARB)based regimen was compared either with placebo79 or with active treatment that was not based on ACE inhibitors or ARBs.78 However, in a subsequent meta-analysis aiming to elucidate the contradictory results of these three small trials, the use of ACE inhibitors or ARBs was not

TABLE 42.3

Outcomes

Randomized Trials Evaluating the Effect of Antihypertensive Agents on Clinical

Study	Design	Patients	N	Intervention	Follow-up	Results
Zannad et al.81	Double-blind RCT	Dialysis patients (not necessarily hypertensive) with LVH	397	Fosinopril 5–20 mg/day vs. placebo	24 mo	No benefit of fosinopril vs. placebo on the combined outcome of fatal or nonfatal CV events (RR, 0.93; 95% CI, 0.68–1.26)
Takahashi et al.79	Open-label RCT	Dialysis patients with clinical evidence of CV disease	80	Candesartan 4–8 mg/day vs. nothing	19 mo	Threefold lower incidence of CV events in the candesartan group than in the control group (45.9% vs. 16.3%, $P < .01$)

Suzuki et al.78

Open-label RCT

Hypertensive dialysis patients

366

ARB treatment (losartan, valsartan, candesartan) vs. control therapy not based on ARBs

36 mo

Compared with control therapy, treatment with ARBs improved by 49% the combined outcome of fatal and nonfatal CV events (HR, 0.51; 95% CI, 0.33–0.9)

Iseki et al.75

Open-label RCT

Hypertensive dialysis patients

469

Olmesartan 10–40 mg/day vs. control therapy not including ACE inhibitor or ARB

42 mo

No benefit of olmesartan vs. control therapy on the combined outcome of fatal or nonfatal CV events (HR, 1.00; 95% CI, 0.71–1.40)

Cice et al.82

Open-label RCT

Dialysis patients with dilated cardiomyopathy

114

Carvedilol (titrated up to 25 mg twice daily) vs. placebo

24 mo

Compared with placebo, carvedilol improved allcause mortality (HR, 0.51; 95% CI, 0.32–0.82) and CV mortality (HR, 0.32; 95% CI, 0.18–0.57)

Agarwal et al.74

Open-label RCT

Hypertensive dialysis
patients with LVH

200

Atenolol (25–100 mg) vs. lisinopril
(10–40 mg), both administered 3
times a week postdialysis

12 mo

Compared with atenolol, the
composite safety outcome of
MI, stroke, or CHF occurred
more commonly in the
lisinopril group (IRR, 2.36;
95% CI, 1.36–4.23)

Tepel et al.80

Double-blind RCT

Hypertensive dialysis
patients

251

Amlodipine 10 mg/day vs. placebo

30 mo

Amlodipine improved the
composite outcome of
all-cause death or nonfatal
CV event relative to
placebo (HR, 0.53; 95% CI,
0.31–0.93)

Matsumoto et al.77

Open-label RCT

Oligoanuric dialysis
patients

309

Add-on spironolactone 25 mg/day
vs. nothing

36 mo

Compared with no add-on
therapy, spironolactone
reduced the composite
outcome of fatal and
nonfatal CV events (HR,
0.379; 95% CI, 0.173–0.832)

Lin et al.76

Open-label RCT

Patients on dialysis
without CHF

253

Add-on spironolactone 25 mg/day
vs. placebo

24 mo

Add-on spironolactone
improved CV morbidity
and mortality relative to
placebo (HR, 0.42; 95% CI,
0.26–0.78)

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IRR, incident rate ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; RCT, randomized controlled trial; RR, risk ratio.

associated with an overall improvement in cardiovascular morbidity and mortality.85 In the Olmesartan Clinical Trial in Okinawa Patients under Okinawa Dialysis Study (OCTOPUS) trial75—the largest trial conducted so far, enrolling 469 hypertensive dialysis patients—the ARB olmesartan was not superior to control for improving the primary composite cardiovascular outcome or all-cause mortality over a mean follow-up of 3.5 years.75

Taken together, unlike the established cardioprotective benefit of these two antihypertensive drug classes in the general population, the evidence to support the use of ACE inhibitors or ARBs for cardioprotection in patients on dialysis is thin. Therefore, we use ACE inhibitors and ARBs as a third-line option in dialysis patients with inadequately controlled BP despite combination treatment with atenolol and a longacting CCB.

in two large ongoing phase III trials. Because of concerns related to hyperkalemia and in anticipation of more reliable evidence, we do not routinely prescribe MRAs to our dialysis patients.

Mineralocorticoid Receptor Agonists

Role of Bilateral Nephrectomy

Among patients not on dialysis with heart failure and reduced ejection fraction, add-on therapy with spironolactone or eplerenone confers a substantial cardioprotective benefit.86 87 However, the safety and efficacy of mineralocorticoid receptor antagonists (MRAs) among patients on dialysis has not been adequately studied.76-88 In a 2016 meta-analysis of nine trials (including 829 patients), MRA use was associated with improvement in cardiovascular and all-cause mortality, but this benefit was accompanied by a threefold higher risk of hyperkalemia.89 These results should be interpreted with caution because most of the included trials had short follow-up and small sample sizes, indicating lack of high-quality evidence.89 The benefit/risk ratio of MRAs in patients on dialysis is currently under investigation

We have rarely seen patients with bilateral nephrectomies as a strategy to treat hypertension in dialysis. In one such patient, BP was still elevated several months after surgery and the patient was being administered an intravenous agent to control hypertension in the intensive care unit. Two days of continuous venovenous hemofiltration normalized the BP and required removal of several antihypertensive drugs including the intravenous agent, attesting to the fact that the optimal control of volume and an adequate delivery of dialysis are central to the management of hypertension in most hemodialysis patients. Instead of an as-needed prescription of an antihypertensive drug for the patient with asymptomatic elevation of BP to 200 mm Hg systolic, we prefer to address volume and dialysis delivery for the holistic care of the patient.

Vasodilators

Many patients on dialysis are prescribed vasodilators such as hydralazine or minoxidil. Hydralazine is short acting, which is why it needs to be administered 3 times daily. In reviewing ABPM data on patients on this drug, we often note large drops in SBP with rapid increases to baseline; we therefore discourage its use. Minoxidil prescription is associated with hirsutism that is troublesome for women and sometimes can cause pericardial effusions. Patients who require a vasodilator to achieve blood pressure control typically will benefit from nonpharmacologic strategies for the control of hypertension.

SELF-ASSESSMENT QUESTIONS

1. Which of the following methods is useful to screen for hypertension in a dialysis patient at bedside?
A. Predialysis BP recordings averaged over six consecutive dialysis treatments.
B. Postdialysis BP recordings averaged over six consecutive dialysis treatments.
C. Median intradialytic BP from a single midweek dialysis treatment.
D. None of the above methods provides a satisfactory combination of high sensitivity and high specificity for diagnosing hypertension.

2. A 60-year-old patient on chronic dialysis with a known history of hypertension receives stable treatment with nebivolol 5 mg/day, amlodipine 10 mg/day, and olmesartan 20 mg/day, but the average of home BP recordings taken with a validated automatic device twice daily for 4 days after the midweek dialysis session is 149/78 mm Hg. The patient is asymptomatic, and the physical examination reveals no clinical signs of volume excess. Which of the following would be the optimal approach to achieve an adequate control of home BP in this patient?
A. Increase the dose of olmesartan
B. Add spironolactone
C. Add clonidine
D. Probe dry weight

3. In a dialysis patient who gains 1 kg during the interdialytic interval, the predialysis BP is of 154/82 mm Hg. During dialysis, BP increases to 180/89 mm Hg, and the nurse calls you with this high BP. Which of the following interventions would be the best next step to treat the patient?
A. Stop ultrafiltration immediately and administer 10 mg sublingual nifedipine
B. Stop ultrafiltration
C. Administer clonidine 0.3 mg orally
D. Probe dry weight

REFERENCES

1. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. J Am Soc Nephrol. 2014;25:1630–1646.
2. Georgianos PI, Agarwal R. Epidemiology, diagnosis and management of hypertension among patients on chronic dialysis. Nat Rev Nephrol. 2016;12:636–647.
3. Agarwal R. Pro: Ambulatory blood pressure should be used in all patients on hemodialysis. Nephrol Dial Transplant. 2015;30:1432–1437.
4. Drawz PE, Abdalla M, Rahman M. Blood pressure measurement: clinic, home, ambulatory, and beyond. Am J Kidney Dis. 2012;60:449–462.
5. Agarwal R, Peixoto AJ, Santos SF, Zoccali C. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol. 2006;1:389–398.
6. Agarwal R, Lewis RR. Prediction of hypertension in chronic hemodialysis patients. Kidney Int. 2001;60:1982–1989.
7. Rohrscheib MR, Myers OB, Servilla KS, et al. Age-related blood pressure patterns and blood pressure variability among hemodialysis patients. Clin J Am Soc Nephrol. 2008;3:1407–1414.
8. Agarwal R, Andersen MJ, Bishu K, Saha C. Home blood pressure monitoring improves the diagnosis of hypertension in hemodialysis patients. Kidney Int. 2006;69:900–906.
9. Rahman M, Griffin V, Kumar A, Manzoor F, Wright Jr JT, Smith MC. A comparison of standardized versus “usual” blood pressure measurements in hemodialysis patients. Am J Kidney Dis. 2002;39:1226–1230.
10. Agarwal R, Metiku T, Tegegne GG, et al. Diagnosing hypertension by intradialytic blood pressure recordings. Clin J Am Soc Nephrol. 2008;3:1364–1372.
11. Parati G, Stergiou GS, Asmar R, et al. European Society of Hypertension practice guidelines for home blood pressure monitoring. J Hum Hypertens. 2010;24:779–785.
12. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127–e248.
13. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
14. Georgianos PI, Agarwal R. Can we study hypertension in patients on dialysis? Yes we can. Am J Kidney Dis. 2021;77:4–6.
15. Agarwal R, Satyan S, Alborzi P, et al. Home blood pressure measurements for managing hypertension in hemodialysis patients. Am J Nephrol. 2009;30:126–134.
16. da Silva GV, de BS, Abensur H, Ortega KC, Mion Jr D. Home blood pressure monitoring in blood pressure control among haemodialysis patients: an open randomized clinical trial. Nephrol Dial Transplant. 2009;24:3805–3811.
17. Agarwal R, Brim NJ, Mahenthiran J, Andersen MJ, Saha C. Out-ofhemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. Hypertension. 2006;47:62–68.
18. Agarwal R. Blood pressure and mortality among hemodialysis patients. Hypertension. 2010;55:762–768.
19. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. Clin J Am Soc Nephrol. 2007;2:1228–1234.
20. Peixoto AJ, Gray TA, Crowley ST. Validation of the SpaceLabs 90207 ambulatory blood pressure device for hemodialysis patients. Blood Press Monit. 1999;4:217–221.
21. Peixoto AJ, Santos SF, Mendes RB, et al. Reproducibility of ambulatory blood pressure monitoring in hemodialysis patients. Am J Kidney Dis. 2000;36:983–990.

22. Parati G, Stergiou G, O’Brien E, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32:1359–1366.

23. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med. 2003;115:291–297.
24. Del VL, Lusenti T, Del RG, Malandra R, Balducci A, Losito A. Prevalence of hypertension in a large cohort of Italian hemodialysis patients: results of a cross-sectional study. J Nephrol. 2013;26:745–754.
25. Rahman M, Dixit A, Donley V, et al. Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. Am J Kidney Dis. 1999;33:498–506.
26. Salem MM. Hypertension in the hemodialysis population: a survey of 649 patients. Am J Kidney Dis. 1995;26:461–468.
27. Agarwal R. Epidemiology of interdialytic ambulatory hypertension and the role of volume excess. Am J Nephrol. 2011;34:381–390.
28. Sarafidis PA, Mallamaci F, Loutradis C, et al. Prevalence and control of hypertension by 48-h ambulatory blood pressure monitoring in haemodialysis patients: a study by the European Cardiovascular and Renal Medicine (EURECA-m) working group of the ERA-EDTA. Nephrol Dial Transplant. 2019;34:1542–1548.
29. Tsikliras N, Georgianos PI, Vaios V, et al. Prevalence and control of hypertension among patients on haemodialysis. Eur J Clin Invest. 2020;50:e13292.
30. Vaios V, Georgianos PI, Liakopoulos V, Agarwal R. Assessment and management of hypertension among patients on peritoneal dialysis. Clin J Am Soc Nephrol. 2019;14:297–305.
31. Han YC, Tu Y, Zhou LT, et al. Peridialysis BP levels and risk of all-cause mortality: a dose-response meta-analysis. J Hum Hypertens. 2019;33:41–49.
32. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD. Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. Hypertension. 2005;45:811–817.
33. Port FK, Hulbert-Shearon TE, Wolfe RA, et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis. 1999;33:507–517.
34. Zager PG, Nikolic J, Brown RH, et al. U curve association of blood pressure and mortality in hemodialysis patients. Medical directors of dialysis clinic, Inc. Kidney Int. 1998;54:561–569.
35. Georgianos PI, Agarwal R. Blood pressure and mortality in long-term hemodialysis-time to move forward. Am J Hypertens. 2017;30:211–222.
36. Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. Hypertension. 2009;53:860–866.
37. Heerspink HJ, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2009;373:1009–1015.
38. Kidney Disease: Improving Global Outcomes (KDIGO) Blood PressureWork Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012;2:337–414.
39. Miskulin DC, Gassman J, Schrader R, et al. BP in dialysis: results of a pilot study. J Am Soc Nephrol. 2018;29:307–316.
40. Sinha AD, Agarwal R. Can chronic volume overload be recognized and prevented in hemodialysis patients? The pitfalls of the clinical examination in assessing volume status. Semin Dial. 2009;22:480–482.
41. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. Hypertension. 2009;53:500–507.
42. Agarwal R, Bouldin JM, Light RP, Garg A. Probing dry-weight improves

left ventricular mass index. Am J Nephrol. 2011;33:373–380.
43. Torino C, Gargani L, Sicari R, et al. The Agreement between auscultation and lung ultrasound in hemodialysis patients: the LUST study. Clin J Am Soc Nephrol. 2016;11:2005–2011.
44. Agarwal R, Andersen MJ, Pratt JH. On the importance of pedal edema in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3:153–158.
45. Sinha AD, Light RP, Agarwal R. Relative plasma volume monitoring during hemodialysis AIDS the assessment of dry weight. Hypertension. 2010;55:305–311.

References

46. Georgianos PI, Sarafidis PA, Zoccali C. Intradialysis hypertension in end-stage renal disease patients: clinical epidemiology, pathogenesis, and treatment. Hypertension. 2015;66:456–463.
47. Van Buren PN, Kim C, Toto R, Inrig JK. Intradialytic hypertension and the association with interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol. 2011;6:1684–1691.
48. Agarwal R, Light RP. Intradialytic hypertension is a marker of volume excess. Nephrol Dial Transplant. 2010;25:3355–3361.
49. Mallamaci F, Benedetto FA, Tripepi R, et al. Detection of pulmonary congestion by chest ultrasound in dialysis patients. JACC Cardiovasc Imaging. 2010;3:586–594.
50. Moissl UM, Wabel P, Chamney PW, et al. Body fluid volume determination via body composition spectroscopy in health and disease. Physiol Meas. 2006;27:921–933.
51. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. Hypertension. 2010;56:512–517.
52. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant. 2009;24:1574–1579.
53. Zoccali C, Torino C, Tripepi R, et al. Pulmonary congestion predicts cardiac events and mortality in ESRD. J Am Soc Nephrol. 2013;24:639–646.
54. Zoccali C, Moissl U, Chazot C, et al. Chronic fluid overload and mortality in ESRD. J Am Soc Nephrol. 2017;28:2491–2497.
55. Huan-Sheng C, Yeong-Chang C, Ming-Hsing H, et al. Application of bioimpedance spectroscopy in Asian dialysis patients (ABISAD-III): a randomized controlled trial for clinical outcomes. Int Urol Nephrol. 2016;48:1897–1909.
56. Liu L, Sun Y, Chen Y, et al. The effect of BCM guided dry weight assessment on short-term survival in Chinese hemodialysis patients: Primary results of a randomized trial: Body Composition Monitor (BOCOMO) study. BMC Nephrol. 2020;21:135.
57. Onofriescu M, Hogas S, Voroneanu L, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. Am J Kidney Dis. 2014;64:111–118.
58. Reddan DN, Szczech LA, Hasselblad V, et al. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. J Am Soc Nephrol. 2005;16:2162–2169.
59. Siriopol D, Onofriescu M, Voroneanu L, et al. Dry weight assessment by combined ultrasound and bioimpedance monitoring in low cardiovascular risk hemodialysis patients: a randomized controlled trial. Int Urol Nephrol. 2017;49:143–153.
60. Beaubien-Souligny W, Kontar L, Blum D, Bouchard J, Denault AY, Wald R. Meta-analysis of randomized controlled trials using tool-assisted target weight adjustments in chronic dialysis patients. Kidney Int Rep. 2019;4:1426–1434.
61. Covic A, Ciumanghel AI, Siriopol D, et al. Value of bioimpedance analysis estimated “dry weight” in maintenance dialysis patients: a systematic review and meta-analysis. Int Urol Nephrol. 2017;49:2231–2245.
62. Fouque D, Vennegoor M, ter WP, et al. EBPG guideline on nutrition. Nephrol Dial Transplant. 2007;22(suppl 2):ii45–ii87.
63. Kayikcioglu M, Tumuklu M, Ozkahya M, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. Nephrol Dial Transplant. 2009;24:956–962.
64. Ozkahya M, Toz H, Qzerkan F, et al. Impact of volume control on left ventricular hypertrophy in dialysis patients. J Nephrol. 2002;15:655–660.
65. Basile C, Lomonte C. It is time to individualize the dialysate sodium prescription. Semin Dial. 2016;29:24–27.
66. Munoz MJ, Sun S, Chertow GM, Moran J, Doss S, Schiller B. Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? Nephrol Dial Transplant. 2011;26:1281–

1287.
67. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. Cochrane Database Syst Rev. 2019;1:CD011204.
68. Arramreddy R, Sun SJ, Munoz MJ, Chertow GM, Schiller B. Individualized reduction in dialysate sodium in conventional in-center hemodialysis. Hemodial Int. 2012;16:473–480.
69. de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. Kidney Int. 2004;66:1232–1238.

70. Munoz MJ, Bayes LY, Sun S, Doss S, Schiller B. Effect of lowering dialysate sodium concentration on interdialytic weight gain and blood pressure in patients undergoing thrice-weekly in-center nocturnal hemodialysis: a quality improvement study. Am J Kidney Dis. 2011;58:956–963.
71. Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2012;27:4180–4188.
72. Rahman M, Fu P, Sehgal AR, Smith MC. Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. Am J Kidney Dis. 2000;35:257–265.
73. Tandon T, Sinha AD, Agarwal R. Shorter delivered dialysis times associate with a higher and more difficult to treat blood pressure. Nephrol Dial Transplant. 2013;28:1562–1568.
74. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant. 2014;29:672–681.
75. Iseki K, Arima H, Kohagura K, et al. Effects of Angiotensin Receptor Blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. Nephrol Dial Transplant. 2013;28:1579–1589.
76. Lin C, Zhang Q, Zhang H, Lin A. Long-term effects of low-dose spironolactone on chronic dialysis patients: a randomized placebocontrolled study. J Clin Hypertens (Greenwich). 2016;18:121–128.
77. Matsumoto Y, Mori Y, Kageyama S, et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol. 2014;63:528–536.
78. Suzuki H, Kanno Y, Sugahara S, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis. 2008;52:501–506.
79. Takahashi A, Takase H, Toriyama T, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis-a randomized study. Nephrol Dial Transplant. 2006;21:2507–2512.
80. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. Nephrol Dial Transplant. 2008;23:3605–3612.
81. Zannad F, Kessler M, Lehert P, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int. 2006;70:1318–1324.
82. Cice G, Ferrara L, D’Andrea A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003;41:1438–1444.
83. Georgianos PI, Agarwal R. Effect of lisinopril and atenolol on aortic stiffness in patients on hemodialysis. Clin J Am Soc Nephrol. 2015;10:639–645.
84. Agarwal R. Supervised atenolol therapy in the management of hemodialysis hypertension. Kidney Int. 1999;55:1528–1535.
85. Tai DJ, Lim TW, James MT, Manns BJ, Tonelli M, Hemmelgarn BR. Cardiovascular effects of angiotensin converting enzyme inhibition or

angiotensin receptor blockade in hemodialysis: a meta-analysis. Clin J Am Soc Nephrol. 2010;5:623–630.
86. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709–717.
87. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–1321.
88. Georgianos PI, Vaios V, Eleftheriadis T, Zebekakis P, Liakopoulos V. Mineralocorticoid antagonists in ESRD: an overview of clinical trial evidence. Curr Vasc Pharmacol. 2017;15:599–606.
89. Quach K, Lvtvyn L, Baigent C, et al. The safety and efficacy of mineralocorticoid receptor antagonists in patients who require dialysis: a systematic review and meta-analysis. Am J Kidney Dis. 2016;68:591–598.

SECTION VII

Renovascular Disease

43

Renovascular Hypertension, Atherosclerotic Renal Vascular Disease, and Thromboembolic Kidney Disease

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NORMAL RENOVASCULAR ANATOMY

The clinical presentations of renovascular disease are influenced by the acuity, nature, and site of renal vascular compromise. In most individuals, the kidney has a single renal artery (RA) with a lumen diameter of 3 to 7 mm. The main RA branches in a double or triple fork pattern or ladder pattern.1 The incidence of multiple RAs is about 31%, with bilateral supernumerary arteries in 11%.2 The collaterals to the kidney, depicted in Fig. 43.1, can maintain renal parenchymal viability in the face of main RA occlusion.

Renal veins (RVs) begin in the subcapsular region of the kidney, communicate with perirenal and cortical venous channels, and empty into interlobular and then arcuate veins. The venae rectae drain the pyramids and join the arcuate veins, which leave the renal parenchyma through interlobar vessels, converging into four to six trunks near the hilum of the kidney. Approximately 20% of people have two or more RVs. The main RVs empty into the inferior vena cava. The left RV is three times longer than the right (7.5 cm vs. 2.5 cm) and traverses behind the splenic vein and body of the pancreas before it crosses in front of the aorta near its termination at the inferior vena cava. About 25% of people have retroaortic or circumaortic RVs. RV anatomy is shown in Fig. 43.2.

CLINICAL SYNDROMES ASSOCIATED WITH RENAL VASCULAR DISEASE

Impairment of blood flow is associated with one or more distinct clinical syndromes. These are summarized in Box 43.1. Discussion of these syndromes as distinct entities is meant to help with recognition and understanding that often, in clinical practice, there is significant overlap. The first section will focus on the three most common clinical presentations of RA stenosis: renovascular hypertension (RVH), atherosclerotic renovascular disease (ARVD; formerly called ischemic renal disease [IRD]), and unstable cardiac syndromes including flash pulmonary edema. The second section will address the distinct clinical presentations of transplant renovascular disease, renal infarction, atheroembolic disease, and RV thrombosis.

RENOVASCULAR HYPERTENSION

A reduction in renal perfusion pressure activates a series of hormonal and neuronal responses that raise systemic arterial pressure to restore

RA perfusion pressures.3 Renovascular hypertension (RVH) is defined as a syndrome of elevated blood pressure (BP) produced by any condition that leads to reduced perfusion of the kidneys.

Central to the pathogenesis of RVH is activation of the reninangiotensin-aldosterone system (RAAS) with release of renin from the juxtaglomerular apparatus. This is mediated in part by stimulation of neuronal nitric oxide synthase and cyclooxygenase-2 in the macula densa. Blockade of RAAS during creation of an experimental RA stenosis prevents development of hypertension.4 Studies in transgenic mice without receptors for angiotensin II (Ang II) confirm that development of RVH requires an intact RAAS.5 In the absence of RAAS blockade, systemic arterial pressures increase until renal perfusion is restored. Studies in experimental models and humans indicate that additional mechanisms contribute to long-term BP elevation in the presence of RA stenosis, including activation of the sympathetic nervous system, impairment of nitric oxide generation, release of endothelin, and hypertensive microvascular injury to the kidney.[6]

Mechanisms responsible for sustained RVH differ depending on whether one or both kidneys are affected; these mechanisms have been studied in animal models in which RA perfusion is reduced by clipping the vessel proximally. The nomenclature distinguishes between a situation in which one clip is present with a normal contralateral unclipped kidney (“1-clip–2-kidney hypertension”) and a situation in which the entire renal mass is affected (“1-clip–1-kidney hypertension”). Both these situations begin with impaired renal perfusion and initial activation of RAAS with sodium retention. However, in the 1-clip–2-kidney hypertension model, the elevated pressure generated by RAAS activation mediates a pressure natriuresis in the nonstenotic kidney. This restores plasma volume and results in sustained hypoperfusion and RAAS activation in the poststenotic kidney. This sequence of events produces Ang II–dependent hypertension (Fig. 43.3A).

By contrast, 1-clip–1-kidney hypertension represents a model in which the entire kidney mass is exposed to reduced perfusion pressure. As a result, sodium retention leads to expanded blood volume and sustained elevation in pressure, which then restores renal perfusion pressure beyond the stenosis and inhibits RAAS activation (see Fig. 43.3B). Hypertension in this model is typically more volume dependent than Ang II dependent. It may be less responsive to RAAS blockade than 1-clip–2-kidney hypertension. Box 43.2 lists causes of RVH based on these mechanisms.

Renal Collateral Blood Supply

Renal Vein Anatomy

Intercostal
artery
Adrenal
artery
Adrenal vein
Gonadal
artery
Lumbar vein

Lumbar
artery

Gonadal vein
Ureteral
artery

A

Fig. 43.1 The potential collateral renal arterial vessels to the kidney.

In RA stenosis, RAAS activation occurs when luminal stenosis is relatively severe, usually in the range of at least 60% to 80% cross-sectional diameter narrowing (Fig. 43.4). In experimental models, the relative importance of pressor mechanisms, including measurable activation of the RAAS, changes with time. Levels of circulating plasma renin activity tend to decrease. Several mechanisms have been proposed to explain such changes, including a slowly developing pressor action of Ang II, transition to alternative pressor mechanisms, and hypertensive injury to the nonstenotic kidney. In experimental models, this translates into a time limit for reversibility of RVH by removal of the clip.

Clinically, this makes it difficult to determine when patients are most likely to benefit from RA revascularization for cure of hypertension.

Widespread use of RAAS blockers to manage hypertension, congestive heart failure (CHF), and diabetic and other proteinuric nephropathies has increased the exposure of individuals with undetected RVH to these agents. Therefore, many cases of RVH go undiagnosed unless hypertension becomes more difficult to control or kidney dysfunction develops. Patients who typically undergo diagnostic evaluation for RA stenosis are a subset of patients with more severe or resistant hypertension or those presenting with renal impairment or cardiac syndromes.

Clinical differentiation of RVH and primary hypertension is difficult, and they may be superimposed. If secondary to unilateral RA stenosis, for example, RVH often can be easily controlled with the use of RAAS blockers. Certainly, some cases of RVH present with accelerated, resistant, or hypertension emergency. Clinical studies suggest that for any level of BP, patients with RVH have higher nocturnal pressures (“nondippers”) and have more severe target organ manifestations, such as left ventricular hypertrophy (LVH) and albuminuria, than patients with primary hypertension.7 Patients with RVH may present with hypokalemia and metabolic alkalosis, which are clues to secondary aldosteronism. Clinical suspicion for RVH arises when hypertension develops either very early (<30 years) or later in life (>70 years) or when well-controlled hypertension becomes more resistant. Renovascular hypertension may rarely be associated with reninmediated and hemodynamically induced nephrotic range proteinuria

Renal pelvis
Renal artery
and vein

B

Fig. 43.2 Renal Vein Anatomy. (A) There is extensive communication between the renal venous plexus and lumbar, gonadal, and adrenal veins, which provide alternative outflow in the setting of renal vein thrombosis, particularly on the left. (B) Transverse section of the kidney showing relative position of vascular structures in the renal pelvis. (From Graham SD, Keane TE, Glenn JF, eds. Glenn’s Urologic Surgery. 7th ed. Wolters Kluwer/Lippincott Williams & Wilkins Health; 2010.)

Clinical Presentations of Renovascular Disease

BOX 43.1

- Renovascular hypertension
- Ischemic renal disease
- Unstable cardiac syndromes
- Renal infarction
- Atheroembolic renal disease
- Renal vein thrombosis
- Transplant renovascular disease

Bilateral Renal Artery Stenosis

Unilateral Renal Artery Stenosis

Stenosis of
solitary kidney

Bilateral
Reduced renal perfusion

↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Increased renal perfusion
Reduced renal perfusion

Suppressed Increased
RAS
Na+ excretion
(pressure natriuresis)

Angiotensin II–dependent
hypertension

↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone
Inhibit RAS

Impaired Na+ and
water excretion
Volume expansion

Normal or low angiotensin II
Increased arterial
pressure

A

Effect of blockade of RAS
Reduced arterial pressure
Enhanced lateralization of diagnostic tests
Glomerular filtration rate (GFR) in stenotic kidney may fall

Effect of blockade of RAS
Reduced arterial pressure only after volume depletion
May lower GFR

Diagnostic tests
Plasma renin activity elevated
Lateralized features, e.g., Doppler ultrasound, renin levels
in renal veins, captopril-enhanced renography

Diagnostic tests
Plasma renin activity normal or low
Lateralized features: none

B

Fig. 43.3 Pathogenesis of Renovascular Hypertension in One-Kidney Versus Two-Kidney Model. (A) In unilateral stenosis with two kidneys, opposing forces between the stenotic kidney, which has reduced perfusion pressures, and the nonstenotic contralateral kidney, which has increased perfusion pressures, result in laboratory and clinical features of angiotensin-dependent hypertension. (B) In unilateral stenosis with a solitary functioning kidney or in a patient with bilateral critical renal artery stenosis, reduced perfusion pressure to the stenotic kidney in the absence of a normal kidney excreting sodium leads to sodium and volume retention, ultimately associated with hypertension without persistent activation of the renin-angiotensin system (RAS). GFR, Glomerular filtration rate.

that resolves with treatment. A syndrome of polydipsia associated with hyponatremia attributed to the dipsogenic action of Ang II has also been observed in patients with RVH. Clinical features of RVH are summarized in Box 43.3

Renal Artery Stenosis

The most common cause of RVH is RA stenosis. Fibromuscular dysplasia (FMD) and atherosclerotic disease are the two most common causes of RVH. The unique clinical presentations of congenital and inflammatory arteritis as exemplified by aortic coarctation and Takayasu arteritis will also be discussed.

Fibromuscular Dysplasia

Fibromuscular dysplasia is the most common cause of RVH in children and young adults and is defined as an idiopathic, segmental, noninflammatory, nonatherosclerotic disease of the muscular arterial wall.
Fibromuscular dysplasia is defined by pathognomonic arteriographic abnormalities, most commonly either a focal stenosis involving any portion of the vessel or multifocal stenoses in a string of beads appearance (Fig. 43.5) in mid to distal portions of small and medium-sized arteries. Nonstenotic angiographic findings associated with FMD include aneurysms, dissection, or vessel tortuosity, the latter often seen in the carotid circulation as an S-curve or in the coronary circulation.
The presence of focal or multifocal stenosis in at least one vascular bed is necessary for the diagnosis of FMD, with the recognition that tortuosity, aneurysm, or dissection in another vascular bed may be associated but not sufficient for the diagnosis.[8]

The vascular distribution of FMD involves primarily the renal and extracranial cerebral and vertebral arteries but may involve any artery. In the FMD registries, RAs are involved with FMD in 66% to 92% of cases.[8] Bilateral RA involvement is seen in 25% to 35% of adult cases. Cerebrovascular involvement was identified in 80% and 59% of patients in the US and European registries, respectively.[8,9] Evaluation of 489 patients for RA and cerebral vascular involvement found that 48% had two territories involved, and 66.1% had dysplastic stenosis, aneurysms, or dissections at another site.[10] Of those with imaging of other vascular beds reported in the US registry, 48% had coronary involvement and 45% had lower extremity vascular involvement. Less common extrarenal sites of involvement with FMD include mesenteric, celiac, splenic, and aortic arteries.
Given the potentially systemic nature of FMD, we recommend thorough imaging assessment with computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) of the entire vasculature at least once in patients with FMD to look for involvement at other sites, including occult aneurysms.[8]
The prevalence of renovascular FMD is estimated at 4 in 1000.[11]

Angiography data from potential kidney donors suggest that the prevalence may be higher, with FMD observed in 3.8% to 6.6% of individuals.12 Approximately 80% to 90% of cases of FMD occur in women, with most of these having multifocal FMD. Men with FMD tend to have a more aggressive phenotype, with a greater prevalence of focal FMD and aneurysms.13

Of those enrolled in the US FMD registry, 91% are White, and the mean age of onset of hypertension is 44.8 years. The mean age at diagnosis was 53.3 years. As this presentation overlaps with the age of onset of primary hypertension, FMD may be missed in many adults. This racial predilection could represent recruitment or geographic bias.

Causes of Renovascular Hypertension

BOX 43.2

Two-Kidney Hypertension[a]
- Unilateral fibromuscular dysplasia
- Unilateral atherosclerotic renovascular disease
- RA aneurysm
- RA embolism and infarction
- Traumatic arterial occlusion
- Arteriovenous fistula
- RA dissection or thrombosis
- Aortic dissections with compromise to renal ostium
- Page kidney
- Takayasu arteritis
- Metastatic tumor compressing renal parenchyma
- Pheochromocytoma compressing RA
- Phakomatosis pigmentovascularis type IIb
- Neurofibromatosis
- Behçet disease
- Covering of origin of RA by aortic stent graft
- RA spasm

Histologically, FMD is associated with distortion of the architecture of the arterial wall involving one or more layers. The former distinction between adventitial, medial, intimal, and perimedial variants is no longer considered clinically relevant. Both genetic and environmental factors have been implicated in the etiology of FMD. In current registries, less than 7.5% of cases have family history of FMD. Data are biased by the significant percentage of asymptomatic cases and underdiagnosis. Genome-wide association studies have identified a single nucleotide polymorphism in the PHACTR1 locus on chromosome 6 as a risk allele. This genetic location is associated with regulation of expression of endothelin 1, which has effects on vascular tone and remodeling.14 The current consensus is that there is no genetic test specific for FMD, and relatives of patients with FMD should be screened clinically and with imaging if signs, including hypertension, or symptoms develop. Environmental factors implicated in the etiology of FMD include cigarette smoking, hormonal influences, and vascular trauma or stretching of the RA during development or associated with nephropthosis.13 US registry data observed a higher incidence of aneurysms and major vascular events among smokers with FMD.15 Ongoing research is exploring potential roles of circulating transforming growth factor-β (TGF-β) and proinflammatory lipid mediators in the vascular wall in the pathogenesis of FMD.16

Clinical Features of Renovascular Hypertension

BOX 43.3

One-Kidney Hypertension[b]
- Stenosis to solitary kidney
- Bilateral arterial stenosis or dissection
- Coarctation of the aorta

• Vasculitis involving RAs
• Congenital vascular anomalies
• Atheroembolic renal disease
aTwo-kidney

hypertension implies that a contralateral, nonaffected
kidney is present.
bOne-kidney hypertension implies that the entire renal mass is beyond the
vascular lesion, either bilateral disease or a solitary functioning kidney.
RA, Renal artery.

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Activation of renin-angiotensin system (early)
Early-onset (<30 years) or late-onset (>60 years) hypertension
Activation of sympathetic nervous system
Abnormal circadian rhythm: loss of nocturnal fall
Secondary aldosteronism: hypokalemia
Accelerated target organ damage
Microvascular disease
Left ventricular hypertrophy
Reduced glomerular filtration rate
Hyponatremic hypertensive syndrome
Unstable cardiac syndromes
Rarely, nephrotic range proteinuria

Hemodynamic Effects of Stenotic Lesions in Renal Arteries
Blood flow and
renal stenosis

Perfusion pressure
and stenosis
100
Perfusion pressure (%)

Blood flow (% of normal)

100
80
60
40
82%
20
0

80
60
40
80%
20
0

0

20

40

60

80

100

0

20

40

60

80

100

Stenosis (%)
Stenosis (%)

Fig. 43.4 Hemodynamic Effects of Stenotic Lesions in Renal Arteries. Changes in blood flow and arterial pressure across a carefully quantitated arterial lesion are barely detectable until cross-sectional area diminishes by 75% to 80%.

The most common adult clinical presentation is early-onset RVH in young to middle-aged women. Cerebrovascular lesions may manifest with headaches, pulsatile tinnitus, and bruits over the carotid arteries. Fibromuscular dysplasia should be considered in younger patients presenting with hypertension and stroke, transient ischemic attacks, subarachnoid hemorrhage, or amaurosis fugax. Clinical presentations of FMD and associated disorders are shown in Box 43.4

The natural history of FMD has not been adequately studied. Progression of disease may manifest as new lesions within the same arterial bed, worsening arterial luminal narrowing within a specific lesion, involvement of a new vascular territory, or development or enlargement of arteriovenous fistulas or aneurysms. Up to 37% of patients may demonstrate angiographic progression of FMD, with few patients developing new or progressive lesions after the age of 40 years.17 Progression may be associated with kidney cortical thinning but rarely causes advanced kidney failure.

Atherosclerotic Renal Artery Stenosis

Atherosclerotic RA stenosis is the most common cause of RVH in patients over 50 years old. Estimates of the prevalence of atherosclerotic RA stenosis depend on the population screened. One populationbased study of 870 patients over 65 years old and screened with RA duplex ultrasound found a 6.8% prevalence of atherosclerotic RA stenosis, defined as greater than 60% stenosis.18 Autopsy series report an overall prevalence of 4% to 20%, with progressively higher prevalence for those older than 60 years (25%–30%) and older than 75 years (40%–60%). Atherosclerotic RA stenosis occurs in patients with more generalized atherosclerosis involving the aorta, peripheral vasculature, and coronary arteries. Approximately 14% of patients with hypertension and 20% of patients with hypertension and diabetes mellitus (DM) have evidence of atherosclerotic RA stenosis. Coexistent RA stenosis is found in 11% to 30% of patients undergoing coronary angiography

A

and in up to 45% of patients undergoing peripheral angiograms.19 Among patients with chronic CHF, RA stenosis has been reported in 50% to 68%.20 The American College of Cardiology and American Heart Association recommend screening for atherosclerotic RA stenosis in patients presenting with resistant or accelerated hypertension and those presenting with heart failure.

Predictors of RA stenosis include a history of hypertension, presence of chronic kidney disease (CKD), coexisting peripheral vascular or coronary artery disease, the presence of abdominal bruits, and a history of smoking. Atherosclerotic RA stenosis is bilateral in 20% to 40% of patients. In many of these cases, the degree of stenosis is below the threshold to cause activation of RAAS or have other clinical implications. However, the presence of atherosclerotic RA stenosis is a marker for increased cardiovascular and mortality risk.21 Accordingly, its presence should prompt clinical attention to cardiovascular risk factors, including the use of high-dose statin therapy, efforts to promote smoking cessation, and optimal control of BP and metabolic syndrome.

Some patients with atherosclerotic RA stenosis will experience progressive RA luminal narrowing and develop RVH or other clinical syndromes described later. Prospective studies between 1990 and 1997 using duplex ultrasound in patients with atherosclerotic RA stenosis indicated progression in 30% over 3 years, varying by degree of initial stenosis, with progression more common in those with more than 60% luminal diameter stenosis. Total occlusion is rare but devastating, often leading to loss of kidney function. There are few prospective data assessing progression in patients treated with optimal medical therapy targeting atherosclerotic risk factors in the modern era.

Clinical presentations and treatment of atherosclerotic RA stenosis are discussed later in this chapter.

Takayasu Arteritis

Initially described in 1761, Takayasu arteritis, often termed pulseless disease, is one of several inflammatory disorders involving the renal

B

Fig. 43.5 Fibromuscular Dysplasia. (A) Selective renal arteriogram illustrating the beaded appearance of fibromuscular dysplasia with multiple webs characteristic of multifocal fibromuscular dysplasia in a 39-year-old woman. (B) Selective injection of the same renal artery after technically successful percutaneous transluminal renal angioplasty. (Courtesy Michael McKusick, MD, Mayo Clinic, Rochester, MN.)

Clinical Manifestations and Disorders Associated With Fibromuscular Dysplasia

BOX 43.4

Clinical Manifestations
- Incidental finding (e.g., living kidney donors)
- Renovascular hypertension
- Renal infarction
- Loin or flank pain
- Hematuria
- Retroperitoneal hemorrhage
- Cerebrovascular accident (stroke)
- Transient ischemic attack
- Headaches
- Pulsatile tinnitus
- Horner syndrome
- Neck pain
- Dizziness
- Imaging finding of aneurysm dissection
- Amaurosis fugax
- Myocardial infarction
- Ischemic chest pain/dyspnea
- Postprandial abdominal pain
- Weight loss
- Hemobilia
- Claudication

Associated Disorders
- Tuberous sclerosis
- Marfan syndrome
- Ehlers-Danlos syndrome
- Cystic medial necrosis
- Coarctation of the aorta
- Alport syndrome
- Renal agenesis or dysgenesis
- α1-Antitrypsin deficiency
- Medullary sponge kidney
- Cigarette smoking
- Collagen III glomerulopathy
- Atherosclerotic renovascular disease
- Alagille syndrome
- Ask-Upmark kidney
- Celiac disease
- Cocaine exposure (intrauterine)
- Crohn disease
- Homocystinuria
- Macrophagic myofasciitis
- Neurofibromatosis
- Williams syndrome
- Pheochromocytoma
- Infantile myofibromatosis
- Ergotamine preparation, methysergide

vasculature causing RVH. Although rare in the United States, its prevalence varies geographically, with reports as high as 1 in 3000 in Japan.22 Takayasu arteritis usually presents between the ages of 25 and 41 years. The diagnosis should be considered in any child or young adult with hypertension and/or asymmetric peripheral pulses. In half of cases, identification of arterial stenosis is preceded by a prodromal illness characterized by fever, night sweats, malaise, and weight loss.

Inflammatory markers are often elevated during this phase. Later, vascular stenoses can lead to RVH, kidney dysfunction, stroke, cerebral hemorrhage, myocardial infarction, or CHF, depending on sites of involvement.22

The diagnosis of Takayasu arteritis requires arteriographic narrowing or occlusion of a vascular territory of the aorta, its branches, or large arteries not attributable to atherosclerosis, middle aortic syndrome, or FMD.23 One distinguishing feature of Takayasu arteritis is the presence of inflammatory thickening of the vascular wall seen on imaging.23

Theories about the pathophysiology of Takayasu arteritis include autoimmunity and hypersensitivity response to proposed antigens, including heat shock protein and Mycobacterium tuberculosis. Histologically, granulomatous inflammation involves all layers of the vessel wall during the active phase of disease, followed by fibrotic stenosis.

Treatment generally starts with corticosteroids or other immunomodulatory therapy during the inflammatory phase of disease, followed by medical or interventional treatment to reduce organ injury.24

Coarctation and Middle Aortic Syndrome

Coarctation occurs in about 1 in 1550 births and accounts for about one-third of all causes of RVH in infants. Interestingly, only 35% of isolated coarctation cases are diagnosed in the first year of life. Cases missed in childhood present as early onset hypertension in adults. Those cases treated in childhood can develop restenosis of the coarct segment later in life. It is estimated that 1 in 150 adults have congenital heart disease, with aortic coarctation accounting for 5% to 10%.

Adult presentations of RVH associated with coarctation include signs and symptoms of collateral development. Bruits may be heard over the carotids, and intercostal pulses may be palpable. A radialfemoral pulse delay is a sensitive physical examination finding. Present in only about 50% of cases, a harsh, systolic blowing murmur is heard best over the posterior thorax. Either MRA or CTA is necessary to confirm coarctation in adults. Indications for the treatment of coarctation in adults include upper limb hypertension and greater than 20 mm Hg systolic BP gradient across the stenosis with evidence of significant collateral flow. These patients have a fivefold excess risk of cerebral aneurysms, and screening cerebrovascular imaging is recommended.

Current guidelines recommend multispecialty consultation among cardiologists, interventionalists, and surgeons to determine the optimal approach (endovascular vs. surgical) to repair. Success rates for cure of hypertension range from 69% to 80%, with highest chance for cure and best survival data when treated in children younger than 10 years. Adults with prior coarctation have a higher risk of developing hypertension than the general population. This risk is attributed to vascular noncompliance, reduced aortic arch baroreceptor sensitivity, early kidney injury with sustained RAAS activation, and, in some cases, restenosis of the repaired coarct segment.

A rare entity, middle aortic syndrome is a congenital segmental or diffuse narrowing of the abdominal or distal descending aorta, causing RVH usually noted in infancy. Concomitant proximal RA stenosis occurs in up to 80% of cases, with variants including RA atresia, hypoplasia, or dysplasia.25 Associations between middle aortic syndrome and FMD, neurofibromatosis, Williams syndrome, and Takayasu arteritis have been reported, and these cases can present later in life. Middle aortic syndrome can cause claudication of the lower extremities and mesenteric ischemia. Angioplasty and stenting of stenotic segments, surgical bypass grafting, and autotransplantation of ischemic organs are treatment options.25

Renal Artery Aneurysms

Renal artery aneurysms are a rare cause of RVH and can be associated with atherosclerosis, FMD, and vasculitis. Thrombosis within an aneurysm can lead to distal emboli and renal infarcts (Fig. 43.6). Aneurysms

B

A

Fig. 43.6 Computed Tomography Angiogram of Renal Artery Aneurysm With Area of Infarction in Right Kidney. (A) Coronal image demonstrates area of intact tissue with no blood perfusion within the kidney parenchyma (arrow). (B) Reconstructed view with vascular aneurysm (arrow) and minimal flow in the distribution beyond this segment consistent with near-total occlusion. This patient presented with accelerated renovascular hypertension treated primarily with renin-angiotensin system blockade.

with diameters of greater than 1.5 cm have a significant risk of rupture. Other complications of RA aneurysms include vessel dissection and arteriovenous fistula formation.

ATHEROSCLEROTIC RENOVASCULAR DISEASE OR ISCHEMIC RENAL DISEASE

A second clinical presentation of renovascular disease is kidney dysfunction. Recent investigations have broadened our understanding of the processes leading to kidney injury, atrophy, and reduced glomerular filtration rate (GFR) in the setting of ARVD. Formerly called ischemic renal disease (IRD), it is now recognized that other factors in addition to ischemia are important in the pathogenesis. Severe RA stenosis or occlusion can decrease GFR by reducing glomerular capillary pressure below the threshold for renal autoregulatory compensation. This hemodynamic effect on kidney function occurs when renal blood flow is severely compromised. The histologic correlates of this reduced renal perfusion pressure include glomerular involution with basement membrane wrinkling and tubular cell atrophy and simplification and loss of brush border. The reduced energy-dependent tubular function and energy expenditure matches the reduction in oxygen delivery. Revascularization to improve renal blood flow can restore GFR and reverse these adaptive changes. In this scenario, the kidney is not chronically ischemic. Studies using blood oxygen level–dependent magnetic resonance imaging (BOLD MRI) indicate that, despite reductions in blood flow and GFR, many patients with RA stenosis maintain normal renal cortical and medullary tissue oxygenation.[26,27] Thus, many poststenotic kidneys have no more ischemia than normal kidneys.

However, it is clear from randomized controlled trials evaluating the effects of revascularization on retrieval of kidney function, studies in experimental RA stenosis, and renal biopsies of poststenotic kidneys that factors other than hemodynamics play a significant role in the pathogenesis of ARVD (Fig. 43.7). Severe RA stenosis may cause intermittent ischemic insults associated with acute or chronic regional or global hypoxia, which trigger maladaptive processes and ongoing kidney injury even when perfusion is restored.[28] These insults might be caused by fluctuations in BP and renal perfusion, embolic events, or progression of stenosis. Biopsies from poststenotic kidneys demonstrate influx of inflammatory cells and macrophages and increased expression of inflammatory cytokines including monocyte chemoattractant protein-1, tumor necrosis factor-α, interferon-γ, and interleukin-6. Biomarkers of tubular injury, including neutrophil gelatinase–associated lipocalin, are increased in poststenotic kidney RVs. Profibrotic factors including TGF-β and mitogen-activated protein kinase p38 are upregulated and associate with interstitial fibrosis and tubular atrophy.

Ischemia leads to production of reactive oxygen species, which cause increased renal microcirculatory vascular tone and endothelial cell dysfunction.29 This results in remodeling and rarefaction of the renal microvasculature at the level of the interlobar, arcuate, interlobular arteries and small arterioles.30 This is associated with a decrease in expression of angiogenic factors including vascular endothelial growth factor (VEGF). Kidney hypoperfusion and ischemic-reperfusion insults also result in renal mitochondrial dysfunction.31

Through these processes, unilateral atherosclerotic RA stenosis leads to atrophy and dysfunction of the poststenotic kidney. The contralateral kidney often hypertrophies and compensates with hyperfiltration but develops progressive parenchymal injury mediated by the combined effects of high pressure and Ang II. In some cases, the kidney with the patent RA has worse function than the poststenotic kidney. In addition, studies in animal models of RA stenosis support the concept that the contralateral kidney participates in activation of proinflammatory and profibrotic pathways, which negatively affect the response of the poststenotic kidney to revascularization. In rats, nephrectomy of the contralateral kidney promotes recovery of the poststenotic kidney after reperfusion.32

In summary, reduced renal perfusion and ischemia ultimately activate numerous mechanisms of tissue injury. This results in macrophage

Factors Involved in the Pathogenesis
of Ischemic Kidney Disease
Activation of RAAS, SNS

Post-stent
reduced GFR

Contralateral
kidney
Reduced
blood flow
Contralateral
kidney injury

Critical
stenosis
Ischemic
hypoxia

Processor of inflammation and fibers

Adaptive
Reduction in tubular
function simplification
of structure, glomerular
involution
Maladaptive changes
- Microvascular rarefaction
- Oxidative stress
- Mitochondrial dysfunction
- Profibrotic cytokines
- Inflammation

Fig. 43.7 The factors involved in the pathogenesis of ischemic renal disease (kidney dysfunction associated with atherosclerotic renal vascular disease). GFR, Glomerular filtration rate; RAAS, renin-angiotensinaldosterone system; SNS, sympathetic nervous system.

accumulation with progressive tubular cell loss and interstitial fibrosis. Glomeruli are usually preserved but often appear involuted. The ischemic kidney develops microvascular rarefaction, contributing to ongoing irreversible structural and functional changes. Atherosclerotic renovascular disease or IRD comprises both the potentially reversible hemodynamic component and these adaptive and structural changes, some of which are not reversed by revascularizing the kidney.

Clinical presentations of ARVD or IRD are outlined in Box 43.5. The most common is unexplained CKD in patients with generalized atherosclerosis. Often, BP is well controlled, particularly when RAAS blockade is used, though it may present with resistant hypertension. Risk factors for atherosclerosis are often present: long-standing hypertension, cigarette smoking, and hyperlipidemia. When investigated, these patients are found to have unilateral or bilateral RA stenosis and often have small or asymmetric kidneys. As an etiology of CKD, ARVD is usually associated with minimal proteinuria. Proteinuria develops in response to kidney injury over time and is a predictor of poorer response to revascularization. Urinary sediment is bland.

Atherosclerotic renovascular disease can also present as acute kidney injury (AKI) in patients with RA stenosis treated medically or in those with recurrent stenosis within a stented RA. New or episodic AKI, or AKI on CKD with recent rapid decline in eGFR in patients with known RA stenosis or those with diffuse atherosclerosis, should prompt evaluation for ARVD. In patients with high-grade RA stenosis, AKI can follow normalization of systemic BP with any agent. The sudden reduction in systemic BP can reduce RA pressure below levels needed to sustain GFR. With RAAS inhibitors, these alterations in glomerular hemodynamics may be more common or pronounced.[33] Normally, activation of Ang II causes efferent arteriolar vasoconstriction, which preserves transcapillary filtration pressures at the glomerulus when preglomerular pressures are reduced, thereby maintaining GFR. The loss of this compensatory mechanism induced by RAAS blockade can result in functional AKI. This typically occurs within a few days from the start of therapy and is usually reversible. An acceptable rise in serum creatinine above baseline is less than 0.5 mg/dL or a less than 30% change in estimated GFR (eGFR). If the change exceeds this, ARVD should be considered. An excessive drop in eGFR after initiation of RAAS inhibitors is not specific for the presence of RA stenosis and is seen frequently in patients with cardiac or hepatic dysfunction or patients with intravascular volume depletion because, in these settings, maintenance of GFR is also Ang II dependent. Oligoanuria in the setting of AKI in patients with atherosclerosis or risk factors should prompt testing for critical renovascular disease. Often, concomitant RVH is present.

Clinical Presentations of Ischemic Renal Disease Associated With Atherosclerotic Renal Artery Stenosis

BOX 43.5

- AKI with control of BP: ACE inhibitors or ARBs
- AKI with aggressive diuresis in patients with congestive heart failure
- CKD otherwise unexplained in atherosclerotic age range
- CKD with asymmetric renal size
- Acute or chronic kidney disease and renovascular hypertension
- Acute on chronic kidney injury with episodes of “flash” pulmonary edema
- Unexplained rapid decline in GFR in CKD
- Oligoanuric kidney failure not otherwise explained in a patient with atherosclerosis and hypertension
- Renal atrophy

ACE, Angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate.

RENOVASCULAR DISEASE AND HEART FAILURE AND UNSTABLE CARDIAC CONDITIONS

Some patients with RA stenosis present with recurrent episodes of “flash” pulmonary edema, called Pickering syndrome.[34] These presentations are usually characterized by hypertensive urgency or emergency, hypervolemia, and echocardiographic evidence of diastolic dysfunction.[35] Such patients have increased mortality and hospitalization rates compared with those who have CHF without renovascular disease.36 Case series and retrospective reviews suggest that renal revascularization can facilitate volume management, reduce hospitalizations, and improve GFR and cardiac function in this high-risk subgroup of patients with atherosclerotic RA stenosis.37 38 This cohort of patients has been underrepresented in randomized controlled trials evaluating the relative efficacy of revascularization and medical therapy. Some believe that chronic stimulation of the RAAS secondary to RA stenosis contributes to the abnormal left ventricular remodeling in patients with chronic systolic heart failure, as well as to the frequency of CHF decompensation.39

Patients with CHF have a high prevalence of concomitant RA stenosis. About half of patients with a diagnosis of systolic heart failure have concomitant RA stenosis and nearly 70% of those with both CHF and CKD.40 The presentation of decompensated CHF, worsening kidney function, and hypertension should raise suspicion for this diagnosis along with other forms of cardiorenal syndrome. In cases with severely depressed left ventricular function, hypertension may be absent. Clinicians should consider the presence of critical RA stenosis if GFR continues to deteriorate during treatment of decompensated CHF.

Finally, some patients with RA stenosis and LVH can present with chest pain syndromes with no significant lesions in the coronary arteries.

IMAGING RENOVASCULAR HYPERTENSION AND RENAL ARTERY STENOSIS

Conventional direct angiography remains the reference standard to define the RA anatomy. Noninvasive options include RA duplex ultrasound, CTA, and MRA, each with their limitations and strengths.

Renal artery duplex scanning is often used to identify and follow hemodynamic effects of RA stenoses. It is most effective in detecting lesions of the main RA near the ostium and thus is a good screening test for atherosclerotic RA stenosis. The reliability of duplex ultrasound depends on the skill and experience of the operator and the body habitus of the patient. Duplex ultrasound provides little functional information beyond the vascular lesion, although structural features such as kidney size and echogenicity can be determined. The duplex diagnostic criteria for hemodynamically significant RA stenosis consider the comparative rates of blood flow in the stenotic area to that in the remaining segments of the RA and the aorta. Parameters measured include peak systolic velocity (PSV) at various sites along the RA and in the suprarenal aorta; the renal aortic ratio (RAR), which compares the PSVs at these segments; acceleration time and index, which help evaluate the RA waveform; and the intrarenal resistive index. The resistive index has been associated with intrinsic small vessel renal disease, and a value greater than 0.80 has a strong negative predictive value for a good BP response to intervention.41 Normal PSV in the RA will depend on the lumen diameter of the vessel and ranges from about 120 to 160 cm/sec. Peak systolic velocity greater than 200 to 220 cm/sec and RAR greater than 3.0 to 3.5 usually indicate RA stenosis of greater than 60% narrowing.42 Most laboratories provide interpretation as to whether parameters support at least 60% luminal diameter narrowing, but clinicians should be familiar with aortic and RA velocities and waveforms to evaluate the validity of these interpretations. Generally, the higher the PSV, the more severe is the stenosis. However, a very blunted (tardus-parvus) RA waveform can represent critical RA stenosis in the absence of an elevated PSV. Renal artery duplex allows for serial testing, hence monitoring for progression and changes in kidney size. It is the preferred test for evaluating for restenosis of a stented RA segment. Duplex screening can miss accessory renal vessels.

Three-dimensional MRA with gadolinium enhancement provides excellent visualization of the arteries and functional information about the kidneys (Fig. 43.8). Limitations include interobserver variability, a tendency to overestimate degree of stenosis, interference by motion and breathing artifact, and limited sensitivity for middle and distal vascular lesions and small accessory vessels. Magnetic resonance angiography has

A

B

Fig. 43.8 Magnetic Resonance Angiogram With and Without Gadolinium Contrast Enhancement. (A) High-grade stenosis affecting the left inferior renal artery is evident, with functioning kidney tissue as reflected by gadolinium nephrogram (black arrow). Concerns about the role of gadolinium in the development of nephrogenic systemic fibrosis have greatly reduced the use of this contrast agent. (B) As a result, methods to image the vasculature without contrast material are being developed that produce excellent reconstructed images (white arrow).

the advantage of avoiding radiation exposure. The use of group II gadolinium-based contrast media is now considered safe for use in imaging in patients with AKI and advanced CKD or kidney failure with an extremely low incidence, if any, of nephrotoxicity or nephrogenic sclerosing dermopathy.[43]

In CTA with vascular reconstruction, imaging definition is nearly equal to that of conventional angiography but requires significantly more contrast, usually 100 to 125 mL. Focal vascular calcification often obscures accurate assessment of stenoses. Computed tomographic angiography is highly sensitive for identifying lesions in the mid and branch vessels often associated with FMD and is the recommended screening test for these patients based on recent consensus recommendatons.[8]

Angiography remains the gold standard for defining the degree of stenosis and is the most reliable modality for identifying distal and branch or small vessel disease, which may be missed by other screening modalities. Aortography provides the opportunity to perform intravascular ultrasound to assess lesions and for the measurement pressure gradients across a stenosis, an aid in determining the hemodynamic significance of a lesion. When there is complete proximal arterial occlusion, direct aortography can identify distal reconstitution by collaterals and a renal "blush" confirming parenchymal viability. Limited selective renal angiography can be performed with as little as 10 mL of contrast. In cases at highest risk for contrast-induced AKI, carbon dioxide can be used instead of nonionic iodinated contrast.

In cases of unilateral RA disease, captopril renography provides functional information regarding the size and excretory capacity of the kidney and demonstrates the rate of isotope appearance as an index of renal blood flow and filtration. It detects the presence of a differential role of Ang II on GFR between the kidneys. This test has a high negative predictive value for the presence of RVH when completely normal.44 It is less specific in the setting of intrinsic kidney dysfunction.

Renal vein renin measurements may help predict the BP response to renal revascularization. Previous studies indicated that lateralization of RV levels (>1.5:1 stenotic-to-nonstenotic kidney ratio) predicts a favorable BP response for more than 90% of patients. Because failure to lateralize also carries a favorable response in almost half of patients, the negative predictive value is limited. Some clinicians use these measurements to verify lower renin levels in the pressor (i.e., nonstenotic) kidney before undertaking nephrectomy.

TREATMENT OF FIBROMUSCULAR DYSPLASIA AND ATHEROSCLEROTIC RENOVASCULAR DISEASE

Medical and Endovascular Treatments

Fibromuscular dysplasia of hemodynamic significance should be treated with revascularization. Current consensus defines significance as having a translesional pressure gradient of 10% of the mean aortic pressure. The treatment of choice for FMD is percutaneous renal artery angioplasty (PTRA). Stenting is not recommended and is reserved as a rescue procedure for complications of PTRA such as dissection. Successful PTRA results in disruption of the abnormal collagen bands in the lumen of the artery and the vascular wall leading to larger lumen diameter and less turbulent RA blood flow. Complete cure, defined as normalization of BP without the need for medications, occurs in 35% to 45% of cases. In more than 85% of cases treated with PTRA, BP is improved with reduction in the number of antihypertensive medications.45 Predictors of response to intervention include lower preintervention systolic BP, younger age at treatment, shorter duration of hypertension, and a positive pretreatment captopril renogram.46 Primary technical success rates exceed 90%. Inadequate initial treatment or restenosis has been reported in up to 34% of treated cases and is most common with multifocal variant. Subsequent procedures to address all areas of stenosis may be required. Use of intravascular ultrasound to guide endovascular treatment of these lesions can improve treatment success. When FMD is associated with aneurysmal dilations greater than 1.5 cm in diameter, surgical revascularization or endovascular exclusion using a covered stent may be required. Women of childbearing age with RA aneurysms should be treated before pursuing pregnancy because of the risk for rupture during pregnancy or delivery. Other recommended treatments for patients with FMD are antiplatelet agents and smoking cessation.

The optimal treatment of atherosclerotic RA stenosis presenting with RVH or other clinical syndromes is controversial. Primary percutaneous renal artery stenting (PTRS) became standard treatment in many centers during the mid to late 1990s. Target vessel patency rates using PTRS regularly exceed 95%. Between 1996 and 2005, enthusiastic application of PTRS in the treatment of atherosclerotic RA stenosis led to a marked rise in stent placement in these patients. Most case series and observational studies reported stabilization of BP and renal function in half of patients undergoing PTRS, improvement in up to 25%, and a decline in kidney function after PTRS in 25%.

The relative effectiveness of endovascular treatment of atherosclerotic RA stenosis compared with medical therapy has now been studied in several randomized controlled trials. These are summarized in Table 43.1. The two largest trials, the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), comparing medical therapy and stenting to medical therapy alone, demonstrated no differences in the primary endpoints between groups.47,48 In the ASTRAL trial, 806 subjects with hypertension, many with CKD, were randomized to PTRS versus medical therapy and followed for a mean of 33.6 months. Of the enrolled patients, 53% had bilateral RA stenosis; the mean degree of luminal narrowing was 75.5%. The ASTRAL trial reported no difference in the primary endpoint of change in kidney function as measured by reciprocal creatinine. Investigators in the CORAL trial enrolled 947 patients, all treated with well-defined medical therapy addressing all cardiovascular risk factors, used RAAS blockade as the cornerstone of antihypertensive therapy, and randomized half the group to medical therapy plus stent. The CORAL trial had an imaging oversight laboratory and allowed enrollment based on angiographic as well as CTA, MRA, and duplex ultrasound definition of RA stenosis greater than 60%. At a median of 43 months of follow-up, there were no differences in the composite endpoint of mortality, cardiovascular and renal events, or any of the individual components between the treatment groups.

Current consensus is that the initial treatment of patients with RVH and stable CKD associated with atherosclerotic RA stenosis should be a focused medical management approach to addressing all cardiovascular and renal risk factors in addition to hypertension. In CORAL, there was no difference in number of medications required to control BP between groups. For those patients with diabetes and CKD, attention to achieving hemoglobin A1C, as well as CKD mineral bone disease and anemia targets, are important therapeutic goals. Statins are recommended in these patients both for cardiovascular risk reduction and with the goal of slowing progression of the RA lesion; there are also experimental data suggesting that statins attenuate kidney parenchymal injury associated with atherosclerotic renovascular disease.49,50

Whether all patients with RA stenosis should be treated with RAAS blockade remains controversial. There is a risk for RAAS blockers to induce AKI, and this risk is higher in patients with bilateral RA stenosis or stenosis to a single functioning kidney. Although the unique properties of RAAS blockers allow more effective BP control in patients with RVH, there is the potential for early loss of filtration pressure in patients with critical RA stenosis.

Clinical experience with RAAS blockers in the treatment of RVH is reassuring. Registry data and prospective follow-up studies in patients with atherosclerotic RA stenosis indicate that blockade of the RAAS is usually well tolerated.51,52 In the CORAL trial, in which 20% of patients had bilateral RA stenosis, most patients received an angiotensin receptor blocker or angiotensin-converting enzyme (ACE) inhibitor. The lack of differences in kidney endpoints suggests that this was generally well tolerated. However, it is strongly advised that patients with atherosclerotic RA stenosis who are prescribed these agents have electrolytes and creatinine measured within 2 to 4 weeks after starting these agents and regularly over the course of follow-up.

Indications to Consider Kidney Revascularization in Atherosclerotic Renal Artery Stenosis

Despite the lack of randomized controlled data and the risks, some high-risk patients may benefit from RA revascularization when medical therapy falls short.53 Indications to consider revascularization are listed in Box 43.6. First, uncontrolled hypertension, despite all efforts

TABLE 43.1 Randomized Controlled Trials Comparing Medical Therapy to Medical Therapy With Renal Artery Stenting for Renal Artery Stenosis

Study	ASTRAL (2009)	STAR (2009)	CORAL (2014)
Cohort	Hypertension	Hypertension and CKD	Hypertension and/or CKD
Entry BP	No BP threshold required	BP <140/90 mm Hg and stable for 1 month and eGFR <80 mL/min	SBP >155 mm Hg on two or more medications or eGFR <60 mL/min
Stenosis	>50% by MRA, CTA, angiography	>50% by MRA, CTA, or angiography	>60% by MRA, CTA, angiography, DUS
Excluded	Clinician certain patient would benefit from stent or require stent within 6 months	Malignant hypertension Pulmonary edema with bilateral RA stenting Intolerance to ACEI/ARBs as evidenced by >20% drop in CrCl	Entry creatinine >4 mg/dL Kidney length <7 cm
% Stenosis	75.5 mean %	NA	67.3%/66.2%
CKD			

Mean creatinine 2.0 mg/dL

Mean creatinine 1.7 mg/dL

Mean eGFR 58 mL/min/1.73 m2

% Bilateral

53.5%

47.9%

22%

Subjects per arm
(N/N)

403/403

76/64

459/472

Follow-up

33.6 months

24 months

43 months

Treatment

Stent

Stent

Stent

Medical treatment

At discretion of sites BP control with
or without ACEI or ARB
No specified target BP

BP target <140/90 mm Hg
ACEI/ARB last resort
ASA
Statin
Smoking cessation counseling

BP target <140/90 mm Hg
130/80 mm Hg for DM and CKD
ACE/ARB first-line
ASA
Statin goal LDL <70 mg/dL
Hb A1c <7.0% for DM
Smoking cessation counseling

Endpoint

Rate of progression of CKD based on
reciprocal creatinine over time

≥20% decrease in CrCl

Composite cardiovascular and renal events

Outcome

No significant difference

No significant difference

No significant difference

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; ASTRAL, Angioplasty and Stent for Renal Artery Lesions; BP, blood pressure; CKD, chronic kidney disease; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; CrCl, creatinine clearance; CTA, computed tomography angiography; DM, diabetes mellitus; DUS, Doppler ultrasound; eGFR, estimated glomerular filtration rate; HbA1c hemoglobin A1c; LDL, low-density lipoprotein; MRA, magnetic resonance angiography; NA, not applicable; N/N, number of subjects in each arm; RA, renal artery; SBP, systolic blood pressure; STAR, Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function.
Data from Postma CT, van Oijen AH, Barentsz JO, et al. The value of tests predicting renovascular hypertension in patients with renal artery stenosis treated by angioplasty. Arch Intern Med. 1991;151:1531–1535; Ritchie J, Green D, Chrysochou C, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis. 2014;63(2):186–197; and Weinreb J, Rodby RA, Yee J, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2021;298:28–35.

Clinical Indications to Consider Renal Artery Revascularization

BOX 43.6

- Worsening kidney function due to IRD
- Uncontrolled hypertension failing medical therapy
- Intolerance to medical therapy
- Recurrent hospitalizations for pulmonary edema without other obvious cause while on optimal medical therapy
- Other unstable cardiac or renal trajectories
- Progressive renal atrophy (controversial)
- Potentially reversible dialysis dependence due to IRD

IRD, Ischemic renal disease.

to optimize pharmacologic and dietary interventions and to enhance adherence, should prompt evaluation for all potential causes of resistance. Blockade of the RAAS should be included in the antihypertensive regimen in these resistant cases. Some patients will be intolerant of the very medications they need to control BP. Others may present with

hypertensive urgency or emergency despite therapy. Some of these patients may respond to PTRS. Second, when RA stenosis critically reduces glomerular capillary pressure such that there is a rapid decline in GFR, renal revascularization may improve kidney function and avoid the need for dialysis. In these cases, there are often multiple other potential contributors to declining GFR that must be considered. Given the need to balance the potential risks and benefits of intervention, input from a multidisciplinary team including nephrologists, vascular surgeons, and interventionalists is often helpful. In one series, PTRS in dialysis-dependent patients with ARVD led to enough improvement in kidney function to allow for discontinuation of dialysis.54 Finally, some patients with recurrent hospitalizations for decompensated heart failure or flash pulmonary edema that is attributed to medically resistant RA stenosis may benefit from RA revascularization.53

Fig. 43.9 outlines a proposed clinical algorithm for managing patients with atherosclerotic RA stenosis.

For patients who undertake PTRS, surveillance for in-stent RA stenosis should be undertaken based on changes in either control of BP or kidney

Evaluation and Management
of Atherosclerotic Renovascular Disease
Clinical syndrome
suggestive of renovascular disease
- Hypertension (see text)
- Ischemic renal disease

Stable kidney function
BP control

No

? Progressive disease
? Total renal mass
Comorbid risk: life expectancy
? Working kidney function

Noninvasive imaging
Duplex ultrasound
CTA/? MRA
Yes

No

Optimize medical therapy
RAAS blockade
with ACEI/ARB,
statin therapy,
smoking cessation, aspirin

? Bilateral disease
? High-grade stenosis
? Progressive
Working kidney function
Yes
Endovascular:
stent (atherosclerosis)

OR

Surgery:
complex disease
Failed stent
Aortic disease

? BP/creatinine rise
Re-image: ? Restenosis
Follow-up imaging
(e.g., Doppler) to
look for progression
Goal: stable kidney function,
excellent BP control

Fig. 43.9 Algorithm for the Management of Renal Artery Stenosis. The intensity of imaging and revascularization depends on both the level of kidney function and the blood pressure (BP), in addition to the comorbid disease risks for the individual patient. The overall goal should focus on stable kidney function and BP levels. As with any other vascular disease, monitoring for disease progression and recurrence is an

important element of long-term management. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; RAAS, renin-angiotensin-aldosterone system.

function. In-stent stenosis remains a significant complication occurring in up to 33% of cases and can occur at any time after stent placement, with the highest risk within the first year after primary PTRS.55 Patients with RA stents should be followed closely at regular intervals for this complication, which can be treated to prevent occlusion. An example of stent fracture as a cause of RA thrombosis and infarction is demonstrated in Fig. 43.10.

Clinicians should inform patients with atherosclerotic RA stenosis about the risk and uncertain benefits of PTRS.

Surgical Renal Revascularization

Before the introduction of endovascular techniques, surgical revascularization was the standard treatment for patients with ARVD and inflammatory biomarkers. Other studies looking at administering VEGF and strategies to mitigate mitochondrial dysfunction in models of ARVD have also shown promising results.59

Renovascular Disease in the Renal Transplant

Fig. 43.10 Thrombosis of Renal Artery Complicating Renal Artery Stenting. Right and left renal artery stents. The left renal stent (arrow) is triangular, indicating crimping of the proximal portion, which in this patient was associated with thrombosis of the renal artery, seen here as no contrast entering the vessel. The right renal stent is patent.

RVH. Such procedures carry considerable risk, cost, and morbidity. As a result, surgical intervention for renovascular disease is generally reserved for patients who do not respond to best medical and endovascular therapy or who have associated aortic disease that is not amenable to endovascular therapy. Despite these caveats, successful surgical revascularization in well-selected cases provides durable restoration of kidney blood supply with good long-term patient survival.56 Overall, the effects of surgical revascularization on BP and renal function response in patients with atherosclerotic RA stenosis mirror those for PTRS. Surgical revascularization in the modern era may provide more durable patency than PTRS with lower complication rates and risk for restenosis.

Surgical revascularization should be considered in patients with total occlusion of the RA and abrupt loss of GFR for retrieval of kidney function. Some dialysis-dependent patients and some with advanced CKD with ARVD experience recovery of kidney function after revascularization.57 Treatment involves assessment of the risks versus potential benefits of heroic revascularization procedures. The status of the contralateral kidney and overall residual kidney function should be weighed against the potential retrievable function from the underperfused kidney, as well as the perioperative risk associated with surgery. Predictors of GFR recovery with revascularization in the setting of critical RA occlusion include preserved kidney size, evidence of a renal blush or nephrogram by imaging, recent decline in GFR, and recent baseline creatinine concentration less than 3 mg/dL.58

When a poorly functioning atrophic kidney causes RVH refractory to optimal medical therapy including RAAS blockade, nephrectomy of this pressor kidney may improve BP control with minimal impact on total GFR.

Atherosclerotic Renal Vascular Disease: Beyond the Stenosis

The recognition that ARVD or IRD is more than a hemodynamic disorder has led to early investigation into targeting the inflammatory ischemic-reperfusion and vascular rarefaction aspects of this form of kidney disease. Early studies suggest that intraarterial infusion of autologous mesenchymal stem cells increase tissue oxygenation, blood flow, and GFR in poststenotic kidneys, with associated reduction in

Recognition of vascular complications of renal transplantation can prolong allograft survival. Early posttransplant, RA, and vein stenosis or thrombosis are rare but treatable complications.

Renal artery thrombosis occurs in about 0.4% of transplants within minutes to hours after transplantation. Causes include hyperacute rejection, kinking of the RA, anastomotic arterial occlusion, or intimal flap. It has also been reported associated with decubitus positioning. Transplant RV thrombosis is more common, occurring in 5% of adult transplants and 8.2% of pediatric cases, usually within the first 5 days after transplantation, and is more common with right kidney donation. It usually leads to graft infarction, but rupture of the allograft can occur. Risk factors include donor age over 60 years, donor artery atherosclerosis, and longer allograft cold ischemia time. Recipient risk factors include age younger than 6 years or older than 50 years, hypovolemia in the perioperative period, multiple RVs, DM, technical or surgical complications, and prior peritoneal dialysis. When thrombotic vascular complications occur without obvious cause, an evaluation for hypercoagulable state is recommended. There are some data supporting the protective effects of low-dose aspirin in this population. Renal salvage is possible with early diagnosis, surgical exploration, and thrombectomy.

The most common posttransplant vascular complication is transplant RA stenosis, which occurs between 3 months and 2 years posttransplantation and accounts for about 5% of all posttransplant hypertension. The incidence ranges from 1.3% to 23%, depending on the screening tests used.60 In many cases, anastomotic stenoses are not hemodynamically significant. Renal artery stenosis is more common in deceased donor transplants than in living donor transplants and in allografts with multiple renal vessels. The use of pediatric kidneys in adult recipients is associated with a higher rate of stenosis because of greater turbulent flow from mismatch between donor and recipient vessel size.

The cause for transplant RA stenosis is usually intimal scarring and hyperplasia in response to trauma to the vessel during harvesting or anastomotic stenosis, which is most commonly associated with endto-end anastomoses and may be related to suture technique. In end-toside anastomoses, stenosis is typically postanastomotic, suggesting that turbulence or other hemodynamic factors play a role. Immunologic causes of transplant RA stenosis have been proposed on the basis of histologic similarities with chronic vascular rejection and association with prior acute rejection. In addition, de novo class II donor-specific antibodies have been associated with postanastomotic stenosis.61 Other possible pathogenic mechanisms include atherosclerosis of the donor artery, calcineurin inhibitor toxicity, and cytomegalovirus infection. External compression on the transplant artery by large native polycystic kidneys or pseudoaneurysms have also been reported causes. Renal artery stenosis occurring many years after transplantation most often represents atherosclerotic disease. As the transplant population ages, there has been increasing recognition of another subset of patients with pseudo-transplant RA stenosis, in which atherosclerotic vascular disease proximal to the allograft artery, particularly involving the iliac vessel, results in reduced kidney perfusion.

Patients typically present with new-onset or worsening hypertension with or without kidney dysfunction. An example of the 1-clip–1-kidney Goldblatt model, transplant RA stenosis often presents with fluid retention and even flash pulmonary edema. Often, a two-component RA bruit can be heard over the allograft.

Pseudo-transplant RA stenosis, which is suprarenal iliac artery stenosis, often presents with ipsilateral lower extremity claudication along with hypertension and worsening allograft function. Risk factors for the development of transplant RA stenosis include older donor age and extended criteria donor and recipient male sex, DM, hyperlipidemia, smoking, ischemic heart disease, and elevated serum creatinine at discharge from transplantation.62

Renal duplex ultrasound is the initial screening test for transplant RA vascular complications, with the sensitivity and specificity ranging from 90% to 100% and 67% to 100%, respectively, depending on parameters and cut-off values. Compared with native renal arteries, data show that PSVs are often higher at the anastomosis even without stenosis due to the angle at the anastomosis, with 26% of normal transplant RAs having a PSV greater than 250 cm/sec at 9 months posttransplant.63 Using a combination of a PSV greater than 300 cm/sec, acceleration time of more than 0.1 second, and the presence of poststenotic spectral broadening (indicative of turbulent flow), the probability of stenosis approaches 99%.64 Magnetic resonance angiography provides excellent anatomic definition of the transplant RA. It may be associated with clip artifact at the anastomosis. Non–contrastenhanced MRA has emerged as a good option for visualizing the iliac artery and the transplant arteries.65 Computed tomographic angiography is comparable to renal arteriography but requires more contrast. Carbon dioxide angiography can allow for visualization and successful treatment using as little as 9 mL of iodinated contrast.66

Percutaneous renal artery angioplasty with or without stenting is often the initial approach to transplant RA stenosis, with success rates of 90% for technical outcomes and 66% to 94% for clinical outcomes (BP and kidney function improvement) and a complication rate of 9.9% including vessel dissection, thrombosis, and site hematoma.67 Restenosis rates are higher after primary PTRA (18.9%) versus stenting (9.1%). Long-term outcomes for transplant patients treated for transplant RA stenosis are reported to be equal to those without this complication.68 Surgical renal revascularization of allografts is difficult and associated with high complication rates. Extensive fibrosis develops around the allograft and often involves the renal vessels, making surgical access to the renal vessels risky. Historically, complications include graft loss (in 15%–30% of cases), ureteral injury (14%), and death (5%). A recent small study of 10 cases requiring surgery for transplant RA stenosis or occlusion reported better patient and longterm graft outcomes.69

KIDNEY INFARCTION

Kidney infarction represents a distinct clinical syndrome associated with abrupt loss of blood flow to kidney parenchyma. Small areas of the cortex or medulla or the entire kidney may be affected. Autopsy series suggest the incidence is between 0.5% and 1.5%, with incidences reported from emergency department series at 0.004% to 0.007%, indicating that this diagnosis is often missed.70 Bilateral renal infarction is reported in up to 20% of cases. The clinical presentation of kidney infarction mimics that of more common disorders, such as kidney stones, pyelonephritis, and muscle strains. A high clinical suspicion is needed to pursue the diagnosis.

Risk factors associated with kidney infarction include preexisting hypertension, cigarette smoking, arrhythmias (especially atrial fibrillation), hyperlipidemia, structural heart disease, prior embolic events, and diabetes.

The most common symptom is loin, flank, or abdominal pain, occurring in over 95% of cases. Transient RVH occurs in about 50% of cases. Nausea and/or vomiting are present in up to 45% of cases. However, nearly 25% of cases are asymptomatic, identified only by

BOX 43.7

Causes of Renal Infarction

Renal Artery Thrombosis

Spontaneous
- Renal artery atherosclerosis or fibromuscular dysplasia
- Renal artery or aortic dissection
- Renal or aortic aneurysms

Traumatic
- Postprocedure
- Endovascular stents
- Renal transplantation
- Hypercoagulable disorders
- Malignancy
- Antiphospholipid syndrome
- Renal artery vasculitis
- Vascular rejection
- Thrombotic microangiopathies
- Genetic
- Ehlers-Danlos vascular variant

Renal Embolism
- Atrial fibrillation
- Cardiac mural thrombi
- Valvular heart disease
- Paradoxical embolism
- Tumor or fat embolism
- Atheroemboli

Renal Vein Thrombosis
- Nephrotic syndrome
- Post–kidney transplantation
- Traumatic

enhancement or functional defects on kidney imaging. Laboratory abnormalities include elevated lactate dehydrogenase levels in over 90% of cases, with leukocytosis and elevated inflammatory markers such as C-reactive protein in up to 78% of cases, and may last up to 30 days from presentation. Microhematuria and proteinuria are present in 20% to 60% of cases.71

Acute kidney injury frequently accompanies kidney infarction, reported in between 11.1% and 64.7% of cases. When bilateral occlusion of the RAs or infarction of a single functioning kidney occurs, the patient may present with oliguric or anuric AKI. The development of CKD after kidney infarction has been reported in between 6% and 44% of cases.72

Computed tomography with intravenous contrast is the imaging modality of choice for the diagnosis of renal infarction. Findings include focal wedge-shaped areas of decreased attenuation or global infarction with or without a rim sign indicating intact collateral circulation. Perinephric stranding is common. Simultaneous infarcts in the liver and spleen occur in 10% to 15% of cases. Other potential imaging techniques include MRA with gadolinium or nuclear scintigraphy with dimercaptosuccinic acid.

Causes of kidney infarction are listed in Box 43.7. Common causes include RA embolism from a cardiac source, arterial injury from dissection, trauma, or complications of endovascular procedures, and hypercoagulable or prothrombotic factors. In approximately 18.4% of cases, no cause is found.73 In a review of over 186 patients with renal infarction, a RA lesion (atherosclerotic, dissection, hematoma, or FMD) was the cause in over 81.2% of cases, with emboli accounting for only 9.1%.[74] Spontaneous RA thrombosis or dissection can lead to RA occlusion. Spontaneous RA dissection has a male predominance, with a 4:1 male-to-female ratio and average age of onset in the mid 40s. Renal infarction secondary to traumatic RA injury occurs in 1% to 4% of all nonpenetrating abdominal trauma associated with deceleration injury and direct blunt trauma to the loin or flank regions.

Evidence of lumbar vertebral injury should raise suspicion in the emergency department for renovascular trauma. Traumatic renal vascular occlusion often leads to kidney infarction within 3 to 6 hours. The success rate for revascularization of traumatic RA thrombosis remains low, even when diagnosed early.[75]

Emboli to the right and left RA occur with equal frequency, with 12% of cases being bilateral. Atrial fibrillation, cardiac thrombus after myocardial infarction, atrial myxoma or other cardiac tumors, endocarditis, paradoxical emboli, and aortic thrombus are the most common conditions associated with embolic kidney infarction. Atrial fibrillation is the most common cardiac cause with the highest risk during the first year after the onset and when anticoagulation is subtherapeutic.[76] When echocardiography is performed, cardiac thrombus is rarely detected. There is a 30-day mortality rate of 10% to 13% after renal infarction, due to atrial fibrillation. Other sources of emboli to the kidneys include fiber related to cardiac bypass, gel foam due to embolization procedures, calcium from valve annuli, and even “bullet emboli” in the setting of trauma. Paradoxical RA embolism may occur in patients with right-to-left cardiac shunts, most commonly due to atrial septal defects present in 9% to 35% of the general population. The diagnosis requires clinical, angiographic, or pathologic evidence of systemic embolization and an abnormal communication between the right and left circulations with a favorable pressure gradient (typically diagnosed by “bubble” echocardiography) for the passage of a clot from the right to the left side of the heart. The presence of source of venous thrombus should be sought.

Less common causes of infarction include hypercoagulable states, inflammatory diseases of the retroperitoneum, thrombotic microangiopathies, and RA vasculitis or vasospasm. Antiphospholipid antibody syndrome is associated with both arterial and venous thrombotic events and is the most common cause of spontaneous arterial thrombosis.[77] Rare causes of kidney infarction include autoimmune diseases and drug abuse, such as intravenous injection or nasal insufflation of cocaine or even marijuana smoking. During the COVID-19 pandemic, several reports of kidney infarction due to COVID-19-associated hypercoagulability emerged.[78]

Aortic dissection can compromise renal blood flow and cause kidney infarction. Aortic dissection occurs most commonly in association with atheromatous vascular disease of the thoracic aorta, but it can occur in collagen disorders, such as Ehlers-Danlos type IV or Marfan syndrome, and with arteritis, such as Takayasu arteritis.

Kidney infarction can be a complication of endovascular procedures. Endovascular aortic stents commonly used to treat abdominal aortic aneurysms can compromise flow to main or accessory RA orifices.[79,80] Increasingly, fenestrated or branched covered stent grafts have been designed to allow for preservation of branch visceral vessels. Accessory RAs supplying less than half of the kidney may be intentionally sacrificed during these procedures in up to 25% of cases. When this occurs, up to 75% of patients will experience renal infarction postprocedure. In some reports, this is associated with significant decline in eGFR at 3 years.[81] Furthermore, RA stents are usually placed through fenestrations with a goal of preserving RA flow. Renal artery occlusion can complicate these procedures with development of occlusion or stenosis in up to 30% of cases by 4 years postprocedure. The aortic graft and branch stents alter the natural RA motion during the cardiac cycle, and kinetic forces over time can result in RA stent fracture or kinking, leading to vessel occlusion. Aortic stent graft migration and endoleaks can also impair RA inflow.82

Treatment of kidney infarction is usually conservative and includes pain control and treatment of associated RVH. If RA occlusion is caused by thrombosis associated with a hypercoagulable state or an embolism from a central source, systemic anticoagulation is indicated, and consideration should be given to thrombolytic therapy. Anticoagulation for idiopathic renal infarction is controversial. Echocardiography is indicated to seek intracardiac or aortic arch thrombi and valvular abnormalities. Emergent endovascular recanalization of thrombosed stents associated with fenestrated aortic grafts can sometimes be successful in averting global kidney infarction.

ATHEROEMBOLIC KIDNEY DISEASE

Atheroembolic kidney disease describes a subacute kidney injury due to occlusion of small arteries and arterioles by cholesterol emboli. It is estimated to account for up to 10% of unexplained kidney failure in the elderly, with 7% of renal biopsies in a large study of patients with AKI over 60 years of age showing histologic findings of atheroembolism.83

Atheroembolism may occur in up to 30% of patients with extensive aortic atherosclerosis after endovascular interventions. The incidence of atheroembolism after cardiac catheterization is estimated near 1.4%.84 Furthermore, studies using filters to capture embolic material confirm that PTRA and PTRS release thousands of atheromatous particles of various sizes in 70% to 100% of cases.85 Preprocedural treatment with antiplatelet agents and intraprocedural use of embolic protection devices may reduce the burden of embolic atheromata.86 However, use of distal protection devices can be particularly challenging in the RAs due to shorter length and bifurcations.

Risk factors for atheroembolic disease include older age, male sex, cigarette smoking, diabetes, hypertension, and hyperlipidemia. Atheroembolic disease is iatrogenic in 70% of cases, that is, associated with arterial intervention such as angiography, cardiovascular surgery, thrombolytic therapy, or anticoagulation. Spontaneous aeroembolism may occur in patients with extensive atherosclerosis and unstable plaque.

Acute or subacute reduction in eGFR caused by kidney microinfarctions developing as long as 6 months after the atheroembolic insult is the most common presentation leading to the diagnosis. It is important to differentiate atheroembolic from thromboembolic disease. Atheroembolic particles originate from upstream unstable atherosclerotic plaque and cause downstream partial occlusion of small vessels. The cholesterol cleft induces a foreign body reaction leading to an interstitial inflammatory response and subacute kidney injury.

The clinical picture is multisystemic and involves the kidneys in about 75% of patients. If a large atheroembolic shower induces significant renal tubular damage, the resulting AKI may manifest with an oliguric phase characterized by a high fractional excretion of sodium. More often, the kidney failure is nonoliguric, slowly progressive, often with a stair-stepping subacute course. Some patients will have only moderate impairment in GFR, whereas others progress to kidney failure.87 Urinalysis findings are nonspecific but may include mild proteinuria, microhematuria, pyuria, and eosinophiluria. Renin release by ischemic zones in areas of embolization can lead to labile hypertension early in the course, sometimes associated with transient marked proteinuria. Fever, often low grade, is characteristic.

Although the kidneys are the organs most commonly involved, extrarenal cholesterol embolization may provide clues to aid in the diagnosis. Eosinophilia and hypocomplementemia commonly occur in the acute phase, reflecting immunologic activation.88 Cutaneous findings are seen in up to 60% of patients during initial presentation.

Fig. 43.12 Cholesterol Emboli in Kidney Biopsy Specimen. Biconvex cholesterol clefts with giant cell reaction (asterisks) and recanalization of the lumen of a medium-sized renal vessel. (Periodic acid–Schiff stain.) (Courtesy Dr. R. Horn, Vanderbilt University, Nashville, TN.)

Fig. 43.11 Livedo Reticularis. The mottled skin changes associated with peripheral cholesterol embolization may be seen over the legs, buttocks, back, or flank and may be transient.

These findings include blue or purple toes, mottled serpiginous rash (livedo reticularis; Fig. 43.11), petechiae, and purpura or necrotic ulceration in areas of skin embolization, such as the lower back, buttocks, lower abdomen, legs, feet, or digits.

Other organs often involved include the spleen (55% of cases), pancreas (52%), gastrointestinal tract (31%), liver (17%), and brain (14%). Symptoms associated with extrarenal atheroembolic disease include abdominal or muscle pain, nausea, vomiting, ileus, gastrointestinal bleeding, ischemic bowel, hepatitis, angina, Hollenhorst plaques, and visual and neurologic deficits.

Atheroembolic kidney disease should be suspected when subacute kidney failure develops after a vascular intervention in the presence of livedo reticularis. Many laboratory abnormalities indicative of tissue injury are often present, including elevated erythrocyte sedimentation rate (97% of cases), elevated serum amylase (60%), leukocytosis (57%), anemia (46%), hypocomplementemia (especially low C3) (25%–70%), and elevated lactate dehydrogenase and creatine kinase (38%–60%). Peripheral eosinophilia, which may be transient, is seen in up to 57% of patients. The presence of eosinophilia should raise suspicion for atheroembolic renal disease in the appropriate clinical setting. Definitive diagnosis is made by biopsy of an involved organ. A skin or muscle biopsy in an involved area may preclude the need for kidney biopsy. However, tissue biopsy is usually unnecessary when the classical clinical triad is present: precipitating event, subacute kidney injury, and typical skin findings.

If clinical or other pathologic evidence has not secured the diagnosis, kidney biopsy may be helpful. Diagnosis is based on the presence of birefringent, biconvex, elongated cholesterol crystals or biconcave clefts within the lumina of small vessels left behind in formalin-fixed tissue (Fig. 43.12). Due to the patchy nature of this disorder, openwedge kidney biopsy has a higher likelihood of successful diagnosis relative to a percutaneous approach because it allows visualization and direct sampling of areas of mottled cortex. In frozen sections of tissue, the cholesterol material can be identified with polarized light microscopy. The pathologic findings also may include intimal thickening and concentric fibrosis of vessels, giant cell reaction to the cholesterol particles, vascular recanalization, endothelial proliferation, tubulointerstitial fibrosis with both eosinophil and mononuclear cell infiltrates, glomerular ischemia, and even focal segmental glomerulosclerosis. In the kidney, the most commonly affected vessels are the arcuate and interlobular arterioles, leading to patchy ischemic changes distal to these vessels.

Atheroembolic kidney disease mimics other systemic disorders including vasculitis, infection, or thrombotic microangiopathy. Often these patients have undertaken procedures in which the differential diagnosis would include contrast nephropathy, acute tubular necrosis, renal infarction, or renal infarction. Peripheral eosinophilia and, in some cases, eosinophiluria, rash, fever, and reduced eGFR can be seen associated with acute interstitial nephritis. Chronic Cholesterol embolization syndrome may appear similar to hypertensive nephrosclerosis or IRD. In the kidney transplant recipient, kidney atheroembolism may mimic acute rejection or chronic allograft nephropathy.

The natural history is determined by the extent of organ involvement and the degree of the embolization. In one series of cases, eGFR declined rapidly in 29%, with a slower progressive course seen in 61%.87 Among the latter group, the decline in eGFR was thought to result from a combination of cholesterol embolization and ARVD.

Patients also may manifest acute or subacute reductions in eGFR followed by partial recovery. Conversely, the outcome can be dismal, particularly when cerebral embolization occurs or when there is a large unstable atheromatous burden. Some patients with cholesterol embolization may develop kidney failure.89

There is no specific therapy for atheroembolic disease; treatment is supportive and focused on secondary prevention. As such, statins, aspirin, BP control, smoking cessation, and glycemic control are helpful measures in the prevention of atherosclerosis.

Prevention remains the most effective management strategy.

Patients with extensive aortic atherosclerosis should be considered for alternative approaches to cardiac catheterization, for example, such as through the brachial artery. Once the diagnosis of cholesterol embolization has been established, further endovascular interventions should be avoided. When clinical factors dictate the need for aortic, renal, or peripheral arterial surgery, optimal timing and surgical approach are critical. Conversely, there is a growing surgical experience with segmental aortic replacement to remove the source of emboli, particularly when atheroembolic disease occurs spontaneously. Transesophageal echocardiography is often used to identify mobile ulcerative plaque in the aorta to guide intervention.

Angiotensin-converting enzyme inhibitors are effective in managing the labile hypertension seen early in the course. Corticosteroids have been used with some success in patients with atheroembolic disease and associated inflammatory symptoms.90 Several reports note stabilization of skin signs of cholesterol embolization after administration of statins.91 Because anticoagulation has been associated with atheroembolic disease, it is recommended to avoid anticoagulation in the acute phase. Although direct causality between anticoagulants and cholesterol embolization has not been established, the proposed mechanism is that anticoagulants prevent thrombus organization over the ulcerative plaques.

RENAL VEIN THROMBOSIS

Renal vein thrombosis is rare in adults most often associated with nephrotic syndrome, kidney tumors, hypercoagulable states, and after surgery or trauma to the renal vessels. When it occurs, the diagnosis is often never considered.

Thrombosis of the longer left RV also may involve the ureteral, gonadal, adrenal, and phrenic branches that drain into the left vein, whereas on the right side, the adrenal and gonadal veins drain directly into the inferior vena cava. Because of the larger network of venous complexes, occlusion of the left RV results in enlargement of the systemic collateral vessels, which provides some protection against infarction, which is a rare complication of RV thrombosis on either side.

Experimentally, acute RV thrombosis is associated with immediate enlargement of the kidney, with a marked increase in RV pressure, leading to a significant decrease in renal arterial flow. Complications include hemorrhagic infarction, kidney rupture, and retroperitoneal hemorrhage.

Acute RV thrombosis is usually symptomatic with loin, testicular, or flank pain and even the development of scrotal swelling or hydrocele. The patient may present with fever, leukocytosis, and, in the setting of a single kidney or renal transplant, oliguric AKI. Acute RV thrombosis is associated with renal edema and swelling. Nausea and vomiting often accompany it, and symptoms might be confused with those of acute pyelonephritis. Hematuria is nearly universal and most often is microscopic. The high venous pressures result in a marked increase in proteinuria. Urinalysis sometimes reveals evidence of proximal tubule dysfunction, such as glycosuria. In some patients, RV thrombosis is diagnosed only after the patient has developed an acute pulmonary embolus and the source of the embolus is investigated or with worsening of eGFR in the setting of proteinuric CKD.

Chronic RV thrombosis may be asymptomatic. Extensive venous collaterals may allow for minimal impairment of kidney function and structure. Often, however, microhematuria, proteinuria, and evidence of reduced GFR or tubular dysfunction are present, particularly when indices of differential kidney function are sought, such as with nuclear studies. When RV thrombosis causes renal infarction, the distribution of the hypoperfused region tends to be medullary or subcortical. The hypoperfused areas also tend to be patchy and subtotal. These patients can develop severe hypertension acutely.92

The causes of RV thrombosis are listed in Box 43.8

The prevalence of renal vein thrombosis in nephrotic syndrome is unclear because it is largely undiagnosed; studies report frequencies from 5% to 62%.93 Numerous abnormalities promoting a prothrombotic state occur secondary to heavy proteinuria. It is interesting to note that RV thrombosis appears to be more common in membranous nephropathy and lupus nephritis but can complicate any cause of proteinuric kidney disease. In this setting, RV thrombosis can lead to an increase in baseline proteinuria and present with AKI superimposed on CKD.

BOX 43.8

Thrombosis

Causes of Renal Vein (RV)

- Malignant neoplasia
  - Direct invasion of tumor into the RV
  - Retroperitoneal adenopathy, fibrosis, or tumor compressing the RV
  - Extension of IVC obstruction by tumor invasion
  - Hypercoagulable state associated with malignant disease
- Complication of IVC filters
- Complication of PICC lines
- Nephrotic syndrome
  - Membranous nephropathy
  - Lupus nephritis
- Acute pyelonephritis
- Complicating inflammatory bowel disease
- Acute pancreatitis
- Inflammatory aortic aneurysm
- Neonatal
  - Congenital
  - Dehydration
  - Thrombophilia
  - Complication of umbilical vein catheterization
  - Transmission of maternal procoagulant factors
- Hypercoagulable states
  - Antiphospholipid antibody syndrome
  - Factor V Leiden mutation
  - Antithrombin III deficiency
  - Protein S and C abnormalities
  - Hyperhomocysteinemia
  - Elevated levels of clotting factors VIII, IX, and XI
  - Heparin-induced thrombocytopenia
  - Birth control pill
- Thrombophilia
- Chuvash polycythemia
- Post–renal transplantation
  - Acute rejection, OKT3
  - Vascular rejection
  - Compression or kinking of RV
  - Hypercoagulable disorders
  - Sticky platelet syndrome
  - Calcineurin inhibitors
  - Viral infection of the allograft
- Complication of surgical compression
  - After aortic aneurysm surgery
  - After pyeloplasty
  - After partial nephrectomy
- Traumatic RV thrombosis
- Pregnancy
  - Compression
  - Preeclampsia, eclampsia
- Complication of embolization of gastric varices
- Budd-Chiari syndrome
- Behçet disease

IVC, Inferior vena cava; PICC, peripherally inserted central catheter.

Pregnancy and the postpartum state are hypercoagulable states.

There have been reports of spontaneous RV thrombosis in the postpartum period associated with kidney infarction. Renal vein thrombosis complicating pregnancy should be suspected when clinical clues such as flank pain, proteinuria, and hematuria are present.

Malignancy accounts for the greatest number of cases of RV thrombosis.[94] It can result from invasion of a kidney tumor into the RV. About half of renal cell carcinomas are associated with RV thrombosis at autopsy. In addition, neoplasia originating in the RV or inferior vena cava (IVC), such as leiomyosarcoma or cavernous hemangioma, can cause RV thrombosis. Extrinsic compression of the RV by a tumor or retroperitoneal fibrosis also may cause this syndrome.

Diagnosis of RV thrombosis requires imaging. Conventional ultrasound may demonstrate alterations in size and echogenicity. Sonographic findings include kidney enlargement, loss of corticomedullary differentiation, and linear echogenicity radiating from the renal hilum as a result of interlobular and interlobar venous clot. Later scans may show linear, punctuate, or lace-like calcifications in these regions, representing calcified thrombi. Renal duplex ultrasound may show increases in resistive indices and can directly visualize the filling defect. In patients with renal transplant vein thrombosis, the duplex waveform pattern demonstrates reversal of diastolic flow.[95] Imaging of the RV by magnetic resonance or computed tomographic (CT) venography is needed to confirm thrombosis. In adults, these modalities have much greater sensitivity than RV duplex studies for the diagnosis. Fig. 43.13 is a CT venogram demonstrating unilateral RV thrombosis.

Treatment is controversial and depends on the setting, acuteness, and clinical consequences. If there is no contraindication, most patients are treated acutely with systemic anticoagulation. In adults with acute RV thrombosis that is compromising renal function, catheter-directed thrombolytic therapy with urokinase or tissue plasminogen activator with or without percutaneous mechanical thrombectomy can restore vessel patency.[96] The long-term benefit of this approach is unclear, and it is less successful when the thrombotic process begins in the small intrarenal venules rather than in the major veins, as is often the case when primary kidney disease or a hypercoagulable state initiates the process.

Surgical interventions include nephrectomy, thrombectomy, and retroperitoneal surgery for non–renal-associated abnormalities, such as tumor, retroperitoneal fibrosis, aortic aneurysm, and acute pancreatitis. Surgery tends to be reserved for situations in which the RV thrombosis results in hemorrhage from renal capsular rupture or for long-term consequences, such as hypertension or infection of a nonfunctioning kidney.

Fig. 43.13 Computed tomography venogram demonstrating left renal vein thrombosis (arrow). (Courtesy Dr. S. Rankin, Guy’s Hospital, London.)

A conservative approach may be favored when left RV thrombosis occurs because of the extensive collateral venous supply on that side, ultimately allowing venous drainage and delayed improvement in renal function. Systemic anticoagulation is indicated acutely to prevent extension of thrombus into the IVC and pulmonary emboli. Anticoagulation should be continued indefinitely in patients with a persistent hypercoagulable state.

Long-term kidney-related outcomes following RV thrombosis vary with the cause of thrombosis. When associated with membranous nephropathy, it has a more favorable outcome than with other causes. Normal kidney function prior to RV thrombosis is the most important prognostic factor.[97]

SELF-ASSESSMENT QUESTIONS

1. A 33-year-old White woman presents with hypertension that was

noted during a regular gynecologic check-up. During examination, you note she has equal BP in both arms, no radial-femoral delay, and a soft abdominal bruit. Which is the most appropriate screening test for the cause of her hypertension?

A. RA duplex ultrasound
B. CTA of renal arteries
C. MRA of renal arteries

2. A 76-year-old woman presents to you because her primary care doctor has had difficulty getting her BP controlled. She states she never had hypertension until about 4 years ago. She has a history of smoking one pack per day of cigarettes for 40 years. She had a femoral-popliteal bypass 2 years ago for claudication. Examination is notable for systolic BP of 180 mm Hg. She has a left carotid bruit audible. Her creatinine is 1.3 mg/dL and potassium is 3.4 mg/dL. A renal duplex ultrasound shows normal velocities in the left RA but a peak systolic velocity of 350 cm/sec in the proximal portion of the right RA. She is on the following antihypertensive medications: metoprolol 50 mg twice daily, amlodipine 5 mg/day, hydrochlorothiazide 25 mg/day, and atorvastatin 80 mg/day, and she is taking aspirin. What is the most appropriate next action?

A. Refer for RA stent
B. Start ACE inhibitor and follow BP response and potassium and creatinine closely
C. Refer to vascular surgery for RA bypass

3. A 32-year-old woman with lupus nephritis class V is currently being treated with induction therapy with mycophenolate mofetil 1500 mg twice daily and oral steroids. She continues to have proteinuria, and her last 24-hour quantitative protein concentration was 6 g. Fortunately, her creatinine has remained normal at 0.8 mg/dL. She presents to the emergency department with pleuritic chest pain. A ventilation/perfusion scan shows high probability for pulmonary embolism. On examination, you note that her creatinine is 1.4 and urine protein/creatinine is 30 g/g. She is started on anticoagulation therapy and admitted. Which of the following tests would you recommend the team order?

A. Antiphospholipid antibody
B. Renal vein Doppler study and renal ultrasound
C. CTA of pulmonary arteries
D. Both A and B

4. An 83-year-old woman presents with congestive heart failure and hypertension. She has a history of peripheral vascular disease and chronic kidney disease with a baseline creatinine of 1.5 mg/dL and

a single kidney because she donated one to her son with diabetic nephropathy 30 years earlier. She is admitted and treated with diuretics and achieves a net negative fluid balance of 6 L over 3 days. Her BP, which was 180/90 mm Hg on admission, is now 120/80 mm Hg. An echocardiogram shows left ventricular hypertrophy with diastolic dysfunction, preserved ejection fraction, and no valvular abnormalities. Over the past 24 hours, her creatinine has risen to 3.8, and she has produced almost no urine. She has no flank pain. Despite stopping her diuretics, her creatinine does not improve over the next 72 hours, and she is oliguric. She appears euvolemic and does not respond to empiric intravenous fluids for 24 hours. Her medications are reviewed, and she is receiving no nephrotoxic agents and all diuretics and antihypertensives are on hold. An ultrasound and Doppler examination show a blunted waveform concerning for possible critical RA stenosis. What test would be best to rule out critical RA stenosis?

A. MRA of RAs
B. CTA of RAs
C. Captopril renography
D. Peripheral renin level

5. A 62-year-old man with a history of hypertension presents with acute left-sided abdominal pain with no dysuria. Urinalysis shows hematuria without pyuria. He has a temperature of 99.8°F and a white blood cell count of 12,000. He is in new-onset atrial fibrillation. His creatinine is noted to be 1.3, which is above his recent normal level of 0.9 mg/dL 1 month previously. The kidneys appear normal on abdominal ultrasound. Which of the following tests is most likely to provide a diagnosis?

A. Echocardiogram
B. RA duplex ultrasound
C. CT with and without contrast

6. A 60-year-old White man with a history of hypertension and diabetes undergoes cardiac angiography with stent placement after presenting to the emergency department with symptoms consistent with unstable angina. Two weeks later, he is noted to have a rise in serum creatinine from a baseline of 0.8 to 1.3. Along with this rise, he is noted to have a slight increase in eosinophils on his complete blood count. On examination the patient is noted to have a serpiginous rash on the bilateral lower extremities to the level of the ankles. Which of the following is the likely cause for the acute kidney injury?

A. Cholesterol emboli
B. Contrast-induced nephropathy
C. Acute interstitial nephritis

REFERENCES

1. Shoja MM, Tubbs RS, Shakeri A, et al. Peri-hilar branching patterns and morphologies of the main renal artery: a review and anatomical study. Surg Radiol Anat. 2008;30:375–382.
2. Reginelli A, Somma F, Izzo A, et al. Renovascular anatomic variants at CT angiography. Int Angiol. 2015;34(6 suppl 1):36–42.
3. Textor SC. Pathophysiology of renovascular hypertension. Urol Clin North Am. 1984;11:373–381.
4. Crowley SD, Gurley SB, Oliverio MI, et al. Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system. J Clin Invest. 2005;115:1092–1099.
5. Cervenka L, Horacek V, Vanechova I, et al. The essential role of AT 1a receptor in the development of 2k1c hypertension. Hypertension. 2002;40:735–741.
6. Textor SC, Lerman LO. Renovascular hypertension and ischemic nephropathy: state of the art. Am J Hypertens. 2010;23:1159–1169.
7. Losito A, Fagugli RM, Zampi I, et al. Comparison of target organ damage in renovascular and essential hypertension. Am J Hypertens. 1996;9:1062–1067.
8. Gornick HL, Persu A, Adla D, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. Vasc Med. 2019;24(2):164–189.
9. Pasquini M, Trystram D, Oppenheim C, et al. Cervical and intracranial fibromuscular dysplasia. Presse Med. 2011;40(7–8):713–719.
10. Plouin P, Baguet J, Thony F, et al. High prevalence of multipole arterial bed lesions in patients with fibromuscular dysplasia: the ARCADIA Registry (Assessment of Renal and Cervical Artery Dysplasia). Hypertension. 2017;70(3):653–658.
11. Slovut DP, Olin JW. Current concepts: fibromuscular dysplasia. N Engl J Med. 2004;350:1862–1871.
12. Cragg AH, Smith TP, Thompson BH, et al. Incidental fibromuscular dysplasia in potential renal donors: long-term clinical follow-up. Radiology. 1989;172(1):145–147.
13. Kim ES, Olin JW, Froehlick JB, et al. Clinical manifestations of fibromuscular dysplasia by patient sex: a report of the United States Registry for fibromuscular dysplasia. J Am Coll Cardiol. 2013;62:2026–2028.
14. Kiando SR, Tucker NR, Castro-Vega L, et al. PHACT1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. PLOS Genet. 2016;12:e1006367.
15. O’Connor S, Gornik HL, Froehlick JB, et al. Smoking and adverse outcomes in fibromuscular dysplasia: U.S. Registry report. J Am Coll Cardiol. 2016;67:1750–1751.
16. Shimabukuro M. A new plausible link between lysophosphatidylcholine, TGF-β, and fibromuscular dysplasia. J Atheroscler Thromb. 2016;23:665–667.
17. Goncharenko V, Gerlock Jr AJ, Shaff MI, Hollifield JW. Progression of renal artery fibromuscular dysplasia in 42 patients as seen on angiography. Radiology. 1981;139(1):45–51.
18. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002;36:443–451.
19. De Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. J Hypertens. 2009;27:1333–1340.
20. de Silva R, Loh H, Rigby AS, et al. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. Am J Cardiol. 2007;100:273–279.
21. Wright JR, Shurrab AE, Cheung C, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. Am J Kidney Dis. 2002;39:1153–1161.
22. Greco BA, Cooper LT. Congenital and inflammatory arteritides. In: Lerman LO, Textor SC, eds. Renal Vascular Disease. London: SpringerVerlag; 2014:54–61.
23. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for

Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part ii: final classification criteria. Ann Rheum Dis. 2010;69:798–806.

24. Saadoun D, Lambert M, Mirault T, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. Circulation. 2012;125:813–819.
25. Delis KT, Gloviczki P. Middle aortic syndrome: from presentation to contemporary open surgical and endovascular treatment. Perspect Vasc Surg Endovasc Ther. 2005;17:187–203.
26. Gloviczki ML, Glockner JF, Lerman LO, et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. Hypertension. 2010;55:961–966.
27. Gloviczki ML, Glockner JF, Crane JA, et al. Blood oxygen level–dependent magnetic resonance imaging identifies cortical hypoxia in severe renovascular disease. Hypertension. 2011;58:1066–1072.
28. Eirin A, Gloviczki ML, Tang H, et al. Inflammatory and injury signals released from the post-stenotic human kidney. Eur. Heart J. 2013;34:540–548a.
29. Eirin A, Textor SC, Lerman LO. Emerging paradigms in chronic kidney ischemia. Hypertension. 2018;72(5):1023–1030.
30. Chade AR. Renal vascular structure and rarefaction. Compr Physiol. 2013;3:817–831.
31. Eirin A, Saad A, Tang H, et al. Urinary mitochondrial DNA copy number identifies chronic renal injury in hypertensive patients. Hypertension. 2016;68:401–410.
32. Gobe GC, Axelsen RA, Searle JW. Cellular events in experimental unilateral ischemic renal atrophy and in regeneration after. Contralateral Nephrectomy. Lab Inv. 1990;63:770–779.
33. Van de Ven PJG, Beutler JJ, Kaatee R, et al. Angiotensin-converting enzyme inhibitor–induced renal dysfunction in atherosclerotic renovascular disease. Kidney Int. 1998;53:986–993.
34. Messerli FH, Bangalore S, Makani H, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. Eur Heart J. 2011;32:2231–2237.
35. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. Prog Cardiovac Dis. 2009;52:249–259.
36. Kane GC, Xu N, Mistrik E, et al. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25:813–820.
37. Messina LM, Zelenock GB, Yao KA, Stanley JC. Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. J Vasc Surg. 1992;15:73–82.
38. Gray BH, Olin JW, Childs MB, et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. Vasc Med. 2002;7:275–279.
39. Chrysochou C, Schmitt M, Siddals K, et al. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. Nephrol Dial Transplant. 2013;28:479–483.
40. deSilva R, Loh H, Rigby AS, et al. Epidemiology, associated factors, prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. Am J Cardiol. 2007;100:273–275.
41. Radermacher J, Chavan A, Schaffer J, et al. Detection of significant renal artery stenosis with color Doppler sonography: combining extrarenal and intrarenal approaches to minimize technical failure. Clin Nephrol. 2000;53:333–343.
42. Soares GM, Murphy TP, Singha MS, et al. Renal artery duplex ultrasonography as a screening and surveillance tool to detect renal artery stenosis: a comparison with current reference standard imaging. J Ultrasound Med. 2006;25:293–298.
43. Weinreb J, Rodby RA, Yee J, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation.

Radiol. 2021;298:28–35.
44. Postma CT, van Oijen AH, Barentsz JO, et al. The value of tests predicting renovascular hypertension in patients with renal artery stenosis treated by angioplasty. Arch Intern Med. 1991;151:1531–1535.
45. Trinquart L, Mouneir-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension. 2010;56:525–532.

References

46. Davidson RA, Barri Y, Wilcox CS. Predictors of cure of hypertension fibromuscular renovascular disease. Am J Kidney Dis. 1996;28:334–338.
47. Investigators ASTRAL. Revascularization versus medical therapy for renalartery stenosis. N Engl J Med. 2009;361:1953–1962.
48. Cooper C, Murphy T, Cutlip D, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. New Engl J Med. 2014;370:13–22.
49. Chade AR, Rodriguez-Porcel M, Grande JP, et al. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23:1295–1301.
50. Cheung CM, Patel A, Shaheen N, et al. The effects of statins on the progression of atherosclerotic renovascular disease. Nephron Clin Pract. 2007;107:c35–c42.
51. Van de ven PJG, Beutler JJ, Kaatee R, et al. Angiotensin-converting enzyme inhibitor–induced renal dysfunction in atherosclerotic renovascular disease. Kidney Int. 1998;53:986–993.
52. Chrysochou C, Foley RN, Young JF, et al. Dispelling the myth: the use of renin angiotensin blockade in atheromatous renovascular disease. Nephrol Dial Transplant. 2012;27:1403–1409.
53. Ritchie J, Green D, Chrysochou C, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis. 2014;63(2):186–197.
54. Thatipelli M, Misra S, Johnson CM, et al. Renal artery stent placement for restoration of renal function in hemodialysis recipients with renal artery stenosis. J Vasc Interv Radiol. 2008;19:1563–1568.
55. Boateng FK, Greco BA. Renal artery stenosis: prevalence of, risk factors for, and management of in-stent stenosis. Am J Kidney Dis. 2013;61(1):147–160.
56. Balzer KM, Neuschafer S, Sagban TA, et al. Renal artery revascularization after unsuccessful percutaneous therapy: a single centre experience. Langenbecks Arch Surg. 2012;397:111–115.
57. Marone LK, Crouse WD, Dorer DJ, et al. Preservation of renal function with surgical revascularization in patients with atherosclerotic renovascular disease. J Vasc Surg. 2004;39(2):322–329.
58. Murray S, Martin M, Amoedo ML, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. Am J Kidney Dis. 2002;39:60–66.
59. Eirin A, Textor SC, Lerman LO. Novel therapeutic strategies for renovascular disease. Curr Opin in Nephrol Hypert. 2019;28(4). 383–369.
60. Chen W, Kayler LK, Zand MS, Muttana R, Chernyk V, DeBoccardo G. Transplant renal artery stenosis: clinical manifestations, diagnosis, and therapy. Clin Kidney J. 2015;8:71–78.
61. Willicombie M, Sandhu B, Brookes P, et al. Postanastomotic transplant renal artery stenosis: association with de novo class II donor- specific antibodies. Am J Transplant. 2013;14(1):133–143.
62. Hurst FP, Abbott KC, Neff RT, et al. Incidence, predictors and outcomes of transplant renal artery stenosis after kidney transplantation: analysis of USRDS. Am J Neph. 2009;30:459–467.
63. Robinson K, Kriegshauser JS, Dahiya N, et al. Detection of transplant renal artery stenosis: determining normal velocities at the renal artery anastomosis. Abdom Radiol. 2017;42(1):254–259.
64. Fananapazir G, McGahan JP, Corwin MT, et al. Screening for transplant renal artery stenosis: ultrasound-based stenosis probability stratification. Am J Rad. 2017;209:1064–1073.
65. Zhang LJ, Peng W, Schoepf UJ, et al. Non-contrast enhanced magnetic resonance angiography: a reliable clinical tool for evaluating transplant renal artery stenosis. Eur Rad. 2018;28:4195–4204.
66. Elmously A, Stem JR, Greenverg J, Agrusa CJ, Schneider D, Eliozy SH. Carbon dioxide angiography in the treatment of transplant renal artery stenosis. Ann Vasc Surg. 2020;63:198–203.
67. Ngo A, Maker S, Lijster M, et al. A systematic review of outcomes following

transluminal angioplasty and stenting in the treatment of transplant renal artery stenosis. Cardiov Intervent Radiol. 2015;38:1573–1588.
68. Patel U, Kumar S, Johnson OW, et al. Long-term graft and patient survival after percutaneous angioplasty or arterial stent placement for transplant renal artery stenosis: a 21year matched cohort study. Radiology. 2019;290:555–563.
69. Rouer M, Godier S, Mannot A, et al. Long-term outcomes of transplant renal artery stenosis surgery. Ann Vasc Surg. 2019;54:261–268.

70. Antopolsky M, Simanovsky N, Stalnikowicz R, et al. Renal infarction in the ED: 10-year experience and review of the literature. Am J Emerg Med. 2012;30:1055–1060.
71. Huang CC, Chen WL, Chen JH, et al. Clinical characteristics of renal infarction in an Asian population. Ann Acad Med Singapore. 2008;37:416–420.
72. Yang J, Lee JY, Ca YJ, et al. Risk factors and outcomes of acute renal infarction. Kidney Res Clin Pract. 2016;35(2):90–95.
73. Pizzarossa AC, Merola V. Etiology of renal infarction. a systematic review. Rev Med Chil. 2019;147(7):891–900.
74. Faucon A, Bobrie G, Jannot A, et al. Cause of renal infarction. J Hypertens. 2018;36(3):634–640.
75. van der Wal MA, Wisselink W, Rauwerda JA. Traumatic bilateral renal artery thrombosis: case report and review of the literature. Cardiovasc Surg. 2003;11:27–29.
76. Hazanov N, Somin M, Attali M, et al. Acute renal embolism: forty-four cases of renal infarction in patients with atrial fibrillation. Medicine (Baltimore). 2004;83:92–99.
77. Tektonidou MG. Renal involvement in the Antiphospholipid Syndrome (APS)—APS nephropathy. Clin Rev Allergy Immunol. 2009;36:131–140.
78. Mukherjee A, Ghoss R, Furment MM. Case Report: COVID-19 associated renal infarction and ascending aortic thrombosis. Amer J Trop Med Hyg. 2020;103(5). 1989–1892.
79. Böckler D, Krauss M, Mannsmann U, et al. Incidence of renal infarctions after endovascular AAA repair. J Endovasc Ther. 2003;10:1054.
80. Görich J, Krämer S, Tomczak R, et al. Thromboembolic complications after endovascular aortic aneurysm repair. J Endovasc Ther. 2002;9:180.
81. Lareyre F, Raffort J, Carboni J, et al. Impact of polar renal artery coverage after fenestrated endovascular aortic repair for juxtarenal aortic aneurysms. Ann Vasc Surg. 2019;58:45–53.
82. Grimme FAB, Zeebregts CJ, Verhoeven ELG, Bekkema F, Reijnen MMJP, Rielliu IFJ. Visceral stent patency in fenestrated stent grafting for abdominal aortic aneurysm repair. J Vas Surg. 2014;59:298–306.
83. Haas M, et al. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 2259 cases. Am J Kidney Dis. 2000;35:433.
84. Fukumoto Y, et al. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. Am Coll Card. 2003;42:211.
85. Edwards MS, Corriere MA, Craven TE, et al. Atheroembolism during percutaneous renal artery revascularization. J Vasc Surg. 2007;46:55–61.
86. Radvany MD. Use of embolic protection devices in peripheral interventions. Interv Cardiol. 2017;12(1):31–35.
87. Thandhani RI, et al. Atheroembolic renal failure after invasive procedures. Natural history based on 52 histologically proven cases. Medicine. 1995;74:350.
88. Wilson DM, et al. Eosinophiluria in atheroembolic renal disease. Am J Med. 1991;91:186.
89. Krishnamurthi V, Novick AC, Myles JL. Atheroembolic renal disease: effect on morbidity and survival after revascularization for atherosclerotic renal artery stenosis. J Urol. 1999;161:1093–1096.
90. Graziani G, Sanostasi S, Angelini C, Badalamenti S. Corticosteroids in cholesterol emboli syndrome. Nephron. 2001;87:371–373.
91. Finch TM, Ryatt KS. Livedo reticularis caused by cholesterol embolization may improve with simvastatin. Br J Dermatol. 2000;143:1319–1320.
92. Wysokinski WE, Gosk-Bierska I, Greene EL, et al. Clinical characteristics

and long-term follow-up of patients with renal vein thrombosis. Am J Kidney Dis. 2008;51:224–232.
93. Harris R, Ismail N. Extrarenal complications of nephrotic syndrome. Am J Kidney Dis. 1994;23:477–497.
94. Kayali F, Najjar R, Aswad F, et al. Venous thromboembolism in patients hospitalized with nephrotic syndrome. Am J Med. 2008;121:226–230.
95. Akbar SA, Jafri SZ, Amendola MA, et al. Complications of renal transplantation. Radiographics. 2005;25:1335–1356.
96. Kim HS, Fine DM, Atta MG. Catheter-directed thrombectomy and thrombolysis for acute renal vein thrombosis. J Vasc Interv Radiol. 2006;17:815–822.
97. Asghar M, Ahmed K, Shah SS. Renal vein thrombosis. Eur J Vasc Surg. 2007;34:217–223.

SECTION VIII

Pregnancy and Renal Disease

44

Kidney Physiology and Complications in Normal Pregnancy

Kate Wiles, Mark A. Brown

KIDNEY PHYSIOLOGY IN NORMAL PREGNANCY

Kidney physiology changes significantly in pregnancy. Marked volume expansion and vasodilation result in alterations in systemic and renal hemodynamics and kidney volume, with physiologic urinary tract dilation being common (Fig. 44.1A). Renal plasma flow (RPF) increases by up to 80% and glomerular filtration rate (GFR) by 50%.1 Kidney tubular function responds to these changes with alterations in water and electrolyte handling, leading to clinical changes including lower serum osmolality, gestational hyponatremia, and increased urinary glucose and protein excretion (Table 44.1).

ANATOMY

In pregnancy, there is progressive dilation of the renal pelvis, calyces, and ureters. These changes are thought to be due to a reduction in smooth muscle tone and peristalsis mediated by progesterone, in conjunction with mechanical compression of the ureters by the gravid uterus. Dilation of the ureters is estimated to occur in up to 80% of pregnancies and is more prominent on the right side due to dextrorotation of the uterus by the sigmoid colon and kinking of the ureter as it crosses the right iliac artery.2 Ureteric dilation of up to 20 mm on the right and 8 mm on the left is consistent with the altered physiology and anatomy of pregnancy3 (see Fig. 44.1). Distinction between gestational dilation and pathologic hydronephrosis can be challenging. A dilated ureter distal to the pelvic brim, abnormal resistive indices in the kidney, and an absence of ureteric jets in the supine position are suggestive of obstructive pathology.4 The dilated collecting system can hold 200 to 300 mL of urine, promoting urinary stasis and increasing the risk for clinical infection in women with asymptomatic bacteriuria (ASB).

HEMODYNAMIC CHANGES

Systemic

Plasma volume increases until 32 to 34 weeks’ gestation by as much as 1.25 L (Fig. 44.2). Despite an increase in red blood cells (RBCs), there is a disproportional increase in plasma, causing a physiologic anemia of normal pregnancy.5 Cardiac output increases by 40% to 50% secondary to increased heart rate, stroke volume, and venous return.6 Despite this, systemic blood pressure (BP) decreases as a result of reduced systemic vascular resistance (SVR) thought to be mediated by vasodilatory factors, including progesterone, relaxin, and nitric oxide (NO).

Kidney

Systemic vasodilation, increased arterial compliance and decreased vascular resistance, and increased cardiac output result in increased kidney perfusion and glomerular filtration measurable at as early as 4 weeks’ gestation, peaking at 40% to 50% above prepregnancy values by the second trimester.7 These changes result in decreased serum creatinine concentrations in pregnancy (Table 44.2). Systematic review data show that serum creatinine in pregnancy falls to 86% or less of the nonpregnant upper reference limit. This means that where the nonpregnant reference interval is 0.51 to 1.02 mg/dL (45–90 µmol/L), a serum creatinine of more than 0.87 mg/dL (>77 µmol/L) should be considered outside the normal range for pregnancy and prompt investigation for either acute kidney injury (AKI) or chronic kidney disease

(CKD).[8,8a]

Mechanisms of Increased Glomerular Filtration Rate

The exact mechanisms behind increased GFR in pregnancy are incompletely understood. GFR is calculated as:

$$\text{GFR} = (\Delta P - \pi_{GC}) \times K_f$$

where ΔP is the net hydraulic pressure in the glomerulus, π_{GC} is the oncotic pressure in the glomerulus, and K_f is the glomerular ultrafiltration coefficient. As a result of plasma volume expansion, π_{GC} is decreased in pregnancy, contributing to the rise in GFR. Changes in hydraulic permeability and the surface area for filtration may cause minor changes in K_f. Despite increased RPF, there is no overall change in glomerular pressure because dilation of the pre- and postglomerular resistance vessels are equal.

Measuring Glomerular Filtration Rate

True GFR measurement in pregnancy has historically been achieved using inulin or creatinine clearance methods. Estimation of GFR in pregnancy is challenging because the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas significantly underestimate true GFR in pregnancy. Similarly, cystatin C concentrations do not correlate with other measures of GFR in pregnancy.[9] The absence of large-scale

Hemodynamic and Biochemical
Changes in Normal Pregnancy

40

ERPF
Cardiac output
Plasma volume

30

GFR

50

Change (%)

20
10
SNa
Posm
Sprot
Palb
Screat
SVR
Surea

10
20
30
40
NP

Fig. 44.1 Hydronephrosis in Pregnancy. Intravenous urogram (IVU) at 36 weeks' gestation. Note bilateral hydronephrosis, more marked on the right side. In contemporary clinical practice, ultrasound is the firstline imaging modality in pregnancy, with a possible role for magnetic resonance imaging or limited IVU.

TABLE 44.1 Changes in the Mean Value of
Some Common Indices During Pregnancy
Hemoglobin (g/L)
Hematocrit (%)
Serum sodium (mmol/L)
Serum creatinine, mg/dL (mmol/L)
Serum osmolality (mOsm/kg)
Blood urea nitrogen (mg/dL)
Serum urea (mmol/L)
Serum uric acid, mg/dL (µmol/L)
Serum albumin (g/L)
pH
Arterial Po2, mm Hg (kPa)
Arterial Pco2, mm Hg (kPa)
Serum bicarbonate (mmol/L)
Systolic BP (mm Hg)
Diastolic BP (mm Hg)

Nonpregnant

Pregnant

135
40
140
0.76 (67)
285
12.7
4.5
4.0 (240)
40
7.40
100 (13.3)
40 (5.3)
25
115
70

>105
34
135
0.59–0.63 (52–56)a
270
9.0
3.2
3.2–4.3 (190–260)
30
7.44
112 (15.0)
26 (3.5)
20
113–121b
69–78b

aData

from Ogueh O, Brookes C, Johnson MR. A longitudinal study of the maternal cardiovascular adaptation to spontaneous and assisted conception pregnancies. Hypertens Pregnancy. 2009;28(3):273–289.
bData from Green LJ, Mackillop LH, Salvi D, et al. Gestation-specific vital sign reference ranges in pregnancy. Obstet Gynecol. 2020;135(3):653–664.
BP, Blood pressure.

normative data for eGFR in pregnancy by any formulas means that it cannot be used as a measure of kidney function in pregnancy, despite ubiquitous use outside of pregnancy.10 Serum creatinine concentrations therefore remain the only current method for the clinical assessment of kidney function during pregnancy.

10

20
30
Weeks of gestation

40

Fig. 44.2 Hemodynamic Alterations Induced by Normal Pregnancy.
Increments and decrements in hemodynamic and biochemical parameters shown as percentage of change from nonpregnant baseline.
ERPF, Effective renal plasma flow; GFR, glomerular filtration rate; NP, nonpregnant state; Palb, plasma albumin concentration; Posm, plasma osmolality; S, serum; SVR, systemic vascular resistance.

Renin-Angiotensin-Aldosterone System

In early gestation, vasodilation and decreased systemic vascular resistance activate the renin-angiotensin-aldosterone system to increase circulating concentrations of renin and angiotensin II. This mediates an aldosterone-dependent increase in plasma volume, thought to be essential for adequate uteroplacental blood flow Maternal BP, however, does not increase, perhaps due to reduced responsiveness to the pressor effect of angiotensin II through altered sensitivity of arterial smooth muscle and downregulation of angiotensin receptors. Angiotensin,1–7 which counterregulates angiotensin II and has vasodilatory and antihypertensive properties, is elevated in pregnancy and may contribute to vasodilation. Relaxin is a key mediator for enhanced nitric oxide signaling in pregnancy[11] and probably contributes to the vasodilated state of normal pregnancy. Relaxin is produced in the corpus luteum and the placenta in early gestation, leading to a peak in concentration at 6 weeks’ gestation, returning to nonpregnant levels at 6 weeks postpartum. However, other mechanisms, possibly progesterone and nitric oxide, also have a role. This is evidenced by physiologic adaptation to early pregnancy after assisted conception, in which the corpus luteum is absent and relaxin is not detected.[12]

Sodium Handling and Osmoregulation

In early gestation, serum osmolality decreases by approximately 10 mOsm/kg to a new set point of about 270 mOsm/kg, with a reduction in serum sodium (see Table 44.1).[1] In pregnancy the physiologic vasopressin (AVP) release mechanisms of thirst are reset to recognize this new set point in osmolality, with β-human chorionic gonadotrophin (β-hCG) and relaxin hypothesized to play a role in this resetting. The gestational decrease in serum sodium concentration is thought to be secondary to systemic vasodilation, arterial underfilling, and subsequent release of AVP.[13] Although the natriuretic effects of increased GFR and elevated progesterone promote sodium excretion, this is balanced by increased aldosterone and angiotensin II directly increasing sodium reabsorption, increased deoxycorticosterone promoting

Expected Normal Serum Creatinine Values According–Gestational Week: Derived From 244,866 in Pregnant Women With Uncomplicated Pregnancies

TABLE 44.2

	SERUM CREATININE MG/DL (µMOL/L)		
Gestational Week	50th Percentile	75th Percentile	95th Percentile
4–10	0.54–0.67 (48–59)	0.6–0.72 (53–64)	0.69–0.85 (61–75)
10–32	0.50–0.54 (44–48)	0.55–0.6 (49–53)	0.66–0.69 (58–61)
32–42	0.51–0.62 (45–55)	0.57–0.71 (50–63)	0.68–0.92 (60–81)

TABLE 44.3 Antinatriuretic and Natriuretic Factors Influencing Sodium Excretion During Pregnancy

Antinatriuretic	Natriuretic
Aldosterone	Increased glomerular filtration rate
Angiotensin II	Progesterone
Estrogen	Atrial natriuretic peptide
Deoxycorticosterone	Nitric oxide
Epithelial sodium channel	Prostaglandins
Supine posture	
Upright posture	
Decreased blood pressure	
Increased urethral pressure	
Placental shunting	

sodium retention, and upregulation of the epithelial sodium channel (ENaC).14 Although there is a gradual gain in total body sodium during pregnancy of about 900 to 1000 mmol, there is greater water gain (Table 44.3).

Potassium

Despite increased aldosterone and mild alkalosis in pregnancy, hypokalemia does not occur, and typical serum potassium concentrations in pregnancy are at the lower limit of the nonpregnant reference range. This may be partly due to the antimineralocorticoid effect of progesterone, as well as the capacity of progesterone to inhibit potassium excretion independent of antimineralocorticoid effects.

Uric Acid

Serum uric acid concentrations fall early in pregnancy before a return toward nonpregnant concentrations during late gestation (see Table 44.1). By 37 weeks' gestation, serum uric acid can reach nonpregnant levels. Gestational changes in the handling of uric acid by the kidney include increased clearance secondary to gestational hyperfiltration in conjunction with reduced fractional reabsorption. Other factors include dietary intake of purines and maternal and fetoplacental metabolism of purines; gastrointestinal excretion may also contribute.

Acid-Base

In pregnancy there is typically a chronic mild respiratory alkalosis secondary to an increase in tidal volume that lowers arterial carbon dioxide tension. Increased minute ventilation probably results from direct stimulation of the respiratory centers by progesterone and occurs without a change in respiratory rate.15

Urine Protein

There is a rise in urine protein excretion in normal pregnancy. The mechanisms and clinical implications of proteinuria in pregnancy are discussed later.

Glucose

Glycosuria in pregnancy occurs secondary to increased glucose filtration coupled with decreased tubular reabsorption. Once the filtered load of glucose has reached the maximum resorptive capacity of the proximal tubule, there is physiologic glycosuria, which can occur with normal plasma glucose concentrations.

Calcium

There is increased urinary excretion of calcium but also of magnesium, citrate, acidic glycoproteins, and nephrocalcin, which help prevent calcium stone formation associated with supersaturation.

KIDNEY DISEASE IN PREGNANCY

Urinary tract infection (UTI) is common in pregnancy. The most common causes of kidney injury in late pregnancy are preeclampsia and postpartum hemorrhage.

URINALYSIS AND MICROSCOPY

Many young women have urinalysis and urine microscopy performed for the first time during pregnancy, leading to the detection of hematuria, proteinuria, and pyuria either related to or coincidental to pregnancy.

Hematuria

Definition and Epidemiology

Nonvisible dipstick hematuria (microhematuria) is detected during pregnancy in about 20% of women16 and in isolation, rarely signifies a disorder likely to influence pregnancy outcome. Clinically significant nonvisible hematuria is defined as three or more RBCs per high-power field on microscopic evaluation of two of three properly collected (clean catch, midstream) urine specimens,17 or more than 2500 RBCs/mL. Nonvisible hematuria disappears in the majority of women after delivery, but if it is secondary to glomerular disease, it will persist, warranting further investigation.

Etiology and Outcome

Assessment of urinary RBC morphology differentiates dysmorphic red cells from isomorphic red cells. Outside of pregnancy, this may be used to help distinguish glomerular from nonglomerular sources of blood. However, dysmorphic red cells have been detected in women with severe preeclampsia in the absence of underlying glomerulonephritis.18 In pregnancy, isomorphic hematuria is most likely to be caused by urinary tract infection. Isolated nonvisible hematuria (i.e., without proteinuria and with normal kidney function) has no adverse effect on pregnancy outcome with no measurable difference in gestational age at delivery, birth weight, gestational hypertension, or preeclampsia compared to pregnancies without nonvisible hematuria.19

Visible hematuria (macrohematuria) in pregnancy is most often the result of vaginal bleeding or hemorrhagic cystitis. Less common causes include renal calculi, renal arteriovenous malformations, renal vein thrombosis, polycystic kidneys, and rarely bladder or kidney neoplasms.

Differential Diagnosis

When nonvisible hematuria is found, a urine culture is required to exclude infection. If there is no proteinuria, and BP and serum creatinine values are normal, further investigations can be delayed until 3 months postpartum, when serologic tests and kidney ultrasound can be performed if hematuria persists. When there are significant numbers of dysmorphic urinary RBCs in pregnancy that persist postpartum, the most likely glomerular pathologies are thin basement membrane nephropathy, immunoglobulin A nephropathy, or lupus nephritis.

Treatment

There is no specific treatment for glomerular disease during pregnancy if kidney function and BP are normal, proteinuria is not clinically significant (see “Proteinuria” below), and lupus is excluded. Reninangiotensin blockade is contraindicated in pregnancy due to fetal toxicity in the second and third trimesters. The treatment of UTI and calculi are discussed later.

Proteinuria

There is a physiologic increase in proteinuria in pregnancy due to increased permeability of the glomerular barrier in conjunction with impaired protein resorption in the proximal tubule. The established upper limit for normal protein excretion in pregnancy is based on data from small cohorts and expert opinion rather than an association with adverse pregnancy outcomes. The largest study of protein excretion measured by 24-hour urine collection included 270 women with mean protein excretion of 117 mg/day and an upper confidence interval limit of 259 mg/24 h.[20] This was extrapolated to produce the now established reference limit for pregnancy of 300 mg/24 h, compared with 150 mg/24 h outside of pregnancy. The increase is greater in twin pregnancy. The gestational increase in proteinuria can continue into the postpartum period and may take many months to resolve.[21]

Assessment

Proteinuria is most frequently detected in pregnancy by dipstick urinalysis, but this method is notoriously unreliable, with a significant proportion of false-positive and false-negative results.[22] Inaccuracy generally occurs due to the variable osmolality of a random urine specimen. Coexisting hematuria, alkaline urine (pH >7.0), and additives in the urine collection container also contribute to false positive tests. False-negative results may occur with acidic urine, low specific gravity (<1.001), and high salt concentration. In clinical practice, a dipstick result is sufficiently sensitive for the absence of significant proteinuria when testing is negative and for the detection of pathologic proteinuria when dipstick readings are 3+ (>3 g/L) or more. At intermediate levels, false-positive rates are as high as 71%. Detection is improved using an automated urinalysis device, thereby reducing observer error.[23]

Timed urine collections over 24 hours are limited by underestimation,[24] variability,[25] and the potential for treatment delay.

Consequently, they have been superseded in clinical practice by spot quantification using a ratio of urinary protein or albumin to creatinine (uPCR or uACR, respectively).

Differential Diagnosis

Proteinuria quantified as uPCR greater than 30 mg/mmol (0.30 mg/mg, 300 mg/g) and uACR greater than 8 mg/mmol have high sensitivity and specificity for the detection of clinically significant proteinuria in pregnancy.26 If detected before 20 weeks' gestation, preexisting

kidney disease should be considered. Glomerular disease may present for the first time in pregnancy, or pregnancy may unmask kidney disease secondary to systemic disorders such as diabetes mellitus, systemic lupus, or chronic hypertension. The course of pregnancy in women with prepregnancy proteinuria is discussed in Chapter 45.

Gestational proteinuria is isolated, de novo proteinuria in pregnancy, without features of preeclampsia. Thus, the diagnosis can only be made in retrospect after completion of pregnancy. The significance of this is not known. In the absence of CKD, it is not thought to be associated with adverse effects for fetus or mother,27 though surveillance is warranted for the development of preeclampsia.

Though proteinuria is no longer mandatory for the diagnosis of preeclampsia where other clinical features exist, when preeclampsia does cause proteinuria, it arises after 20 weeks' gestation and requires simultaneous de novo BP higher than 140/90 mm Hg.28 Once above the diagnostic threshold for preeclampsia, the level of proteinuria has not been consistently associated with adverse pregnancy outcomes and repeat quantification is not recommended,28,29 as it does not guide management.

We limit investigation of isolated, normotensive, nonnephroticrange proteinuria during pregnancy to measurement of serum creatinine, electrolyte, and albumin concentrations; antinuclear antibody (ANA) titers; and an ultrasound to confirm normal renal tract morphology. A kidney biopsy is not indicated unless it will change management. In many cases appropriate investigations can be delayed until the postpartum period. However, kidney biopsy may be indicated in the first and early second trimester, when the bleeding risks of biopsy are lower30 and where a histologic diagnosis will determine appropriate treatment during pregnancy, for example, the immunosuppressive management of nephrotic syndromes and lupus nephritis.

Treatment

Nephrotic syndrome due to primary kidney disease (and not preeclampsia) is associated with adverse maternal and fetal outcomes including preeclampsia, AKI, infection, preterm delivery, intrauterine growth restriction, and fetal loss.31,32 Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in the second and third trimesters of pregnancy due to toxic effects on the fetal kidney leading to anuria, oligohydramnios, fetal limb contractures, craniofacial deformities, and pulmonary hypoplasia. Diuretics are prescribed and sodium restriction is implemented for severe, intractable maternal edema including pulmonary complications, as in these settings the clinical benefit outweighs the theoretical concern of reduced plasma volume and uteroplacental perfusion.

There is no established role for the use of intravenous (IV) albumin in managing nephrotic syndrome during pregnancy.

Nephrotic syndrome is a significant risk factor for venous thromboembolism. However, there is no consensus on the definition of nephrotic syndrome in pregnancy, which is complicated by gestational changes in protein excretion and serum albumin concentrations, and physiologic peripheral edema. There is expert consensus that nephrotic range proteinuria (uPCR >300 mg/mmol or uACR >250 mg/mmol) accompanied by low serum albumin warrants thromboprophylaxis with low-molecular-weight heparin (in the absence of contraindications or anticipated delivery within 12 hours) in pregnancy and the immediate postpartum period, with risk reassessed at 6 weeks postpartum. There is also consensus, but insufficient evidence, that subnephrotic levels of proteinuria confer an increased risk of thrombosis.

Nonnephrotic range proteinuria (uPCR >100 mg/mmol or uACR >30 mg/mmol) is therefore considered a risk factor for thrombosis, and prophylactic use of low-molecular-weight heparin should be considered when there are additional risk factors for thromboembolism.33

URINARY TRACT INFECTION

Definitions

Bacteriuria is the detection of a clinically significant quantitative count of bacteria in the urine, defined as more than 105 organisms per milliliter. If this phenomenon exists without symptoms, it is defined as asymptomatic bacteriuria (ASB). Cystitis defines infection in the presence of lower urinary tract symptoms such as frequency, dysuria, and strangury. Although more than 105 organisms/mL defines ASB, as few as 102 organisms/mL may be sufficient to diagnose cystitis if accompanied by pyuria and characteristic symptoms. In acute pyelonephritis there are generally more than 105 organisms/mL in the urine, in association with parenchymal bacterial infiltration causing upper urinary tract symptoms. Pyelonephritis is usually diagnosed clinically by fever and loin pain and may progress to systemic sepsis.

Epidemiology

ASB is estimated to affect 2% to 9% of all pregnant women. The prevalence is higher in women from lower socioeconomic groups and increases with age, parity, and coexistent genital tract infection. ASB is also more common in women with urinary tract abnormalities including reflux nephropathy and neurogenic bladder, in diabetic patients, and in women with previous UTIs. Between 1% and 2% of pregnancies are complicated by acute bacterial cystitis. The overall incidence of acute pyelonephritis in pregnancy is approximately 1%. Pyelonephritis is more common in pregnant women with urologic abnormalities or diabetes and more often affects the right kidney, probably because physiologic dilation of the ureter is greater on the right. It is thought that about 70% of women who develop acute pyelonephritis have preceding covert bacteriuria, but this is difficult to prove. Pyelonephritis is estimated to occur in up to 30% of women with ASB. When ASB is treated, the incidence of pyelonephritis in pregnancy is estimated to be reduced by more than 80%.

Pathogenesis

Certain host characteristics may increase the risk for UTI or pyelonephritis (see Chapter 53). Women, such as those who do not express the antibody to the O antigen of Escherichia coli, may be chronically colonized and have ASB that predates pregnancy. Pregnancy is a state of relative urinary tract stasis; the calyces, pelvices, and ureters dilate, particularly on the right, and this contributes to the risk of ASB developing into ascending acute pyelonephritis. The most common mechanism of infection is through the urethra from perineal bacteria. Box 44.1 lists common organisms causing UTI in pregnancy. Some strains of E. coli are particularly virulent and are associated with both ASB and pyelonephritis. They possess fimbriae, which enable the bacteria to attach themselves to the uroepithelial cells with pili, allowing them to ascend the urinary tract from the perineum. Infection with multiresistant organisms is increasingly common.

Organisms Typically Causing Urinary Tract Infection in Pregnancy

BOX 44.1

•
•
•
•
•
•

Escherichia coli (>70% of infections)

Klebsiella spp.
Proteus spp. (particularly in diabetic women or urinary tract obstruction)
Enterococci
Staphylococci, especially Staphylococcus saprophyticus
Pseudomonas

Clinical Manifestations

Most maternity units operate a policy of screening all pregnant women at least once for ASB, either by dipstick urinalysis or by urine culture. Because isolated pyuria on dipstick testing is very common in normal pregnancy due to contamination from vaginal secretions, primary urine culture is recommended over dipstick testing.

Pyelonephritis most commonly presents between 20 and 28 weeks' gestation. Not all women will describe preceding lower urinary tract symptoms. Pyelonephritis can present in pregnancy as acute abdominal pain and may be associated with preterm labor, which is hypothesized to be triggered by proinflammatory cytokines secreted in response to bacterial endotoxins. The diagnosis of pyelonephritis is usually made on clinical grounds. Definitive diagnosis requires positive urine culture, but treatment should not be delayed while this is awaited. E. coli is the most common infecting organism (>85% of cultures). Bacteremia is a common and usually transient complication of pyelonephritis, although sepsis can develop with sequelae including AKI, disseminated intravascular coagulation, and respiratory distress. Pyonephrosis and perinephric abscess are rare complications but should be suspected in women who do not show a clinical response to treatment. In the preantibiotic era, maternal mortality was 3% to 4%; death from pyelonephritis is now rare in high-income countries.

Treatment

Asymptomatic Bacteriuria

A Cochrane systematic review has indicated that treatment of ASB during pregnancy may reduce the incidence of pyelonephritis, low birth weight (<2500 g), and preterm delivery,[34] though confidence in the effect is limited given the low certainty of the evidence. Most available studies are historical with low methodological quality and do not necessarily reflect contemporary advances in diagnosis and treatment and accessibility to medical services. A more recent study randomized 85 women with ASB (out of 4283 screened) to treatment with either nitrofurantoin 100 mg twice daily for 5 days or placebo. This trial showed no association between ASB and preterm birth. Although there was an increased rate of pyelonephritis with untreated ASB compared with antibiotic use, the absolute risk of pyelonephritis in untreated ASB was low (2.4%). Although such findings question a universal screen-treat policy for ASB in pregnancy, there is consensus in highincome countries that more data are required before this routine and long-standing strategy is reconsidered.

There is no clear evidence that any particular antibiotic or dosage regimen is superior for treatment of ASB in pregnancy. In choosing treatment, the clinician must consider urine culture and susceptibility results, previous antibiotic use, and safety data for pregnancy. In most women, amoxicillin or cephalexin is first-line therapy. Nitrofurantoin is not teratogenic, though it is used with caution close to term or anticipated delivery because of a rare risk of neonatal hemolysis. Trimethoprim can be used in pregnancy but should be avoided in established folate deficiency, low dietary folate intake, and in women taking other folate antagonists. Many clinicians avoid trimethoprim in the first trimester because of its antifolate effects. There is insufficient evidence to compare the effectiveness of a single dose compared with longer treatment duration, or a 3-day with a 7-day course of treatment, and a 7-day treatment regimen is therefore usually recommended. A urine culture should be performed after completion of antibiotic treatment to check for eradication.

Without treatment, ASB will persist in 80% of women, and even with treatment, 20% will have persistent bacteriuria. Those with persistent colonization are difficult to treat, with eradication achieved in only 40% after a second course of antibiotics. Where eradication is not achieved, prophylactic antibiotics may be considered throughout pregnancy to prevent pyelonephritis and its consequences; however, no studies specifically address this situation.

Cystitis

Cystitis is managed in the same way as ASB with a follow-up urine culture to confirm eradication of infection.

Pyelonephritis

It is usual practice to admit pregnant women with pyelonephritis to hospital, although successful outpatient management for milder cases has been reported.35 Initial treatment with a broad-spectrum antibiotic is recommended with review according to clinical response and culture results. Prophylactic antibiotics are then recommended until delivery to prevent recurrence and the risk of preterm labor. Periodic urine culture can be considered to monitor for antibiotic resistance. Kidney ultrasound may be performed to ensure normal renal tract anatomy and is indicated in those not responding to antibiotic treatment. If pyelonephritis persists despite adequate antibiotic therapy and pathologic urinary tract dilation is confirmed, percutaneous nephrostomy under ultrasound guidance may be indicated to definitively manage an infected, obstructed renal tract.

KIDNEY STONES

Epidemiology

Despite normal pregnancy being an ideal environment for kidney stone formation, the incidence of kidney calculi remains similar in pregnant and nonpregnant women, in the range of 1 in 188 to 1 in 4600 in cohort studies, with lower incidences in unreferred pregnant populations.36

Pathogenesis

Most stones in pregnancy are calcium stones. However, in pregnancy, calcium phosphate stones are most common, in contrast to calcium oxalate in the nonpregnant population. Struvite stones are the next most common, usually when the urinary tract is infected with organisms such as Proteus spp. Small proportions of kidney stones are formed from uric acid or cystine. Although pregnancy is a physiologic state of relative urinary stasis and increased calcium and uric acid excretion, this is balanced by enhanced excretion of inhibitors of stone formation, such as magnesium, citrate, and the glycoprotein nephrocalcin.

Clinical Manifestations

Although symptomatic stones during pregnancy are rare, they are a relatively common cause of nonobstetric abdominal pain in pregnancy.

Kidney and bladder stones usually present in the second or third trimester with acute flank pain radiating to the groin or lower abdomen, with hematuria. However, clinical features of kidney calculi may be more difficult to interpret in pregnancy because frequent episodes of diffuse, poorly localized abdominal discomfort and lower urinary tract symptoms can occur in normal pregnancy. Some women with calculi have concomitant UTI. Increased serum calcium concentrations in pregnancy warrant exclusion of hyperparathyroidism, which can lead to adverse maternal and fetal outcomes in untreated women.

Pregnant women with kidney calculi are reported to have an increased risk for superimposed pyelonephritis and obstetric complications including preterm labor, hypertensive disorders, gestational diabetes, and cesarean delivery.37 However, the true risk of kidney stones in pregnancy is difficult to determine from existing studies.

The diagnosis of kidney calculi in pregnancy is difficult because of the radiation exposure to the fetus with computed tomography (CT) imaging, which is the investigation of choice outside of pregnancy. The

fetal radiation exposures from abdominal CT (and most other diagnostic imaging procedures in common use) is below the threshold at which there is risk of fetal death, malformation, growth restriction, or impaired mental development.38 However, as the radiation exposure threshold that leads to an increased relative (though low absolute) risk of childhood cancer is unknown, alternative imaging modalities that do not use ionizing radiation should be used when possible.

Ultrasound is therefore often the first-line investigation in pregnancy, although detection rates are lower than with CT, varying from 29% to 69%.36 Ultrasound will also detect gestational dilation of the urinary tract, which can complicate the diagnosis. An absence of ureteric jets in the contralateral decubitus position may be helpful in the assessment of obstruction. Transvaginal ultrasound can be added to examine for distal ureteral stones. If symptoms persist and further diagnosis is required, magnetic resonance (MR) urography or limited intravenous urography (IVU) have been suggested. MR imaging findings include a signal void, perinephric or periureteral edema, and an abrupt ending of the ureter at the level of obstruction. Limited IVU has been reported to have better diagnostic accuracy (93%) compared with ultrasound (60%).40

Treatment

Approximately 64% to 84% of stones will pass spontaneously during pregnancy, and so initial management of kidney calculi is conservative, including appropriate hydration, antiemetics, analgesia, and antibiotics if infection is suspected. The woman should lie on her side, with the symptomatic side up, enabling relief of pressure on the ureter from the gravid uterus. The dose of nifedipine used for expulsion of stones outside of pregnancy is comparable to that used in pregnancy for both hypertension and tocolysis and so can be safely given if clinically indicated.

Quantitation of urine calcium, uric acid, or other mineral excretion is not performed in pregnancy, as interpretation in the context of gestational change is not clear and specific pharmacologic agents are not used in pregnancy due to limited data. Such investigations can be completed postpartum.

Surgical intervention is considered only when stones cause persistent obstruction, deteriorating kidney function, intractable pain or infection. This is a rare situation in pregnancy. Percutaneous nephrostomy can be used as a temporizing measure until after delivery, although the likelihood of tubal blockage should be considered, and flushing and/or replacement may be required. Ureteroscopic stone removal is increasingly described in pregnancy, with complete stone removal achieved in 86% of 116 procedures.41 Lithotripsy is contraindicated during pregnancy because of the presumed adverse effect of the shock waves on the fetus, with fetal damage and death reported in animal studies. Inadvertent exposure to extracorporeal shock wave lithotripsy has been reported, however, leading to a recommendation for further research on possible utility in pregnancy.36 Rare cases of percutaneous nephrolithotomy are reported in pregnancy; however, prolonged fluoroscopy time and prone positioning mean that it is usually delayed until the postpartum period.36

Women should be assessed for idiopathic hypercalciuria or other causes of kidney calculi after delivery. Clinicians should be aware that gestational calyceal and ureteral dilation may persist for months postpartum.

HYPERTENSION IN PREGNANCY

Definitions

Median BP falls to a nadir of 113/69 mm Hg at 18 to 19 weeks’ gestation and peaks at 121/78 mm Hg at term with an upper reference limit (97th centile) of 136/86 mm Hg in midpregnancy and 144/95 mm Hg

Classification of the Hypertensive Disorders of Pregnancy
Hypertension in pregnancy
BP ≥140/90 mm Hg

Transient hypertension

White-coat hypertension

Gestational hypertension

High BP that normalizes on subsequent testing without treatment

Elevated clinic BP before 20 weeks but normal BP (<135/85) at home

Sustained BP ≥140/90 without features of preeclampsia

Hypertension with systemic endothelial disease: Proteinuria, AKI, transaminitis, CNS disease, thrombocytopenia, uteroplacental dysfunction

Hypertension diagnosed prior to 20 weeks' gestation and persisting after pregnancy

40% risk of gestational hypertension/preeclampsia

8% risk of preeclampsia

25% risk of preeclampsia

Risk of chronic hypertension, CVD, and CKD in later life

Superimposed preeclampsia in 25%

Preeclampsia

Chronic
hypertension

Fig. 44.3 Classification of the Hypertensive Disorders of Pregnancy. AKI, Acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; CNS, central nervous system; CVD, cardiovascular disease.

at term,15 supporting the use of 140/90 mm Hg as the upper threshold for normal BP in pregnancy. The different hypertensive disorders of pregnancy are shown in Fig. 44.3

Gestational hypertension is the development of new hypertension after 20 weeks' gestation in the absence of features of preeclampsia. Approximately 25% will progress to develop preeclampsia. Gestational hypertension usually resolves by 12 weeks postpartum. If hypertension persists beyond that, the possibility of chronic hypertension should be considered.

Preeclampsia is new hypertension after 20 weeks' gestation either with maternal organ dysfunction (proteinuria, AKI, elevated transaminases, cerebral, hepatic or clotting abnormalities) or uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform, or stillbirth). Proteinuria (uPCR >30 mg/mmol or uACR >8 mg/mmol) is not essential for the diagnosis of preeclampsia if other criteria exist42 (Table 44.4).

Eclampsia is seizure activity in a woman with preeclampsia. It is uncommon in high-income countries, with a prevalence of about 0.3% of hypertensive pregnancies. In low- and middle-income countries, eclampsia is more common, with greater risks for maternal mortality and morbidity, as well as perinatal mortality.

Chronic hypertension is BP 140/90 mm Hg or higher that predates pregnancy or is detected before the 20th week of pregnancy on at least two occasions and persists beyond 12 weeks postpartum. This can be confirmed by home BP monitoring or 24-hr ambulatory BP monitoring. Superimposed preeclampsia is the new development of features outlined in Table 44.4 after 20 weeks' gestation in a woman with chronic hypertension.

White-coat hypertension is elevated office or clinic BP (≥140/90 mm Hg) but normal BP measured at home (<135/85 mm Hg). It is not an entirely benign condition with an increased (8%) risk of preeclampsia, which is about double the usual risk.

Epidemiology

Hypertension affects 10% to 12% of all pregnancies, and the global estimate for the incidence of preeclampsia is 4.6% of all pregnancies, though there is variation due to patient factors such as ethnicity and vascular risk, as well as nonstandardization of diagnostic criteria. The incidence of eclampsia is 1.4% of pregnancies globally, though this varies between countries from 0.02% to 2.9%. In low- and middle-income countries, mortality from preeclampsia accounts for nearly 30% of maternal deaths. Such mortality rates are 200 times higher than those of high-income countries that have universal access to health care, consistently applied national guidance for management, and a low threshold for the treatment of severe hypertension in pregnancy.42 Chronic hypertension is estimated to affect 1% of pregnancies, which may increase due to advancing maternal age and rising rates of pregestational diabetes, obesity, and metabolic syndrome. Black, Asian, Hispanic, American Indian, Alaskan Native, and indigenous Australian populations have a higher risk for preeclampsia than non-Hispanic Whites, with a higher prevalence of hypertension, obesity, and diabetes contributing.

PREECLAMPSIA

Box 44.2 lists known risk factors for preeclampsia. The risk is highest in those with a history of preeclampsia, ranging from 15% to 65% depending on the gestation at which preeclampsia developed in a previous pregnancy. Early development of preeclampsia requiring delivery before 34 weeks is associated with the highest risk of recurrence. Antiphospholipid syndrome, diabetes, obesity, chronic hypertension, CKD, and assisted reproduction all confer an increased risk of preeclampsia.43 In general, the risk of preeclampsia is higher in a first pregnancy compared with subsequent pregnancies. However, risk returns to that of a first pregnancy in women who have a new partner or an interpregnancy interval beyond 7 years.

TABLE 44.4

Preeclampsia
Essential
criteria
Additional
criteria

Diagnostic Criteria for

>20 weeks’ gestation and New hypertension: systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on two occasions

Proteinuria:
- uPCR >30 mg/mmol (≥0.3 mg/mg)
- >300 mg/24 h (not indicated if uPCR available)
- Dipstick >2+ (if other methods unavailable)
- uACR >8 mg/mmol (>70 mg/g)

Serum creatinine:
- An increase of serum creatinine to >1.0–1.1 mg/dL (>90–100 μmol/L)[a]
- Doubling of serum creatinine in pregnancy (even if new serum creatinine <1.1 mg/dL)[a]

Hematologic complications:
- Platelets <150 × 109/L[a]
- Hemolysis,[a] disseminated intravascular coagulation[a]

Liver complications:
- AST or ALT >40 U/L or double normal reference limit[a]
- Epigastric/right upper quadrant pain (not attributable to alternate diagnosis)[a]

Neurologic complications:
- Eclampsia[a]
- Altered mental status[a]
- Blindness, persistent visual scotomata[a]
- Stroke[a]
- Clonus
- New onset headache not attributable to alternate diagnosis[a]

Respiratory complications:
- Pulmonary edema[a]

Uteroplacental dysfunction:
- Fetal growth restriction, abnormal umbilical artery
- Doppler waveform, stillbirth

Diagnosis requires one essential and one additional clinical feature for diagnosis.

[a] Severe features.

ALT, Serum alanine transferase; AST, serum aspartate transferase; BP, blood pressure; uACR, urinary albumin:creatinine ratio; uPCR, urinary protein:creatinine ratio.

Modified from Brown MA, Magee LA, Kenny LC, et al; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72:24–43; ACOG practice bulletin no. 202 summary: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:211–214; and Wiles K, Chappell LC, Lightstone L, Bramham K. Updates in diagnosis and management of preeclampsia in women with CKD. Clin J Am Soc Nephrol. 2020;15:1371–1380.

Pathogenesis

The placenta is likely to be key in the development of preeclampsia, secreting factors that cause systemic endothelial dysfunction (Fig. 44.4).44 Hence, preeclampsia can occur in hydatidiform mole, where the fetus is absent, and it resolves after delivery and removal of the placenta.

Normal placental development is characterized by remodeling of the uterine spiral arteries within the endometrium that supply the placenta. The process is driven by cytotrophoblasts derived from the conceptus, which surround the walls of the spiral arteries, leading to destruction of smooth muscle and elastin within the arterial wall and replacement with inert fibrinoid material, thereby preventing vasoactivity and vasoconstriction. This conversion of the spiral arteries produces capacitance vessels capable of carrying blood at a reduced velocity and pulsatility to placental villi, allowing sufficient oxygen exchange between mother and fetus.

BOX 44.2

Risk Factors for Preeclampsia

Maternal Factors

Obstetric

- Nulliparity
- Multiple-gestation pregnancy
- History of previous preeclampsia
- Prior intrauterine growth restriction
- Prior placental abruption
- Prior stillbirth
- Artificial reproductive technology
- Molar pregnancy
- Trisomy 13 or fetal hydrops
- Gestational diabetes
- First trimester biophysical/biochemical markers: uterine artery pulsatility index, uterine mean arterial pressure, serum pregnancy-associated plasma protein A and placental growth factor[a]

Comorbidity

- Chronic hypertension
- Chronic kidney disease
- Pregestational diabetes
- Prepregnancy body mass index >30 kg/m^2
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
- Polycystic ovarian syndrome

Genetic

- Thrombophilia
- Preeclampsia in first-degree relative

Other

- Age >40 years
- Having been born small for gestational age

Paternal Factors

- New partner
- Conception by intracytoplasmic sperm injection
- Father born from pregnancy affected by preeclampsia

[a] Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing blood pressure disorders and related problems. Cochrane Database Syst Rev. 2018;10(10):CD001059.

Although deficient spiral artery remodeling has also been described in normal pregnancies and in fetal growth restriction in the absence of preeclampsia, there is consensus that this finding is most marked in preeclamptic pregnancies. A failure of spiral artery remodeling results in uteroplacental ischemia (though this may not be the only mechanism producing an hypoxic placental environment), indicated by the finding of hypoxia-inducible factor 1α, a marker of cellular oxygen deprivation, in the placentas of women with preeclampsia.[45] Oxidative stress, activation of nuclear factor-κB, increased necrotic trophoblast shedding, and proinflammatory interleukin production have all been mechanistically linked to the hypoxic microenvironment. Pathologic inflammation is also evidenced by acute atheroma, which is seen in 10% of preeclamptic placentas.[46] Placental hypoxia leads to an altered balance between angiogenic (placental growth factor [PlGF], vascular endothelial growth

Pathogenesis of Preeclampsia
Prepregnancy

Early Pregnancy

- Preexisting endothelia dysfunction
- Genetic factors
- Immunologic factors
- Oxidative stress

- Inappropriate spiral artery remodeling
- Abnormal placentation
- Therapeutic role for asprin likely at this stage of pathogenesis

Pre-eclampsia

Angiogenic Imbalance
- Decrease in circulating placental growth factors e.g., PIGF
- Increase in antiangiogenic factors e.g., sFlt-1

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•
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•
•
•

Proteinuria
Loss of kidney function
CNS disease
Liver disease
Thrombocytopenia/hemolysis
Uteroplacental dysfunction

Postpartum
- Risk of chronic hypertension
- Risk of CV disease
- Risk of chronic kidney disease

Fig. 44.4 Pathogenesis of Preeclampsia. Prepregnancy risk factors and hypothesized pathologic mechanisms contribute to the failure of trophoblast uterine interactions in early pregnancy. Stress to the syncytiotrophoblast leads to the release of a range of factors into the systemic circulation producing an imbalance between proangiogenic factors including placental growth factor (PIGF) and antiangiogenic factors including soluble fms-like tyrosine kinase-1 (sFlt-1), which is detectable before the clinical syndrome of preeclampsia manifests. Maternal endothelium dysfunction produces the clinical syndrome of preeclampsia. Preeclampsia confers a risk of chronic hypertension, and cardiovascular (CV) and kidney disease later in life. (Pre-eclampsia image from Maher GM, McCarthy FP, McCarthy CM et al. A perspective on pre-eclampsia and neurodevelopmental outcomes in the offspring: Does maternal inflammation play a role? Int J Dev Neurosci. 2019;77:69–76.)

sFlt-1 and sEng Cause Endothelial Dysfunction
by Antagonizing VEGF and TGF- 1 Signaling

Anticoagulant and
vasodilatory factors

VEGF
PIGF

Flt-1
sFlt-1

Healthy endothelial cell
Healthy
placenta

Blood vessel

Pro-coagulant and
vasoconstricting factors

Dysfunctional endothelial cell
Blood vessel
Preeclampsia
placenta

Fig. 44.5 Proteins Soluble fms-like Tyrosine Kinase 1 (sFlt-1) and Soluble Endoglin (sEng) Cause Endothelial Dysfunction by Antagonizing Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PlGF), and Transforming Growth Factor β1 (TGF-β1) Signaling. There is mounting evidence that VEGF and TGF-β1 are required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiologic levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt-1 and sEng (two endogenous circulating antiangiogenic proteins) inhibits VEGF/PlGF and TGF-β1 signaling, respectively. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins. sFlt-1, Soluble Fms-like tyrosine kinase 1; PlGF, placental growth factor. (Modified from Karumanchi SA, Epstein FH. Placental ischemia and soluble fms-like tyrosine kinase 1: cause or consequence of preeclampsia? Kidney Int. 2007;71[10]:959961.)

factor [VEGF], transforming growth factor beta [TGFβ]) and antiangiogenic (soluble fms-like tyrosine kinase 1 [sFlt-1] and soluble endoglin [sEng]) factors, which are measurable in the maternal circulation. sFlt-1 and sEng are syncytiotrophoblast-derived antiangiogenic factors, which bind to PlGF, VEGF, and TGFβ, preventing their interaction with endothelial receptors, thereby inducing endothelial dysfunction, with increased sensitivity to proinflammatory

factors and inhibition of vasodilatory pathways (Fig. 44.5). Thus, insufficient placental function, the release of antiangiogenic placental factors into the maternal circulation, and an exaggerated maternal inflammatory response produce the preeclamptic phenotype of generalized endothelial dysfunction including clotting activation, glomerular endotheliosis, transaminitis, and cerebral and pulmonary edema.

Renal Abnormalities in Preeclampsia
Altered angiogenesis
Endothelial dysfunction

↑ renin/angiotensin response
↑ uric acid resorption

Complement activation
Podocyte injury/loss

↓ prostacyclin

The hypertensive phenotype can be explained by an exaggerated pressor response, possibly mediated by angiotensin II type 1 receptor (AT1) autoantibodies. These antibodies are detected in some women with preeclampsia and can activate the AT1 receptor, produce reactive oxygen species (ROS), increase thrombin generation, impair fibrinolysis, and cause endothelial cell damage.45 However, the importance of AT1 autoantibodies in the pathogenesis of preeclampsia remains to be determined.

The clinical presentation of preeclampsia depends on how maternal organ systems and the fetus are affected, but once begun, preeclampsia runs a progressive course until removal of the placenta at delivery, which remains the only definitive cure.

Kidney Abnormalities in Preeclampsia
Proteinuria

Fig. 44.6 Renal abnormalities in preeclampsia. GFR, Glomerular filtration rate. (Modified from Hoenig MP, Hladik GA. Overview of kidney structure and function. In: National Kideny Foundation Primer on Kidney Diseases, ed 8. 2022:2–18.)

A

Histologic changes in the kidney include diffuse glomerular endotheliosis, characterized by swelling and vacuolization of endothelial cells, capillary lumen occlusion, and glomerular enlargement (Fig. 44.6). The swollen endothelial cytoplasm encroaches on glomerular capillary lumina, contributing to tuft ischemia (Fig. 44.7). Immunofluorescence

B

CL

C

Fig. 44.7 Glomerular Endotheliosis. (A) Normal glomerulus on light microscopy. (B) Glomerulus from a patient with preeclampsia on light microscopy. Note occlusion of capillary lumina by swollen endothelial cells. (C) On electron microscopy, note glomerular basement membrane (arrows) and marked reduction of capillary lumen (CL) caused by swollen endothelial cell cytoplasm. (A–B, Periodic acid–Schiff reaction; magnification ×40; C, original magnification ×7500.) (Courtesy Prof. P. Furness, University of Leicester, UK.)

may reveal fibrin deposits. However, preeclampsia is a clinical diagnosis and kidney biopsy is not indicated.

BOX 44.3

Proteinuria

Primary Manifestation
- Hypertension

Proteinuria in preeclampsia may be part of the general capillary leak of preeclampsia or a consequence of glomerular endotheliosis. Both glomerular and tubular patterns of proteinuria are reported. Glomerular proteinuria is nonselective and varies from the diagnostic threshold of 300 mg/day up to the nephrotic range. Levels of proteinuria in women with preeclampsia do not consistently correlate with maternal and fetal outcomes.47 48

Kidney Involvement
- Significant proteinuria: spot ratio of urine protein to creatinine >30 mg/mmol (≥0.3 mg protein/mg creatinine)
- Acute kidney injury: serum creatinine >1.0–1.1 mg/dL (>90 mmol/L)
- Oliguria

Decreased Glomerular Filtration Rate
GFR is decreased by approximately one-third in women with preeclampsia compared with normotensive late pregnancy. This reduction in GFR is greater than the measured reduction in blood flow, leading to the conclusion that glomerular endotheliosis is an important causative factor in addition to the hemodynamic changes of preeclampsia, including vasoconstriction, plasma volume contraction, and altered cardiac output.

Sodium Retention
Sodium retention occurs in preeclampsia, thought to be a renal tubular response to the perceived reduction in kidney perfusion, increased sympathetic nervous system activity, and/or altered expression of epithelial sodium channels.

Increased Uric Acid Reabsorption
Hyperuricemia in preeclampsia results primarily from increased renal uric acid retention in the kidney, perhaps with increased placental production. Though hyperuricemia has been correlated with fetal risk, serum uric acid concentrations are not a diagnostic criterion for preeclampsia.

Clinical Manifestations
A diagnosis of preeclampsia requires a combination of new onset of hypertension after the 20th week of pregnancy, with evidence of maternal endothelial dysfunction or uteroplacental compromise (see Table 44.4). Symptoms are not always present but may include headache, visual scotomata, seizures, focal neurologic deficit (manifestations of cerebral involvement), epigastric or right upper quadrant pain (reflecting hepatic disease), oliguria, abdominal pain (placental abruption), or reduced fetal movements (Box 44.3). Neurologic complications include seizures (eclampsia), ischemic and hemorrhagic stroke, retinal detachment, cortical blindness, and posterior reversible encephalopathy. Hepatic complications include transaminitis, subcapsular hematoma, and in rare cases liver rupture. AKI occurs, though requirement for dialysis is rare in the absence of significant hemodynamic complications at

the time of delivery, or severe disease with thrombotic microangiopathy. Cardiorespiratory complications include myocardial ischemia and pulmonary edema.

Diagnosis and surveillance of preeclampsia require the following:

✓ • ✓ Quantitation of proteinuria by uPCR or uACR (diagnostic only)
✓ • ✓ Hemoglobin and platelet count
✓ • ✓ Serum creatinine and electrolytes
✓ • ✓ Serum transaminases
✓ • ✓ Ultrasound assessment of fetal growth, amniotic fluid volume, and umbilical artery flow

Routine evaluation in preeclampsia should include BP measurement, assessment for pulmonary edema, assessment for clonus as a warning sign of impending eclampsia, fetal heart rate patterns measured by cardiotocography (CTG) and assessment of fetal growth.

Clinical Features of Preeclampsia

Hematologic Involvement

- Thrombocytopenia
- Hemolysis
- Disseminated intravascular coagulation

Liver Involvement

- Raised serum transaminases
- Severe epigastric or right upper quadrant pain

Neurologic Involvement

- Seizures (eclampsia)
- Hyperreflexia with sustained clonus
- Severe headache
- Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)
- Cerebrovascular accident (stroke)

Other Major Features

- Pulmonary edema
- Fetal growth restriction
- Placental abruption

Eclampsia

Eclampsia is the occurrence of tonic-clonic seizures in a woman with preeclampsia. The majority, but not all, have premonitory signs and symptoms in the week before a first eclamptic seizure including headache (56%), visual disturbances (23%), epigastric pain (17%), hypertension (48%), proteinuria (46%), or concurrent hypertension and proteinuria (38%).49 Risk for eclampsia is not directly related to the level of BP, and it can occur in treated hypertension and in the absence of proteinuria. Importantly, about half the cases of eclampsia occur after delivery, usually within the first 5 postpartum days.

HELLP Syndrome

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) is considered a severe form of preeclampsia in which hepatic and platelet abnormalities dominate, with thrombotic microangiopathy. Proteinuria may be absent. The diagnosis of HELLP syndrome is based on the following laboratory criteria:

✓ • ✓ Microangiopathic hemolytic anemia: schistocytes (fragments) in a blood film, elevated serum bilirubin, high lactate dehydrogenase, low haptoglobin
✓ • ✓ Increased liver transaminases: aspartate transaminase greater than 70 U/L or more than twice the upper limit of normal
✓ • ✓ Platelet count: less than 100 × 109/L

Maternal mortality from severe HELLP syndrome is about 1% and perinatal mortality between 7% and 34%, largely depending on gestational age.50 It is advisable to treat this as a severe variant of preeclampsia, for which iatrogenic delivery is usually indicated to prevent morbidity and mortality. Maternal steroid administration is therapeutic and is not recommended.

Natural History

In general, the prognosis is favorable for women with preeclampsia, but complications include abnormal liver function or thrombocytopenia (10%–20%), pulmonary edema (<0.5%), AKI (1%–5%), placental abruption (1%–4%), fetal growth restriction (10%–25%), neurologic damage (<1%), preterm birth, and perinatal death.51 After delivery, clinical and laboratory derangements of preeclampsia resolve, but this may be delayed in some women, and it is critical to remain vigilant until there is definite improvement in the clinical picture and hematologic and biochemical parameters. Some patients require antihypertensives for the first time in the postnatal period, which we recommend for BPs in excess of 140/90 mm Hg. Hypertension may persist for days, weeks, or months but will eventually resolve if preeclampsia is responsible for the elevated BP and there is no underlying chronic hypertension.

Prediction

Combination screening, including maternal risk factors, late firsttrimester uterine artery Doppler ultrasound, and various biomarkers, has been shown in some studies to predict early-onset preeclampsia with high sensitivity and specificity,52,53 though clinical validation is awaited. The use of a combined first-trimester screen has shown that the detection of preeclampsia requiring delivery before 34 weeks’ gestation, which is associated with the highest neonatal morbidity and mortality, can be predicted in 50% of cases using maternal characteristics, improved to 75% by the addition of biochemical markers (serum pregnancy-associated plasma protein-A and placental growth factor), to 90% by addition of biophysical markers (uterine artery pulsatility index, uterine mean arterial pressure), and to 95% if biochemical and biophysical markers are both used.54 This strategy was used to detect high-risk women in a randomized controlled trial (RCT) of aspirin for the prevention of preeclampsia, with a detection rate of 77%.55 Such screening may offer clinical utility for women who would not qualify for aspirin prophylaxis based on maternal characteristics alone, provided it is affordable, where standards in measuring pulsatility indices are met, and where appropriate counseling is available.

Changes in angiogenic (lower PlGF) and antiangiogenic (higher sFlt-1) factors are also predictive in preeclampsia. A PlGF concentration lower than 100 pg/mL before 35 weeks’ gestation has been shown to rule out the need for delivery due to preeclampsia within the next 2 weeks with 98% probability.56 Similarly, a ratio of sFlt-1:PlGF lower than 38 has a negative predictive value of 99% for the development of preeclampsia within 1 week and 95% for the next 4 weeks.57 One RCT of revealed versus concealed PlGF testing showed that PlGF testing in suspected preeclampsia reduced the time to diagnosis and maternal adverse event rate, with no difference in perinatal outcomes.58 There has been variable adoption of these markers in the assessment of women with placental insufficiency, including suspected preeclampsia, with the outcome of further studies awaited.

Prevention

The observation that preeclampsia is associated with increased platelet turnover and increased platelet-derived thromboxane levels led to several trials investigating the effect of aspirin in the prevention of preeclampsia. Low-dose aspirin (75–150 mg daily) has been shown to reduce the incidence of preeclampsia.59-62 A recent RCT involving high-risk women was based on maternal risk characteristics and biophysical and biochemical markers. The trial, in which women were given 150 mg aspirin daily versus placebo for 11 to 14 weeks, demonstrated a 62% reduction in preterm preeclampsia.63 We advocate starting aspirin in all high-risk women at a dose of 150 mg/day in early pregnancy (by 16 weeks' gestation) until 36 weeks.

Evidence that high-dose oral calcium supplementation reduces the risk of preeclampsia is of low quality.64 The World Health Organization recommends calcium supplementation (1.5–2 g/day) after 20 weeks' gestation only in women with low dietary calcium intake, and calcium supplementation is not given routinely in most high-income countries. Nutritional supplements, including magnesium, folic acid, fish oils, antioxidants, and garlic, have no efficacy in preventing preeclampsia.65 In particular, combined use of vitamins C and E has been associated with worse maternal and fetal outcomes. Anticoagulation is not recommended for reducing the risk of preeclampsia. Maternal obesity is associated with an increased risk for preeclampsia, and weight loss is recommended to reduce risk.

Management

All women with preeclampsia should be reviewed at the initial diagnosis to assess the severity of the condition and the well-being of the fetus. In some centers, PlGF-based testing is used to predict the risk of preterm delivery and serious maternal complications to guide decisions about the appropriate place of care. If BP is controlled in the absence of severe features, fetal compromise or other clinical concern, outpatient care may be appropriate provided resources, expertise, and regular repeat surveillance are available. Face-to-face clinical reviews should take place at least twice weekly, including platelet count, serum creatinine, liver function, and CTG as clinically indicated. Repeated quantification of proteinuria is not required once the protein-tocreatinine ratio has reached the diagnostic threshold of 30 mg/mmol, because the amount or rate of increase in proteinuria does not reliably predict adverse maternal or perinatal outcome. Ultrasound estimation of fetal growth, amniotic fluid volume, and umbilical artery blood flow should be done at diagnosis and at least every 2 weeks, though a higher frequency may be indicated according to the degree of uteroplacental dysfunction seen.

Blood Pressure Management

The main indication for antihypertensive therapy in preeclampsia is to prevent maternal severe hypertension with risk of intracerebral hemorrhage and placental abruption. Treatment of hypertension does not affect the disease course of preeclampsia, which continues to be driven by irreversible, abnormal placental function. However, control of maternal BP may allow pregnancy to be prolonged, with further fetal maturation.

The BP threshold at which antihypertensive treatment should be initiated is controversial. An RCT of "tight" (target diastolic 90 mm Hg) with "less tight" (target diastolic 100 mm Hg) BP control in pregnancy found that although the achieved BP differences between groups were less than intended (139/90 mm Hg vs. 133/85 mm Hg), tighter BP control was associated with a reduced incidence of severe maternal hypertension (28% vs. 41%) without fetal compromise.66 A secondary analysis showed that in women with less tight BP, severe hypertension was associated with an increased risk of adverse maternal and fetal outcomes.67 A systematic review of 59 trials and 4723 women with BPs in pregnancy between 140/90 and 169/109 mm Hg concluded that antihypertensive treatment halves the risk of severe maternal hypertension, with no adverse effects on maternal and fetal outcomes.68 Such studies have led to a fall in the treatment targets for hypertension in pregnancy over recent years (Table 44.5). An outlier in this trend is the United States, where antihypertensive treatment is not recommended unless BP is higher than 160/110 mm Hg for women with gestational hypertension or preeclampsia69 and 150/100 mm Hg in women with chronic hypertension and end organ damage.70 Falling rates of maternal death from hypertensive disorders in the United Kingdom contrast with

Recommended Blood Pressure Targets in Pregnancy

TABLE 44.5

Professional Society	Blood Pressure for Treatment Initiation (mm Hg)	Treatment Target (mm Hg)
NICE, 2010	>150/100 >140/90 if target organ damage	<150/80–100
ACOG, 2013	≥160/110 ≥160/105 if chronic hypertension	120–160/80–105 for chronic BP
SOGC, 2014	>160/110 140–159/90–109 if comorbid conditions	130–155/80–105 <140/90 if comorbid conditions
SOMANZ, 2014	≥160/110 for mild/moderate BP ≥170/110 for severe BP	NA
ISSHP, 2014	160–170/110 for preeclampsia	NA
ISSHP, 2018	>140/90 (>135/85 home)	110–140/85 Reduce medication if diastolic <80
NICE, 2019	>140/90	110–135/70–85
ACOG, 2020	≥160/110 ≥150/100 if end organ damage	120–160/80–110 if chronic hypertension

global rates and those in the United States. This has been attributed to strict management protocols that include adequate treatment of hypertension to increasingly lower BP targets in addition to avoiding fluid overload, seizure prophylaxis, and planned delivery after 36 ± 6 weeks' gestation.71 Our practice is to target treatment to achieve a BP of 110/70 to 135/85 mm Hg in pregnancy.

The choice of antihypertensive agent in pregnancy is determined by licensing, availability, and clinician experience, with no high-level evidence to guide prescribing. The dosing of antihypertensive medication for pregnancy is shown in Table 44.6. Where urgent blood control is needed, both IV (labetalol, hydralazine) and oral (nifedipine, labetalol, methyldopa)72 agents can be used. Modified-release oral nifedipine is used in this situation to avoid the precipitous drop in BP that can occur with immediate release preparations before admission/monitoring is established llowing for additional treatment including IV preparations if needed. Fewer safety data are available for amlodipine and doxazosin/prazosin, although no adverse fetal effects are commonly reported. ACE inhibitors and angiotensin receptor antagonists are contraindicated due to fetotoxicity in the second and third trimesters. In the absence of pulmonary edema, diuretics are avoided because of concern regarding further intravascular volume depletion on top of the known volume contraction that exists in preeclampsia.

Eclampsia Prophylaxis and Treatment

Over the past 10 years, there has been a trend to reduce the target blood pressure in pregnancy due to evidence of maternal benefit in the absence of fetal harm.

ACOG, American College of Obstetricians and Gynecologists; ISSHP, International Society for the Study of Hypertension in Pregnancy; NA, not applicable; NICE, National Institute for Health and Care Excellence; SOGC, Society of Obstetricians and Gynaecologists of Canada; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand.

TABLE 44.6

Magnesium sulfate loading (4 g over 10–15 minutes) followed by an infusion (1 g/h) is used for eclampsia prophylaxis and treatment. Magnesium is a more effective anticonvulsant in eclampsia than diazepam and phenytoin. When used prophylactically, magnesium halves the risk of eclampsia and therefore likely reduces maternal death.73 It should be continued for 24 hours after a seizure or until 24 hours after delivery when used as prophylaxis. Magnesium sulfate is excreted by the kidney, so caution is required in women with oliguria, AKI, or CKD. In these settings, we advocate that the full loading dose is given

Antihypertensive Treatment in Pregnancy

Medication	Dose	Notes
Labetalol		Avoid in asthma, heart block/bradycardia Short duration of action; consider oral dosing three times per day.
Nifedipine	Oral: 200–1200 mg/day IV: 50 mg every 10 min to a total 200 mg	

IV infusion: 20 mg/h, titrated as required
Oral: 10 mg stat dose, 20–90 mg/day

Methyldopa

Oral: 250–750 mg three times per day

Hydralazine

Slow IV: 5 mg over 5–10 min, repeated after 20–30 min
Oral: 25–50 mg three times/day

Clonidine
Prazosin

Oral: 0.05 mg two to three times per day, maximum 1.2 mg/day
Oral: 0.5–5 mg once to three times/day

Amlodipine

Oral: 5–10 mg/day

Modified-release preparations are used to prevent a precipitous fall in BP and reflex tachycardia.
Sublingual preparations are not recommended. Doses can be repeated after 30–60 min. May cause headache and peripheral edema.
Wean after delivery due to exacerbation of postnatal depression. 1000 mg orally has been used in the treatment of severe hypertension, with less effect compared with nifedipine.[a]
IV is used for control of severe hypertension where labetalol is contraindicated or ineffective.
Monitor for hypotension and tachycardia. Preloading with IV fluid may be indicated if volume deplete on clinical assessment (250 mL and review). Rarely used orally for acute BP lowering due to unpredictable hypotensive effect.

Can cause orthostatic hypotension
Limited safety data
Limited safety data

Oral dosing is recommended where adequate control can be achieved and expectant management is ongoing. IV dosing is recommended for urgent control in severe hypertension (>160/110 mm Hg), where oral agents do not achieve the desired clinical effect or for precise control at the time of delivery.

[a] Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet. 2019;394:1011–1021.

BP, Blood pressure; IV, intravenous.

but the concentration of the ongoing infusion is reduced. Though a serum concentration 1.8 to 3.0 mmol/L has been suggested as therapeutic, monitoring is controversial as concentrations do not correlate with clinical toxicity. In the absence of kidney impairment, we do not routinely measure serum magnesium concentrations. Assessment of respiratory rate, oxygen saturation, examination for hyporeflexia, and electrocardiogram review are required. In our view, seizure prophylaxis should be given to women with preeclampsia and severe features, particularly if there is clinical evidence of cerebral involvement including clonus, severe headaches, and visual scotomata. These women should simultaneously have a plan made for delivery. Withholding seizure prophylaxis in women with preeclampsia without severe features is associated with an extremely low likelihood of seizure and avoids the potential for drug toxicity, which occurs in up to 25% of women treated with magnesium sulfate.73 74

Fluid Balance

Preeclampsia is a volume-contracted, not volume-depleted, state. In addition, increased capillary permeability means that IV volume expansion carries risk, particularly for pulmonary edema. Volume expansion is not warranted in most women with preeclampsia because of the risks of pulmonary edema, and fluid restriction (to ~85 mL/h) in women with preeclampsia with severe features reduces maternal morbidity and mortality. Invasive measures of central pressure are not indicated.

Other

Platelet transfusion is generally given for platelet counts less than 20–30 × 109/L to facilitate delivery. Platelet transfusion is avoided at higher counts, as the pathology of thrombocytopenia in preeclampsia is one of platelet consumption, not platelet deficiency. Coagulopathy should also be corrected. Caution is advised in the use of fresh frozen plasma because of the IV volume required, and the use of concentrated preparations should be considered. There is no evidence that plasma exchange or corticosteroids are of therapeutic benefit in HELLP syndrome. Therapeutic adsorption of sFlt-1 by dextran column apheresis is the subject of an ongoing prospective study.75

Delivery

The only definitive treatment for preeclampsia is delivery of the placenta. The decision to deliver weighs the risk of progressive maternal disease against the likelihood of complications in the infant due to preterm delivery. Assessment of fetal well-being helps to establish the benefit of further intrauterine time. Timing of delivery should be based on optimizing perinatal outcomes while avoiding maternal risks. Indications for delivery include the following:

- Progressive evidence of maternal organ dysfunction: worsening kidney or hepatic function, progressive thrombocytopenia, neurologic symptoms or signs
- Inability to control BP
- Failure of fetal growth or concern about fetal status

The Hypertension and Preeclampsia Intervention Trial at Near Term (HYPITAT) showed that after 37 weeks' gestation, the maternal risks of preeclampsia are significantly reduced with delivery, without additional perinatal risks.76 In contrast, prior to 34 weeks, the advantages of increased fetal maturity mean that, in the absence of the indications listed above, expectant management to prolong pregnancy is the norm. For women with preeclampsia between 34 to 37 weeks' gestation, the situation is less clear. A recent randomized trial of planned delivery versus expectant management for women with preeclampsia between 34 and 37 weeks showed that planned delivery reduced maternal morbidity and severe hypertension compared with expectant management, with three-quarters of expectantly managed women progressing to severe preeclampsia. Although there were more neonatal unit admissions related to prematurity with planned delivery, there was no increase in respiratory or other neonatal morbidity. This suggests that planned delivery for women with preeclampsia can be considered after 34 weeks. The trade-off of a reduced risk of severe hypertension and maternal morbidity, against higher neonatal unit admission without excess morbidity, should be discussed with the mother and the multidisciplinary team involved in her and her baby’s care with shared decision-making regarding time of delivery.

Antenatal corticosteroids for fetal lung maturation are routinely given to women who are less than 34 weeks’ gestation in whom delivery within the next 7 days is anticipated. Use of corticosteroids for fetal lung maturity after 34 weeks remains controversial with limited prospective, randomized trial data to guide practice. Many consensus protocols do recommend steroids at later gestations, particularly for cesarean delivery, which is associated with higher rates of neonatal respiratory distress compared with vaginal delivery.

The antepartum management of preeclampsia is summarized in Fig. 44.8.

Postpartum Management

Recovery should be anticipated over 5 to 7 days after delivery in most women. In many women, the condition may worsen in the first 3 to 5 days after delivery, and they should continue to be monitored and treated in the same way as antepartum. Persistent hypertension at 3 months postpartum warrants investigation for chronic hypertension. Proteinuria can persist for up to 6 months, though regression would be expected. Nonregression of proteinuria and persistent proteinuria at 6 months postpartum warrant renal referral to exclude the possibility of underlying CKD. Investigation to exclude underlying connective tissue, cardiovascular, kidney, and antiphospholipid disorders should be considered for women with early-onset preeclampsia requiring delivery in the second or early third trimester, before another pregnancy.

Preeclampsia has well-recognized long-term implications, including an increased risk for chronic hypertension, coronary heart disease, stroke, venous thromboembolism, and CKD (Box 44.4). Whether preeclampsia causes, accelerates, or reveals underlying endothelial dysfunction is not clear. It is appropriate to counsel women who develop hypertension in pregnancy on cardiovascular risk factor lifestyle modifications, along with interval BP, serum lipid, blood glucose, and kidney function surveillance.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) usually presents in the third trimester and has an incidence of 5 per 100,000 pregnancies,[77] but many milder cases may go unrecognized. Primiparity, twin pregnancies, and low body mass index (<20) are overrepresented in women who develop AFLP compared with the general obstetric population. AKI is a common complication of AFLP.

Pathogenesis and Pathology

AFLP is characterized by lipid microvesicle infiltration of hepatocytes without inflammation or necrosis, though biopsy is not required for clinical diagnosis. AFLP has been linked with rare disorders of mitochondrial fatty acid oxidation, which lead to variable clinical manifestations in those affected including hypoglycemia, hepatic dysfunction, encephalopathy, cardiomyopathy, peripheral neuropathy, and myopathy. Both AFLP and HELLP are described in pregnancies in which the fetus is affected by such a disorder of fatty acid oxidation, of which long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is the best described. The mothers of babies affected by these recessive conditions are default heterozygotes for the same mutation. Although

Management of Preeclampsia
Clinical assessment:
BP
Symptoms and signs
CBC, creatinine and electrolytes, LFT
Urinary protein/albumin:creatinine
Fetal assessment
PIGF-based testing of suspected placental insufficiency

BP >160/110 or other severe features

No

Yes

Urgent BP control to <160/110, then ≤135/85
MgSO4 for prophylaxis of eclampsia
Fluid balance assessment and monitoring; fluid restriction for most (≤85 mL/h)
Platelet count and coagulation safe for delivery

Indications for delivery
≥37 weeks
Uncontrolled hypertension
Worsening renal, hepatic function or thrombocytopenia
HELLP syndrome
Eclampsia
Pulmonary edema
Fetal compromise: Doppler or CTG

<37 weeks

Expectant management
Target BP ≤135/85 and monitor at least alternate days
Twice weekly CBC, creatinine and electrolytes, LFT
Fetal surveillance at least fortnightly
Risk/benefit of delivery >34 weeks' discussed

≥37 weeks

Deliver

In-patient management if:
- Clinical concerns
- High risk for complications/preterm delivery
(e.g., full PIERS, PREP-S models)

Fig. 44.8 Management of Preeclampsia. Management depends on disease severity and gestational age of diagnosis. BP, Blood pressure; CBC, complete blood count; CTG, cardiotocography; HELLP, hemolysis, elevated liver enzymes, and low platelet count; MgSO4 magnesium sulfate; LFT, liver function test; PlGF, placental growth factor. (Modified from Chaiworapongsa T, Chaemsaithong P, Korzeniewski SJ, et al. Preeclampsia part 2: prediction, prevention and management. Nat Rev Nephrol. 2014;10[9]:531–540.)

Long-Term Consequences of Preeclampsia

BOX 44.4

- Fatal and nonfatal coronary heart disease
- Cerebrovascular accident (stroke)
- Hypertension
- Thromboembolism
- End-stage kidney disease
- Diabetes
- Cognitive dysfunction and white matter lesions on cerebral computed tomography scan
- Death from any cause

heterozygosity is insufficient for disease manifestation outside of pregnancy, the excess fetal fatty acid burden in pregnancy is thought to lead to hepatic deposition and overt maternal liver disease in pregnancy. The screening of infants born after pregnancies affected by AFLP for fatty acid oxidation disorders including LCHAD deficiency has been advocated but is not routine, and prospective data are warranted.78

Kidney disease in AFLP is likely to be multifactorial. Kidney biopsy and autopsy studies have shown mild glomerular hypercellularity with thick, narrow capillary loops and tubular free fatty acid accumulation, suggesting that abnormal fatty acid oxidation also may contribute to kidney dysfunction. Hemodynamic changes like those seen in the hepatorenal syndrome, thrombotic microangiopathy, and coexisting preeclampsia may also contribute to kidney injury.

Clinical Manifestations

A diagnosis of AFLP requires six or more clinical criteria (Box 44.5) in the absence of another explanation. The severity of liver involvement in women with AFLP is highly variable, ranging from a moderate isolated increase in transaminases to fulminant hepatic failure with encephalopathy and coagulopathy. Characteristic laboratory abnormalities include hyperbilirubinemia, increased transaminases, hypoglycemia, leukocytosis, and evidence of coagulopathy (hypofibrinogenemia, prolonged prothrombin time, depressed antithrombin III levels).

Differential Diagnosis

Viral hepatitis and biliary obstruction should be excluded. Distinguishing AFLP from HELLP can be challenging because the two disorders share many pathophysiologic and clinical features (Table 44.7). However, new vomiting in late pregnancy, polyuria, coagulopathy, and hypoglycemia increase clinical suspicion of AFLP.

Treatment and Outcome

Early diagnosis, supportive care (reversal of coagulopathy, correction of hypoglycemia and fluid status management), and prompt delivery are critical in the management of AFLP. One-third of cases require admission to intensive care. Kidney disease is described in 14% of women with AFLP, with temporary kidney replacement required in one-quarter of women with AKI.77 In most women, there is complete liver and kidney recovery after delivery, although progressive liver disease requiring transplantation is described. AFLP has maternal and perinatal mortality rates of 2% and 10%, respectively, in a high-income country with universal access to health care.77

THROMBOTIC MICROANGIOPATHY

Pregnancy-associated thrombotic microangiopathy (TMA) is defined by the presence of fibrin and platelet thrombi in the microcirculation, causing organ dysfunction, microangiopathic hemolysis, and thrombocytopenia. HELLP syndrome, atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic purpura (TTP) can all cause a pregnancy-associated TMA.

Criteria for the Diagnosis of Acute Fatty Liver of Pregnancy

BOX 44.5

Clinical
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Laboratory Values
Bilirubin >0.8 mg/dL (>14 µmol/L)
Hypoglycemia <70 mg/dL (<4 mmol/L)
Uric acid >5.7 mg/dL (>340 µmol/L)
Leukocytosis >11 × 109/L
ALT or AST >42 U/L
Ammonia >47 µmol/L
Coagulopathy: PT >14 s or APTT >34 s
Other
Ascites or bright liver on ultrasound
Microvesicular steatosis on liver biopsy

Clinical Manifestations and Differential Diagnosis

Diagnosis requires platelet count less than 100 × 109/L, hemoglobin less than 100 g/L, serum lactate dehydrogenase (LDH) more than 1.5 times the upper limit of normal, undetectable serum haptoglobin, a negative direct erythrocyte antiglobulin test, and either the presence of schistocytes (fragments) on blood smear or features of TMA on biopsy of an affected organ.

Women with atypical HUS typically present with AKI, most commonly at the end of pregnancy or in the first 3 months postpartum, although disease is described throughout pregnancy. Although kidney injury predominates in aHUS, cardiac and neurologic disease are also described, so distinction from TTP may be difficult on clinical grounds alone. TTP tends to present in the second and third trimesters at the same time as a physiologic decline in ADAMTS13, the deficiency of which leads to pregnancy-associated TTP.

In practice, it can be difficult to distinguish aHUS and TTP from preeclampsia with severe features (see Table 44.7). Preeclampsia with severe features is a far more common cause of pregnancy-associated TMA than both aHUS and TTP, which are rare. However, recovery of clinical parameters after delivery is expected in preeclampsia/HELLP, and persistent or progressive thrombocytopenia at 48 to 72 hours postpartum should raise clinical suspicion for alternative pathology. Postpartum hemorrhage is another complicating factor. The risk of postpartum hemorrhage is higher in women with thrombocytopenia at the time of delivery, and postpartum hemorrhage is a cause of both TMA and AKI, particularly if there is ischemic necrosis of the kidney cortex. Coagulation studies and liver function tests are usually normal in aHUS and TTP (with the exception of prehepatic hyperbilirubinemia), unlike in HELLP and AFLP. Whether PlGF-based testing offers utility in the distinction of antepartum disease is unknown.

Treatment

Diagnosis requires six or more criteria in the absence of another explanation.
ALT, Alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; PT, prothrombin time.
Modified from Knight M, Nelson-Piercy C, Kurinczuk JJ, et al. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57(7):951–956.

Delivery should be considered for all cases of pregnancy-associated TMA, depending on fetal maturity. Delivery is indicated if there is fetal compromise or progressive maternal disease. Delivery is sufficient to control TMA due to preeclampsia/HELLP and may help achieve a better response to treatment in TTP.
Plasma exchange should be commenced in atypical presentations of preeclampsia/HELLP with thrombocytopenia (<30 × 109/L) and either life-threatening neurologic features (seizures, altered

TABLE 44.7 Differential Clinical and Laboratory Features of Syndromes That Cause Acute Kidney Injury in Pregnancy

Clinical Features

PE

HUS/TTP

HELLP

AFLP

Hemolytic anemia
Thrombocytopenia
Coagulopathy
CNS symptoms
Kidney failure
Hypertension
Proteinuria
Elevated AST
Elevated ALT
Elevated bilirubin
Anemia
Blood ammonia
Low ADAMTS13 activity
Effect of delivery on disease
Management

+/−
+/−
+/−
+/−
+/−
++
+/−
+/−
+/−
+/−
+/−
Normal

−
Recovery
Supportive care/delivery

+++
+++
−
+/− (HUS) ++ (TTP)
+++ (HUS)
+/−
+/−
+/−
−
++
++
Normal
++TTP (but not HUS)
None
Plasma exchange/eculizumab

++
++
+/−
+/−
+
+++
++
++
++
+
+
Normal
−
Recovery
Supportive care/delivery

+/−
+/−
+
+/−
++
+/−
+/−
+++
+++
+++
+/−
High
−
Recovery
Supportive care/delivery

AFLP, Acute fatty liver of pregnancy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HUS, hemolytic uremic syndrome; PE, preeclampsia; TTP, thrombotic thrombocytopenic purpura.

consciousness, coma) or cardiac disease (persistently elevated troponin levels, electrocardiographic abnormalities, impaired cardiac function). Plasma exchange should be continued until ADAMTS13 tests results are available, which will allow confirmation or exclusion of TTP. In the absence of significant neurologic and cardiac disease, parameters can be monitored for postpartum recovery and plasma exchange commenced if anticipated improvements in hemolytic parameters, platelet count, and kidney function are not seen. Plasma exchange is continued only if TTP (or catastrophic antiphospholipid syndrome) is confirmed. If a diagnosis of aHUS is made by exclusion of preeclampsia, short-term treatment with eculizumab can be started and reviewed depending on response to treatment and the results of complement gene testing.78 Though there are limited data on eculizumab exposure and pregnancy, the benefit in treating organ-threatening disease outweighs risk. Treatment can be ceased if no complement abnormality is demonstrated and clinical recovery occurs quickly after delivery.33

ACUTE KIDNEY INJURY

Definition

International criteria for the diagnosis and staging of AKI (e.g., Acute Kidney Injury Network [AKIN]; Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease [RIFLE]; Kidney Disease: Improving Global Outcomes [KDIGO]; see Chapter 72) have not been validated for use in pregnancy. Diagnosis of AKI in pregnancy is therefore based on serum creatinine concentrations. Meta-analysis data show that the upper reference limits (97.5th centile) for serum creatinine in pregnancy are 85%, 80%, and 86% of the female nonpregnant reference range in the first, second, and third trimesters, respectively.8

This means that for a female reference range for serum creatinine of 45 to 90 µmol/L outside of pregnancy, serum creatinine concentrations greater than 0.86 mg/dL (76 µmol/L), 0.81 mg/dL (72 µmol/L), and 0.87 mg/dL (77 µmol/L) in respective trimesters should trigger investigation for AKI (or undiagnosed CKD).

Epidemiology

AKI is associated with an increased morbidity and mortality regardless of the underlying cause, and it should be considered a serious complication of pregnancy. Audit data demonstrate that AKI complicates 1.4% of obstetric admissions in the United Kingdom. Most cases occur in women without preexisting kidney disease, and it is estimated that more than 40% may be unrecognized by the treating clinical team,15 masked by gestational changes, the limitations of serum creatinine, and by physiologic oliguria in the immediate postpartum period.

The development of AKI in pregnancy follows a bimodal distribution with two incidence peaks: the first and third trimesters. Prerenal causes are more common in the first trimester because of hyperemesis gravidarum and septic abortion, which remains a common global cause of pregnancy-associated AKI. The most common etiologies in late pregnancy are preeclampsia and hemorrhage.

Etiology and Pathogenesis

The etiology of pregnancy-associated AKI can be considered according to the trimester in which it presents, which aids in establishing an appropriate differential (Table 44.8). Diagnosis may be complicated by the overlapping clinical phenotype of pregnancy-associated conditions. Table 44.7 outlines the differentiating clinical features of preeclampsia, HELLP syndrome, aHUS/TTP, and AFLP.

TABLE 44.8

Causes of Acute Kidney Injury in Pregnancy

Gestation

Diagnosis

Clinical Features

Early

Hyperemesis gravidarum
Septic abortion/miscarriage
Acute retention
Preeclampsia/HELLP

Nausea, vomiting, ptyalism
Abdominal pain, vaginal bleeding, hypotension
Retroflexed uterus
New-onset hypertension after 20 weeks’ gestation plus evidence of maternal endothelial
dysfunction and/or uteroplacental dysfunction
Increased risk if single kidney (including transplant), autonomic neuropathy, polyhydramnios,
multiple pregnancy, obstructed labor
Vaginal bleeding, abdominal pain, uterine tenderness
Vomiting, polydipsia, jaundice, elevated transaminases, hypoglycemia
Hemolysis and end organ damage including kidney failure, neurologic symptoms, heart disease

Mid-late

Ureteral obstruction

Peripartum

Any

Placental abruption
AFLP
Microangiopathic hemolytic anemia (TTP/HUS)
Chorioamnionitis
Postpartum hemorrhage
Ureteric injury
NSAIDs
Urosepsis
Lupus nephritis
Glomerulonephritis
Interstitial nephritis
Kidney stone disease
Intravascular volume depletion

Tachycardia, fever, uterine tenderness, abnormal lochia, prolonged rupture of membranes
Hemodynamic instability
Operative delivery, fever, leucocytosis, pain, persistent ileus
Hyperkalemia, exacerbation of hypertension, fluid retention
Dysuria, back or flank pain, renal angle tenderness, hypotension
Proteinuria ± hematuria, malaise, joint pain, hair loss, rash, pancytopenia
uPCR >30 mg/mmol or uACR >8 mg/mmol before 20 weeks warrants nephrology referral
New drug exposure including antibiotics, NSAID, proton pump inhibitors, H2 antagonists; systemic

signs can include rash and fever
Renal colic; increased risk of AKI if single kidney
Sepsis, vomiting, cardiac failure, DKA

AFLP, Acute fatty liver of pregnancy; AKI, acute kidney injury; DKA, diabetic ketoacidosis; HELLP, hemolysis, elevated liver enzymes, and low platelet count; HUS, hemolytic uremic syndrome; NSAID, nonsteroidal antiinflammatory drug; TTP, thrombotic thrombocytopenic purpura uACR, urinary albumin/creatinine ratio; uPCR, urinary protein/creatinine ratio.
From Wiles KS, Banerjee A. Acute kidney injury in pregnancy and the use of non-steroidal anti-inflammatory drugs. Obstet Gynaecol. 2016;18:127–135.

Treatment

Fundamental to the management of AKI is supportive treatment to maintain kidney perfusion. However, assessment of the fluid state of the pregnant patient is complicated by physiologic reductions in blood and oncotic pressure. In addition, young pregnant women can compensate for hypovolemia and hypotension and may present with signs much later than expected. The significance of tachycardia and tachypnea in track and trigger systems, which should be based on parameters for pregnancy,15 is important. Treatment specific to the etiology of AKI, such as antibiotics in sepsis, should be administered promptly.

If AKI leads to hyperkalemia, calcium salts for cardiac stabilization can be safely given in pregnancy. There are limited data on the use of oral potassium binders (patiromer and sodium zirconium cyclosilicate) in pregnancy, but systemic absorption is limited, so benefit in managing hyperkalemia is likely to outweigh any theoretical risk. Insulin with glucose can be used as a temporizing measure to increase intracellular potassium shift while definitive treatment of AKI is undertaken.

Drug doses may need to be adjusted in AKI, including antibiotics, anticoagulants, insulin, and opiate analgesia. The use of nonsteroidal antiinflammatory drugs, which often form part of a standard postpartum analgesic protocol, should be avoided in women with AKI.

Dialysis

Indications for kidney replacement in pregnancy mirror those in the nonpregnant population and include metabolic acidosis, hyperkalemia, and fluid overload refractory to medical treatment. Uremic symptoms (encephalopathy or pericarditis) are very rarely encountered in pregnancy, as dialysis is usually commenced in women with advanced CKD at lower serum urea concentrations than outside of pregnancy due to the risk of fetotoxicity. It is generally recommended to consider initiation of dialysis at blood urea nitrogen (BUN) greater than 42 mg/dL (serum urea >15 mmol/L) depending on etiology, trajectory, and plans for delivery. Both peritoneal dialysis and hemodialysis have been used in pregnancy. However, there are more data on the use of hemodialysis, which is preferentially used as it offers the capacity to increment dialysis provision as required, aiming for a predialysis BUN less than 35 mg/dL (urea <12.5 mmol/L) in contemporary cohorts.33 Dialysis in pregnancy is discussed in more detail in Chapter 45

OVARIAN HYPERSTIMULATION SYNDROME

Definition and Epidemiology

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation therapy, which is used to increase the number of oocytes available for assisted reproductive technology. The clinical picture is of significant fluid shifts detectable as ascites and hemoconcentration. Thromboembolism, kidney injury, and pleural or pericardial effusions represent severe disease. OHSS is estimated to complicate between 0.5% and 5% of stimulatory cycles.

Pathogenesis

OHSS is thought to be due to the release of proinflammatory mediators including VEGF, cytokines, prostaglandins, and histamine, which are produced in response to human chorionic gonadotrophin (hCG) on a background of supraphysiologic ovarian stimulation. These factors increase vascular permeability, resulting in ascites, pleural and pericardial effusions, and edema. Women with severe OHSS are estimated to have lost 20% of their circulating volume.

Clinical Manifestations

Symptoms include abdominal bloating and pain, nausea and vomiting, peripheral edema, oliguria, breathlessness, and orthopnea.

Venous thromboembolism can occur. The combination of elevated hematocrit, reduced serum osmolality, and hyponatremia is suggestive of OHSS.

Patients should be investigated with full blood count and hematocrit; serum creatinine, electrolytes and osmolality; liver function tests; C-reactive protein; β-hCG; and coagulation profile.

Abdominal ultrasound imaging may help clarify the diagnosis. OHSS is not a common cause of fever or peritonitis, in which case ovarian torsion or rupture, intraabdominal infection, and ectopic pregnancy should be excluded.

Management

OHSS is self-limiting, with an average duration of 7 days in nonpregnant women and 10 to 20 days in pregnant women. In the woman with moderate to severe OHSS, hospital admission is required for correcting volume depletion; monitoring and correcting electrolyte abnormalities (particularly hyperkalemia); and providing analgesia, nutrition and psychological support, prophylaxis of venous thromboembolism, and respiratory function support. If IV fluids are necessary, crystalloids are used first line, with close monitoring because of the possibility of third-space accumulation. Paracentesis is sometimes needed to improve symptoms and respiratory function, in which case human albumin solution as a plasma volume expander should be considered. Prophylactic anticoagulation is required because of the risk for thromboembolism.

Women with underlying kidney disease have a higher risk of adverse outcomes in the event of OHSS. In vitro fertilization cycles using gonadotrophin-releasing hormone (GnRH) antagonists have been found to have a lower incidence of OHSS compared with cycles where GnRH agonists are used. Incidence is also higher in cycles when conception occurs compared with cycles without conception, and higher still in cycles resulting in multiple pregnancy, highlighting the important role of endogenous hCG. Stimulation followed by later frozen-embryo transfer may therefore be opted for, rather than fresh-embryo transfer with stimulation and pregnancy in the same cycle.

SELF-ASSESSMENT QUESTIONS

1. Which of the following does not occur in normal pregnancy?
A. Lower serum osmolality
B. Hypernatremia
C. Elevated glomerular filtration rate
D. Glycosuria
E. Reduced serum albumin

2. Which of the following is not an indication for delivery in preeclampsia?
A. Proteinuria 2 g/day
B. Gestation 37 weeks or more
C. Pulmonary edema
D. Rising serum creatinine

E. Hemolysis, elevated liver enzymes, and low platelet count (HELLP)

3. Which one of the following syndromes causing acute kidney injury is least likely to recover after delivery?
A. Preeclampsia
B. HELLP syndrome
C. Hemolytic uremic syndrome
D. Acute fatty liver of pregnancy
E. Acute urinary retention

4. Which of the following can be used to predict the need for delivery in suspected preeclampsia?
A. Proteinuria
B. Placental growth factor concentrations
C. Relaxin concentration
D. Renin concentration
E. Angiotensin receptor antibody concentration

5. Which of the following can be given in early pregnancy to reduce the risk of preeclampsia?
A. Folic acid
B. Vitamin D
C. Iron
D. Aspirin
E. Hydralazine

6. Which of the following is not a risk factor for preeclampsia?
A. First pregnancy
B. Previous preeclampsia
C. Interbirth interval less than 1 year
D. Chronic kidney disease
E. Antihypertensive requirement before 20 weeks’ gestation

REFERENCES

1. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20(3):209–214.
2. Rasmussen PE, Nielsen FR. Hydronephrosis during pregnancy: a literature survey. Eur J Obstet Gynecol Reprod Biol. 1988;27(3):249–259.
3. Faundes A, Bricola-Filho M, Pinto e Silva JL. Dilatation of the urinary tract during pregnancy: proposal of a curve of maximal caliceal diameter by gestational age. Am J Obstet Gynecol. 1998;178(5):1082–1086.
4. Webb JAW. Ultrasonography and doppler studies in the diagnosis of renal obstruction. BJU International. 2000;86(S1):25–32.
5. Brown MA, Gallery ED. Volume homeostasis in normal pregnancy and pre-eclampsia: physiology and clinical implications. Baillieres Clin Obstet Gynaecol. 1994;8(2):287–310.
6. Ogueh O, Brookes C, Johnson MR. A longitudinal study of the maternal cardiovascular adaptation to spontaneous and assisted conception pregnancies. Hypertens Pregnancy. 2009;28(3):273–289.
7. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2019;54:297–307.
8. Wiles K, Bramham K, Seed PT, Nelson-Piercy C, Lightstone L, Chappell LC. Serum creatinine in pregnancy: a systematic review. Kidney International Reports. 2019;4:408–419.
8a. Harel Z, McArthur E, Hladunewich M, et al. Serum creatinine levels before, during, and after pregnancy. JAMA. 2019;321:205–207.
9. Strevens H, Wide-Swensson D, Torffvit O, Grubb A. Serum cystatin C for assessment of glomerular filtration rate in pregnant and non-pregnant women. Indications of altered filtration process in pregnancy. Scand J Clin Lab Invest. 2002;62:141–147.
10. Smith MC, Moran P, Ward MK, Davison JM. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. BJOG. 2008;115(1):109–112.
11. Conrad KP. Maternal vasodilation in pregnancy: the emerging role of relaxin. Am J Physiol Regul Integr Comp Physiol. 2011;301(2):R267–R275.
12. Conrad KP, Baker VL. Corpus luteal contribution to maternal pregnancy physiology and outcomes in assisted reproductive technologies. Am J Physiol Regul Integr Comp Physiol. 2013;304(2):R69–72.
13. Schrier RW. Systemic arterial vasodilation, vasopressin, and vasopressinase in pregnancy. J Am Soc Nephrol. 2010;21(4):570–572.
14. West C, Zhang Z, Ecker G, Masilamani SM. Increased renal alphaepithelial sodium channel (ENAC) protein and increased ENAC activity in normal pregnancy. Am J Physiol Regul Integr Comp Physiol. 2010;299(5):R1326–R1332.
15. Green LJ, Mackillop LH, Salvi D, et al. Gestation-Specific Vital Sign Reference Ranges in Pregnancy. Obstet Gynecol. 2020.
16. Stehman-Breen C, Miller L, Fink J, Schwartz SM. Pre-eclampsia and premature labour among pregnant women with haematuria. Paediatr Perinat Epidemiol. 2000;14(2):136–140.
17. McDonald MM, Swagerty D, Wetzel L. Assessment of microscopic hematuria in adults. Am Fam Physician. 2006;73(10):1748–1754.
18. Leduc L, Lederer E, Lee W, Cotton DB. Urinary sediment changes in severe preeclampsia. Obstet Gynecol. 1991;77(2):186–189.
19. Brown MA, Holt JL, Mangos GJ, et al. Microscopic hematuria in pregnancy: relevance to pregnancy outcome. Am J Kidney Dis. 2005;45(4):667–673.
20. Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol. 1994;171:984–989.
21. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol. 2010;115(2 Pt 1):365–375.
22. Waugh JJ, Clark TJ, Divakaran TG, et al. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. Obstet Gynecol. 2004;103(4):769–777.

23. Waugh JJ, Bell SC, Kilby MD, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG. 2005;112:412–417.

24. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol. 2010;115:365–375.
25. Waugh J, Hooper R, Lamb E, et al. Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis. Health Technol Assess. 2017;21:1–90.
26. National Institute for Health and Care Excellence. How effective are spot protein/creatinine ratio or albumin/creatinine ratio measurements as compared with a 24 hour urine collection for the identification of proteinuria in women with hypertensive disorders of pregnancy? From Hypertension in Pregnancy: diagnosis and management. NICE guildine No. 133 https://www.ncbi.nlm.nih.gov/books/NBK550455/.
27. Morikawa M, Yamada T, Minakami H. Outcome of pregnancy in patients with isolated proteinuria. Curr Opin Obstet Gynecol. 2009;21:491–495.
28. Brown MA, Magee LA, Kenny LC, et al. International Society for the Study of Hypertension in Pregnancy ISSHP: Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72:24–43.
29. ACOG. ACOG Practice Bulletin No. 202 Summary: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133:211–214.
30. Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. Br J Obstet Gynaecol. 2013;120:412–427.
31. De Castro I, Easterling TR, Bansal N, Jefferson JA. Nephrotic syndrome in pregnancy poses risks with both maternal and fetal complications. Kidney Int. 2017;91(6):1464–1472.
32. Packham DK, North RA, Fairley KF, Whitworth JA, Kincaid-Smith P. Membranous glomerulonephritis and pregnancy. Clin Nephrol. 1987;28:56–64.
33. Wiles K, Chappell L, Clark K, et al. Clinical practice guideline on pregnancy and renal disease. BMC Nephrol. 2019;20:401.
34. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2019;25(11):CD000490.
35. Millar LK, Wing DA, Paul RH, Grimes DA. Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. Obstet Gynecol. 1995;86(4 Pt 1):560–564.
36. Meher S, Gibbons N, DasGupta R. Renal stones in pregnancy. Obstet Med. 2014;7(3):103–110.
37. Rosenberg E, Sergienko R, Abu-Ghanem S, et al. Nephrolithiasis during pregnancy: characteristics, complications, and pregnancy outcome. World J Urol. 2011;29(6):743–747.
38. Royal College of Radiologists. Protection of Pregnant Patients during Diagnostic Medical Exposures to Ionising Radiation: advice from the Health Protection Agency. The Royal College of Radiologists and the College of Radiographers; 2009. https://www.rcr.ac.uk/system/files/publication/field_publication_files/HPA_preg_2nd.pdf/.
39. Deleted in review.
40. Butler EL, Cox SM, Eberts EG, Cunningham FG. Symptomatic nephrolithiasis complicating pregnancy. Obstet Gynecol. 2000;96(5 Pt 1):753–756.
41. Laing KA, Lam TB, McClinton S, Cohen NP, Traxer O, Somani BK. Outcomes of ureteroscopy for stone disease in pregnancy: results from a systematic review of the literature. Urol Int. 2012;89(4):380–386.
42. on behalf of MBRRACE-UK. In: Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ, eds. Saving lives, improving mothers' care—lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2013–15. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2017.

43. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for preeclampsia determined in early pregnancy: systematic review and metaanalysis of large cohort studies. BMJ. 2016;353:i1753.
44. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
45. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014;10(8):466–480.

References

46. Kim YM, Chaemsaithong P, Romero R, et al. The frequency of acute atherosis in normal pregnancy and preterm labor, preeclampsia, smallfor-gestational age, fetal death and midtrimester spontaneous abortion. J Matern Fetal Neonatal Med. 2015;28:2001–2009.
47. Thangaratinam S, Coomarasamy A, O'Mahony F, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med. 2009;7:10.
48. Fishel Bartal M, Lindheimer MD, Sibai BM. Proteinuria during pregnancy: definition, pathophysiology, methodology, and clinical significance. Am J Obstet Gynecol. 2020.
49. Knight M. Eclampsia in the United Kingdom 2005. BJOG. 2007;114(9):1072–1078.
50. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004;103(5 Pt 1):981–991.
51. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785–799.
52. Kuc S, Wortelboer EJ, van Rijn BB, et al. Evaluation of 7 serum biomarkers and uterine artery Doppler ultrasound for first-trimester prediction of preeclampsia: a systematic review. Obstet Gynecol Surv. 2011;66(4):225–239.
53. Kenny LC, Black MA, Poston L, et al. Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: the Screening for Pregnancy Endpoints (SCOPE) international cohort study. Hypertension. 2014;64(3):644–652.
54. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther. 2013;33:8–15.
55. Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol. 2017;50:492–495.
56. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation. 2013;128:2121–2131.
57. Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016;374:13–22.
58. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, steppedwedge cluster-randomised controlled trial. Lancet. 2019;393:1807–1818.
59. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369:1791–1798.
60. Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the US Preventive Services Task Force. Ann Intern Med. 2014;160:695–703.
61. Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. Am J Obstet Gynecol. 2017;216:121–128.e2.

62. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216:110–120.e6.
63. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017;377(7):613–622.
64. Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing blood pressure disorders and related

problems. Cochrane Database Syst Rev. 2018:CD001059.
65. Chaiworapongsa T, Chaemsaithong P, Korzeniewski SJ, et al. Preeclampsia part 2: prediction, prevention and management. Nat Rev Nephrol. 2014;10(9):531–540.
66. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372:407–417.
67. Magee LA, von Dadelszen P, Singer J, et al. The CHIPS randomized controlled trial (control of hypertension in pregnancy study): is severe hypertension just an elevated blood pressure? Hypertension 68: 1153–1159,
68. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018;10:CD002252.
69. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2020;135:e237–260.
70. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol. 2019;133:e26–e50.
71. Shennan AH, Green M, Chappell LC. Maternal deaths in the UK: preeclampsia deaths are avoidable. Lancet. 2017;389:582–584.
72. Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet. 2019;394:1011–1021.
73. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database of Systematic Reviews. 2010;11:CD000025.
74. Duley L. Pre-eclampsia, eclampsia, and hypertension. BMJ Clin Evid. 2011:2011.
75. Thadhani R, Kisner T, Hagmann H, et al. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation. 2011;124(8):940–950.
76. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks’ gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009;374(9694):979–988.
77. Knight M, Nelson-Piercy C, Kurinczuk JJ, et al. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57(7):951–956.
78. Yang Z, Yamada J, Zhao Y, Strauss AW, Ibdah JA. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. JAMA. 2002;288(17):2163–2166.

45

Pregnancy With Preexisting Kidney Disease

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Historically, kidney disease was considered a contraindication to pregnancy, but now many pregnant patients with chronic kidney disease (CKD) have successful outcomes. To achieve this, nephrologists and obstetricians need to be skilled in disease optimization before pregnancy, counseling regarding possible pregnancy outcomes, and antenatal and postpartum management of such patients.

ADVERSE EFFECTS OF CHRONIC KIDNEY DISEASE ON PREGNANCY OUTCOMES

CKD affects up to 6% and 9% of women of reproductive age in high- and low-income countries, respectively, approximately one-third of whom have stages 3 to 5 CKD.[1] Pregnancy rates are lower in women with CKD. In Australia and New Zealand, women with kidney transplants and on dialysis had severalfold fewer births compared with the general population (21.4 vs. 5.8 vs. 61.9 live births/1000 women/year: in transplant, dialyzed, no kidney replacement therapy).[2]

More recent studies report an increase in live birth rates even in those with more advanced CKD,[3,4] with considerable improvements in outcomes compared with historic data, likely in part because of enhanced fetal surveillance and neonatal intensive care. The following key prepregnancy factors are the main predictors of pregnancy outcomes:

- Degree of reduction in glomerular filtration rate (GFR)/elevation in serum creatinine
- Presence of coexisting hypertension
- Amount of proteinuria

In most circumstances, these features are more important in predicting outcome than the mother’s specific kidney disease etiology.

Traditionally, most women with mild kidney impairment (serum creatinine < 1.5 mg/dL [130 µmol/L]) and controlled hypertension were thought to have a good pregnancy outcome. However, even CKD stages 1 and 2 are associated with a higher rate of preeclampsia and perinatal mortality, preterm delivery, and small for gestation age rates.[4,5] Development of superimposed preeclampsia appears higher in women with a preconception creatinine value of less than 1.4 mg/dL (124 µmol/L) but greater than 0.9 mg/dL (80 µmol/L) in early pregnancy and, indeed, even in women with normal GFR but dipstick-positive proteinuria and one or more other risk factors for preeclampsia.[6] Those with serum creatinine greater than 1.5 mg/dL (133 µmol/L), particularly when accompanied by hypertension and heavy proteinuria, have a higher chance of preterm deliveries and maternal complications, including loss of kidney function. Pregnancy outcomes according to severity of kidney dysfunction are presented in Boxes 45.1 and 45.2

Severity of Hypertension

Preexisting hypertension is associated with significantly higher risk for adverse pregnancy outcomes than the general population[7] and

in pregnant women with CKD.[8] Preexisting hypertension conferred an approximate doubling of risk for severe neonatal outcome (early preterm delivery, requirement for neonatal intensive care, and/or small for gestational age infant) in a prospective Italian cohort study.[3,9] In a contemporary cohort of women with CKD stages 3 or higher, chronic hypertension was the strongest predictor of preterm delivery before 34 weeks and was associated with a greater decline in maternal kidney function in pregnancy.

Proteinuria

Preexisting proteinuria is another risk factor for poor pregnancy outcome.3,10 Women with prepregnancy CKD stages 3 to 5 and a urine protein creatinine ratio greater than 100 mg/mmol (>0.9 mg/mg) before pregnancy or prior to 20 weeks' gestation are more than twice as likely to deliver a baby weighing less than the 10th percentile compared with women with CKD and less proteinuria.

MANAGEMENT COMMON TO ALL PREGNANCIES WITH PREEXISTING KIDNEY DISEASE

The general principles of management of pregnancy in women with CKD are summarized in Box 45.3.

Prepregnancy Counseling

All women with CKD should receive prepregnancy counseling, especially those with CKD stages 3 to 5, but women with CKD 1 or 2 may also have worse pregnancy outcomes than the general population.4 Issues that should be covered in counseling are shown in Box 45.4, including relevant information on pregnancy outcomes in CKD shown in Boxes 45.1 and 45.2.

Pregnancy may be unplanned in women with CKD, and detailed discussion regarding maternal and fetal outcomes should be provided in early pregnancy. Furthermore, pregnancy may be the first opportunity for identification of CKD; for example, in a prospective cohort study 16% of women with CKD were diagnosed in pregnancy.11

Fertility Assessment

Fertility is reduced in women with moderate to severe CKD. Some individuals have raised prolactin, luteinizing hormone, and lower antimüllerian hormone concentrations, suggesting altered pituitary axis response and/or reduced ovarian follicle reserve.12,13 With the advent of assisted conception, nephrologists may be approached for advice regarding hormone stimulation therapies and embryo transfer. There is no evidence that hormonal manipulation has additional adverse consequences in women with CKD unless they develop ovarian hyperstimulation syndrome (see Chapter 44), which may further compromise kidney function. Single embryo transfer is recommended because of the additional maternal and neonatal risk for multiple fetal pregnancies.

BOX 45.1

Maternal Kidney Outcomes
According to Prepregnancy CKD Stage

BOX 45.4

CKD Stage 1 to 2
- Permanent loss of GFR in <10% of cases
- Greatest risk if GFR is <40 mL/min and proteinuria is >1 g/day
- Major determinant of progressive kidney loss is hypertension
- 40% risk for preeclampsia if baseline proteinuria is >500 mg/day

Maternal Risks
- Accelerated decline in glomerular filtration rate, sometimes precipitating dialysis during pregnancy or soon after in women with advanced chronic kidney disease
- Severe maternal hypertension with risk for stroke
- Superimposed preeclampsia with kidney, hepatic, thrombotic, or bleeding and neurologic risks
- Exacerbation of proteinuria, including nephrotic syndrome with risks for thrombosis

CKD Stage 3
- Decline or permanent loss of GFR in 30% of cases
- Increased to 50% if uncontrolled hypertension
- 10% ESKD soon after pregnancy
- Accelerated decline in GFR because of pregnancy by 1.7–2.1 years

CKD Stage 4
- Progression to ESKD highly likely during or soon after pregnancy
- Accelerated decline in GFR because of pregnancy by up to 4.9 years

Note that the Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease-Epidemiology (CKD-Epi) formula for estimation of glomerular filtration rate are not valid in pregnancy.
CKD, Chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate.

Fetal Outcomes According to
Maternal Prepregnancy CKD Stage 3

BOX 45.2

Outcomes After Accounting for First-Trimester Miscarriage

CKD Stage 1 to 2
- Live births in most pregnancies
- Up to 50% preterm delivery, up to 18% small for gestational age

CKD Stage 3
- Live births in most pregnancies
- Up to 60% preterm delivery (mainly iatrogenic due to superimposed preeclampsia/fetal growth restriction)

CKD Stage 4 to 5
- Live births in most pregnancies
- 90% preterm delivery, two-thirds small for gestational age, 50% admission to neonatal unit

CKD, Chronic kidney disease.
Note that the Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease-Epidemiology (CKD-Epi) formula for estimation of glomerular filtration rate are not valid in pregnancy.

BOX 45.3

CKD88

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Principles of Antenatal Care With

Management of hypertension aiming for BP < 135/85 mm Hg
Aspirin (75–150 mg daily) for all women with CKD
Regular medication review: Discontinue statins, ACE inhibitors, ARBs
Correct interpretation of gestational changes in serum creatinine
Clinical assessment and maintenance of volume homeostasis
Interpretation and management of proteinuria, including nephrotic syndrome
Identification of superimposed preeclampsia
Identification and management of urinary tract infection
Consideration of the primary kidney disease
Assessment for fetal well-being and consider if delivery is indicated (see Box 43.5)

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; CKD, chronic kidney disease.

Prepregnancy Counseling for Women With Chronic Kidney Disease

Fetal Risks

- Fetal growth restriction or intrauterine fetal death from placental insufficiency
- Preterm delivery, with both short-term and long-term consequences
- Teratogenicity and/or fetotoxicity of some drug therapies for kidney disease
- Inheritance of a kidney disorder

Contraception should be offered to women with CKD of reproductive age who do not wish to conceive, including those on dialysis and with kidney transplants. For the majority, estrogen-containing preparations are contraindicated because of exacerbation of hypertension or thrombotic risk, and progesterone methods including the progesterone-only pill, implant, and intrauterine device are preferred. Women taking immunosuppression have historically been advised against intrauterine devices because of concerns related to failure and pelvic inflammatory disease, although there is no robust evidence to support this recommendation.14

Urinalysis: Proteinuria

Preexisting proteinuria is often exacerbated during pregnancy because of increased glomerular permeability and plasma blood flow and stopping renin-angiotensin system blockade. However, when there is an increase in protein excretion during pregnancy in women with kidney disease, there are few therapeutic options apart from ensuring blood pressure (BP) control (see later discussion) and managing thrombotic risk. Isolated nonnephrotic proteinuria may develop de novo during pregnancy, which usually indicates one of the following scenarios and usually does not require antenatal kidney biopsy:

1. Developing preeclampsia (after 20 weeks of gestation).
2. No pregnancy complications occur, proteinuria resolves postpartum (gestational proteinuria).

3. Intrinsic glomerular disease has developed either before or during pregnancy and remains postpartum (uncommon). Management of glomerulonephritis (GN) in pregnancy is discussed in more detail later.

Serum albumin falls in most pregnancies as a result of volume expansion and may be less than 30 g/L even in healthy women, thus hypoalbuminemia is not a reliable indicator of nephrotic syndrome. Similarly, peripheral edema and a rise in serum cholesterol are commonly seen in healthy pregnancy. A spot urine protein-to-creatinine ratio (uPCR) greater than 300 mg/mmol (or >3 mg/mg) generally indicates protein excretion is greater than 3 g/day. Diuretics are rarely needed but are indicated for pulmonary edema.

Nephrotic syndrome in pregnancy may create a prothrombotic state and a propensity for intravascular volume contraction (see Chapter 16) that may lead to reduced uteroplacental compromise and worsening maternal kidney function. Treatment requires prophylaxis of thromboembolism with low-molecular-weight heparin, and maternal kidney function surveillance. Thresholds for commencing heparin are undefined, but most clinicians initiate treatment at higher serum albumin and/or lower proteinuria concentrations than in the nonpregnant state because of the prothrombotic nature of pregnancy.

We recommend prophylaxis of venous thromboembolism for all pregnant women with uPCR greater than 300 mg/mmol in pregnancy in the absence of contraindications and where delivery is not anticipated within 12 hours. Lesser degrees of proteinuria (uPCR 100–300 mg/mmol) are considered a risk factor for thromboembolic events, and prophylaxis may be warranted if there are additional risk factors. Lowmolecular-weight heparins are safe during pregnancy and do not cross the placenta. Dose adjustment may be indicated for women with CKD. Warfarin is teratogenic and should be avoided during pregnancy.

Hypertension

Many pregnant patients with CKD will not exhibit the usual firsttrimester fall in BP, and, in many women, BP increases as the pregnancy progresses. Normal pregnancy is accompanied by significant volume expansion, which does not induce hypertension. However, in CKD, there is often inability to excrete a sodium load with accompanying hypertension. Other potential contributory factors include stimulation of the renin-angiotensin and sympathetic nervous systems; alterations in endothelial factors such as prostacyclin, nitric oxide, and endothelin; and drugs such as calcineurin inhibitors and corticosteroids. Regardless of its cause, persistence of hypertension is an adverse factor in pregnancy outcome and inadequate use of antihypertensives in pregnancy has been associated with poorer pregnancy outcomes, at least in women with kidney transplants.15 BP often rises after delivery and should be monitored postpartum and treated according to nonpregnant targets, with agents that are safe in lactation.

Hypertension in pregnancy is defined as BP of 140/90 mm Hg or greater (see Chapter 44). A large randomized controlled trial comparing tight BP control (target diastolic blood pressure [DBP], 85 mm Hg) or less tight control (target DBP, 100 mm Hg) reported no difference in neonatal outcomes, but a reduction in episodes of severe maternal hypertension including requirement for intravenous (IV) antihypertensive treatment and associated liver and platelet abnormalities in those with tighter BP control16; thus tight blood pressure control is recommended for pregnant women with hypertension.

BP targets for nonpregnant proteinuric women with CKD are lower than pregnancy recommendation. Although there is no direct evidence for optimum BP in pregnant women with CKD, BP less than 130/80 mm Hg may be recommended to avoid prolonged periods with suboptimal control, while avoiding sustained blood pressures less than 110/70 mm Hg. Suitable antihypertensive agents include labetalol, nifedipine, methyldopa, hydralazine, and prazosin in conventional doses (see Chapter 44). Choice of first-line agent is based on availability, licensing, and clinician preference and experience. The frequency of dosing may need to be increased because of altered drug metabolism in pregnancy. Diltiazem may have a small benefit in reducing proteinuria, but this has not been addressed specifically among pregnant patients. Diuretics are not recommended during pregnancy because any reduction in maternal plasma volume may have adverse effects on uteroplacental or kidney perfusion but are indicated for the treatment of pulmonary edema or where substantial peripheral edema leads to skin breakdown.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) cannot be used in pregnancy because of fetotoxicity in the second and third trimesters. It had previously been recommended to cease ACE inhibitors in advance of pregnancy;

however, population studies have shown no increased risk compared with women exposed to other antihypertensive agents in the first

trimester.17 Women with kidney or cardiac indications can therefore continue ACE inhibitors during the unknown length of time it will take to conceive, provided they are counseled to undertake regular pregnancy testing and stop at a positive pregnancy test. There are less data supporting ARB safety, so these agents are usually discontinued in advance of pregnancy. Enalapril or captopril may be used in patients after delivery for those who wish to breastfeed. Aldosterone antagonists should be avoided in pregnancy, and atenolol is associated with fetal growth restriction.

KIDNEY BIOPSY IN PREGNANCY

It is rare to require kidney biopsy in pregnancy except for:

✓1.✓ De novo onset of nephrotic syndrome or unexplained kidney injury with abnormal urine sediment in the first and early second trimester when the risks of kidney biopsy are lower18 and when a histologic diagnosis will change management in pregnancy. Nephrotic syndrome after this stage can generally be managed until delivery, with postpartum investigations for those with persistent proteinuria/nephrosis that cannot be attributed to preeclampsia.

✓2.✓ Where the clinical picture warrants exclusion of acute rejection in a female with a kidney transplant.

Complications of kidney biopsy in pregnancy are more common in the late second and third trimester of pregnancy compared with those in general nephrology practice; a systematic review reported bleeding complications in 7% of biopsies performed in pregnancy compared with 1% performed postpartum.18

SUPERIMPOSED PREECLAMPSIA

Preeclampsia (see Chapter 44) is a placental disorder that presents after 20 weeks of gestation and has several predisposing risk factors, including an association with increasing severity of CKD.19 Superimposed preeclampsia in a female with CKD frequently leads to exaggerated hypertension and proteinuria with risks for nephrotic syndrome, progression of maternal kidney impairment, fetal growth restriction, preterm delivery, and perinatal mortality.

Superimposed preeclampsia is challenging to diagnose in a patient with preexisting hypertension, elevated serum creatinine, and/or proteinuria; however, when accompanied by additional features such as clonus, abnormal liver transaminases, or new-onset thrombocytopenia, superimposed preeclampsia is likely, although few patients with superimposed preeclampsia present with extrarenal manifestations11 and delivery decisions may be required without waiting for other severe systemic features to develop. Proposed criteria for diagnosis of superimposed preeclampsia in patients with CKD are highlighted in Table 45.1.

Placental growth factor (PlGF) testing (reduced in isolation or increased as a ratio to soluble fms-like tyrosine kinase 1 [sFlt-1]) can be used to predict the need for delivery due to preeclampsia (see Chapter 44). PlGF-based testing has been shown to distinguish preeclampsia without CKD from pregnant patients with CKD without preeclampsia in a small cohort.20 A larger, prospective cohort including patients with chronic hypertension or kidney disease reported comparable diagnostic performance for superimposed preeclampsia and preeclampsia without preexisting disease.11 PlGF-based testing offers a quantitative assessment of placental function and, at gestational concentrations, will not measure maternal endothelial disease caused by CKD. A recent prospective cohort study has shown increased surveillance for need for delivery should take place in patients with CKD and plasma PlGF less than 150 pg/mL after 20 weeks’ gestation, compared with a threshold of less than 100 pg/mL in women without CKD. However, this testing

TABLE 45.1
Diagnostic
Criteria
Essential

Additional

Diagnostic Criteria for Preeclampsia a

Preeclampsia
>20 weeks' gestation
New hypertension: systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg on two occasions

Proteinuria:
- uPCR > 30 mg/mmol (or 0.3 μg/mg)
- uACR > 8 mg/mmol (or >800 μg/mg)
- > 300 mg/24 h (not indicated if uPCR available)
- Dipstick > 2+ (if other methods unavailable)

Serum creatinine:
- Serum creatinine>1.0b to 1.1c mg/dL (90–100 μmol/L)d
- Doubling of serum creatinine less than 1.1 mg/dL (100 μmol/L)c d

Preeclampsia in Women With CKD
Hypertension:
- In women without chronic hypertension: as for preeclampsia
- In women with chronic hypertension: no diagnostic threshold, de novo severe BP (systolic BP > 160 or diastolic BP > 110 mm Hg) or an increase in treatment to maintain BP < 160/110 mm Hg used in research cohorts6 8

Proteinuria:
- In women with nonproteinuric CKD: as for preeclampsia
- In women with proteinuric CKD: no diagnostic threshold, > 100% increase and UPCR ≥ 0.3 mg/mg (> 30 mg/mmol) used in research cohorts6 8

Serum creatinine:
- In women with CKD and preserved excretory function: as for preeclampsia
- In women with CKD and abnormal prepregnancy function: no consensus on diagnostic threshold for change in creatinine, > 50% increase within 7 days used in research cohorts8

aDiagnosis

requires one essential and one additional clinical feature. 84–87
from Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88:950–957.
cModified from Bramham K, Briley AL, Seed PT, et al. Pregnancy outcome in women with chronic kidney disease: A prospective cohort study. Reprod Sci. 2011;18:623–630.
dSevere features.
BP, Blood pressure; CKD, chronic kidney disease; uACR, urinary albumin/creatinine ratio; uPCR, urinary protein/creatinine ratio.

bModified

is not needed if increased surveillance is already planned and decisions regarding delivery should not be made on the basis of PlGF results alone. The indications for delivery in patients with preeclampsia are the same in women with or without underlying CKD (Box 45.5). PlGF can be a useful adjunct to interpreting gestational changes in hyperten sion, proteinuria, and creatinine in patients with CKD.

Limited studies suggest that aspirin is of benefit in reducing the risk of superimposed preeclampsia and perinatal death in patients with underlying kidney disease.21 Our practice is to use low-dose aspirin (75–150 mg/day) for all patients with CKD, using data generalized from high-risk cohorts (see Chapter 44).

ASSESSMENT OF FETAL WELL-BEING

Preterm delivery, fetal growth restriction, and stillbirth are the major concerns for women with kidney disease, particularly if superimposed preeclampsia develops. Avoidance of preterm delivery reduced both short-term and lifelong complications, including higher mortality in later life.

Early pregnancy ultrasound between 11 and 14 weeks is advised to estimate accurately the expected date of delivery and to offer trisomy screening, followed by fetal morphology scan at 18 to 20 weeks of gestation to screen for fetal anomalies, assess fetal well-being, and check placental function and position. Blood human chorionic gonadotropin (hCG) levels are often elevated in patients with kidney impairment and may overestimate the risk for fetal abnormalities.22

Additional ultrasound scans should be offered at 2- to 4-weekly intervals from 28 weeks of gestation in women with CKD to assess fetal growth and amniotic fluid volume, with Doppler studies of umbilical artery blood flow. Absent end-diastolic flow on umbilical artery velocimetry is usually an indication for the need for delivery, depending on gestation. The development of reversed end-diastolic flow indicates a high risk for fetal hypoxia, acidosis, and death.

Indications for Delivery in Women With Preeclampsia and Chronic Kidney Disease

BOX 45.5

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Gestation ≥37 weeks
Inability to control blood pressure
Deteriorating kidney function
Neurologic abnormalities, such as eclampsia, headaches with accompanying clonus and hyperreflexia, or repeated visual scotomata
Worsening thrombocytopenia
Increasing liver transaminase levels
Failure of fetal growth
Reversed or absent end-diastolic flow on cardiotocography

The decision to deliver is based on a global clinical assessment rather than on specific thresholds for each parameter.

TIMING OF DELIVERY

In patients with stable CKD and no evidence of fetal compromise, pregnancies should be continued to term and spontaneous labor awaited. The method of delivery, either vaginal or by cesarean delivery, is determined by obstetric issues rather than CKD. Indications for delivery are described in Box 45.5

The goal is to time delivery such that the risks of prematurity are less than the risks of the pregnancy continuing, which requires multidisciplinary consultation among obstetrician, neonatologist, nephrologist, or obstetric medicine physician and midwife. Decision making regarding the timing of iatrogenic preterm delivery is a balance between the need for fetal maturity and concern regarding maternal health, which for patients with CKD is usually the development of superimposed preeclampsia or worsening kidney function.

Final pregnancy outcomes for patients with CKD are usually successful for both mother and baby, although there may be long-term implications for childhood development and maternal health. Clinicians can take a positive approach, at all times emphasizing the need for diligence and assessment for potential complications, and aim to relieve some of the stress that accompanies pregnancy for patients with CKD.

COURSE OF CHRONIC KIDNEY DISEASE DURING AND AFTER PREGNANCY

For most women with CKD, the risk for progression of kidney disease during pregnancy is determined by the severity of kidney disease prior to pregnancy, chronic hypertension, and the development of superimposed preeclampsia, rather than the underlying cause of CKD.

Rapid deterioration during a pregnancy is unlikely in patients with mild CKD (prepregnancy CKD stage 1 to 2), other than lupus nephritis, which may flare. However, 50% of patients with moderate baseline kidney impairment (serum creatinine > 1.5 mg/dL [130 µmol/L]) or worse have a significant rise in serum creatinine in the third trimester or early postpartum, and almost 1 in 5 of these will require kidney replacement within 6 months.23 In a series of 49 women with stage 3 to 5 CKD before conception whose pregnancy proceeded beyond 20 weeks, GFR was lower after pregnancy than before conception, and this fall was predicted by the combination of preconception GFR less than 40 mL/min/1.73 m2 and proteinuria greater than 1 g/day, but not by GFR alone.24 In a more recent study of 179 pregnancies in women with prepregnancy CKD stages 3 to 5 not on dialysis, 46% of women had lost 25% of their prepregnancy eGFR or required kidney replacement therapy by 1 year postpartum. There was a measurable loss of GFR associated with pregnancy, equating to 1.7, 2.1, and 4.9 years of prepregnancy kidney disease for women with prepregnancy CKD stages 3a, 3b, and 4 to 5, respectively. Chronic hypertension was a significant predictor of pregnancy-associated loss of kidney function, and absence of an early fall in maternal serum creatinine was a significant predictor of delivery before 34 weeks’ gestation and further loss of maternal kidney function.3

The course of kidney disease postpartum is unpredictable. Some women with stable antenatal kidney function acutely deteriorate postpartum. Surveillance and hypertension control should continue postpartum. ACE inhibitors (captopril or enalapril if breastfeeding) or ARBs (after lactation) can be commenced after delivery for their antiproteinuric effect.25

Norwegian women with biopsy-proven kidney disease had slightly faster progression to a requirement for kidney replacement if their pregnancy required preterm delivery but not if they had preeclampsia.26 A neglected issue is the association between preterm birth, low birth weight, and later-life cardiovascular and kidney disease. This may transmit an increased risk for kidney disease to offspring even if the kidney disease is not hereditary. On balance, it is prudent to consider both preeclampsia and preterm delivery as risk factors for later kidney disease.

MANAGEMENT OF COMMON KIDNEY DISORDERS DURING PREGNANCY

Immunoglobulin A Nephropathy

Pregnancy outcomes for patients with immunoglobulin A (IgA) nephropathy are generally positive, and comparable to other causes of CKD. Long-term follow-up of women with IgA nephropathy diagnosed in childhood showed that pregnancy was complicated by hypertension in half of them and preterm delivery in one-third.27 A Swedish cohort study comparing pregnancy outcomes in women with and without IgA nephropathy described an increased risk of preterm birth (adjusted odds ratio [OR], 2.69), preeclampsia (adjusted OR, 4.29), and small for gestational age (adjusted OR, 1.84), but no reduction in live birth28 rates, although stratification according to CKD stage was not possible. Pregnancy in IgA nephropathy did not accelerate kidney dysfunction in those with CKD stage 1 or 2,29–31 but proteinuria may increase in the third trimester.32 However, there is limited evidence that women with proteinuria before pregnancy33 and those with preterm delivery, low birth weight, and preeclampsia34 have a more rapid decline in function postpartum.

Diabetic Kidney Disease

In the United Kingdom, more pregnant women have type 2 than type 1 diabetes, and 8% of pregnant women with type 1 diabetes and 5% with type 2 diabetes have diabetic kidney disease (DKD).35 Diabetes per se increases risks for congenital abnormality, preterm birth, cesarean section, and perinatal mortality. The presence of overt nephropathy more than doubles the risk for fetal death after 20 weeks. There is an added risk for congenital abnormalities if blood sugar was not adequately controlled at the time of conception, which is not uncommon. For example, the UK National Audit reported that 7 out of 8 women were not well prepared for pregnancy according to national guidelines.35 A large cohort study indicated that the presence of DKD is an independent risk factor for congenital abnormalities.36

The Diabetes Control and Complications Trial and EURODIAB trial both concluded that pregnancy does not increase progression to albuminuria. It is likely that women with DKD have worse pregnancy outcomes than women with other causes of CKD and comparable kidney function. For example, a retrospective cohort study of women with type 1 diabetes and DKD (median prepregnancy serum creatinine 0.8 mg/dL [70 µmol/L]) reported high complication rates (e.g., preeclampsia 42%, preterm before 34 weeks 21%, neonatal care admission 49%).37 In a recent cohort of women with moderate and advanced CKD, none of the 11 women with DKD had a normal pregnancy course.3

The outcome of DKD during pregnancy depends on the usual factors of severity of kidney impairment and hypertension. Specialistled meticulous control of blood glucose and BP during pregnancy is required. One study showed that failure to achieve mean arterial pressure (MAP) less than 100 mmHg was associated with increased risk for early delivery, even after adjusting for glucose control.38 Risk for permanent decline in kidney function for women with more severe DKD has not been formally evaluated. Ideally, ACE inhibitors (enalapril or captopril if breastfeeding) should be introduced soon after delivery for prevention of progression of DKD.

Having gestational diabetes mellitus (GDM) without developing overt diabetes after the pregnancy is still associated with approximately 10% risk for microalbuminuria by age 50, an intermediate risk between that of nondiabetic and diabetic women.39 This means that women with a history of GDM, not just those with type 1 or 2 diabetes, should be followed after pregnancy because of their risk for later developing diabetes.

Lupus Nephritis

Women with active disease at conception are more likely to have active lupus nephritis during pregnancy, which is then associated with high fetal risk, with approximately 1 in 5 pregnancies ending in miscarriage, stillbirth, or neonatal death.40 Ideally, women with lupus should be in remission for at least 6 months before conception on medications known to be safe in pregnancy. Prepregnancy assessment may include cessation of renin angiotensin blockade to allow assessment of proteinuria, with repeat kidney biopsy before attempts to conceive if active disease is suspected.

In addition to low-dose aspirin to reduce the risk of superimposed preeclampsia, all women with previous lupus nephritis should receive hydroxychloroquine.41 Hydroxychloroquine in pregnancy is associated with reduced risks of lupus flare and fetal growth restriction.42–44

Lupus nephritis flares are described in 30% of women during pregnancy and in 15% of women immediately postpartum,45 but a prophylactic postpartum increase in corticosteroid dosing is not indicated.

Although rare, the major cause of maternal death in lupus nephritis is sepsis, so immunosuppression should be maintained at the lowest possible dose to control disease.46 New onset or a flare of lupus nephritis, evidenced by increasing proteinuria, active urine sediment, and rising serum creatinine, is a major concern. Distinguishing a flare of lupus nephritis from preeclampsia can be challenging because the phenotype of both conditions includes hypertension, proteinuria, kidney injury, and thrombocytopenia. A kidney biopsy can be arranged in the first and early second trimester when bleeding risks are lower, and only if a histologic diagnosis will change management in pregnancy. Serological markers of disease, including complement and double-stranded DNA antibody concentrations, may also be clinically helpful.

Lupus nephritis can be treated with corticosteroids and azathioprine in pregnancy. Tacrolimus is an alternative agent that has been used with increasing success in women with active lupus nephritis in pregnancy.47 Cyclophosphamide and mycophenolate mofetil (MMF) are contraindicated in pregnancy because of teratogenicity and should be ceased at least 6 weeks before conception. MMF is associated with microtia (underdeveloped external ear), auditory canal atresia, cleft lip and palate, and micrognathia. Although cyclophosphamide has been used successfully in a few cases of lupus nephritis in later pregnancy after the period of fetal organogenesis, its use is not routinely recommended. Rituximab is not teratogenic but crosses the placenta and causes B-cell depletion in the fetus as in the mother48 and is therefore not recommended for use in pregnancy, where other treatment options exist.49 The use of belimumab in pregnancy is described in isolated case reports, with insufficient data to confirm safety.50 There are no pregnancy-specific contraindications to the use of IV immunoglobulin and plasma exchange in pregnancy if clinically indicated.

Prior histologic class of lupus nephritis has no influence on pregnancy outcome. Predictors of poor pregnancy outcome include baseline creatinine greater than 0.9 mg/dL (79 µmol/L), proteinuria greater than 0.5 g/24 hours, antiphospholipid syndrome, hypertension, non-White ethnicity, and maternal disease flare.51 A prospective cohort study of women with lupus, including those with mild nephritis, recently reported that pregnancy outcomes were favorable for women without adverse risk factors (including lupus anticoagulant, antihypertensive use, active disease, or low platelets), with 92% having uncomplicated pregnancies. However, when counseling about future pregnancies, women should be advised that even if their lupus nephritis has been well treated, they appear to have a greater risk for maternal complications and lupus flare in their next pregnancy than do women with systemic lupus erythematosus (SLE) who have never had nephritis; this is only partly explained by increased activity of the SLE at conception. Fortunately, fetal outcomes are not affected adversely in this group and postpartum GFR appeared unaffected.52 This means that such patients need more surveillance during pregnancy than usual, to detect a kidney flare or preeclampsia, their two biggest maternal risks.

Women with anti-Ro and anti-La antibodies should be counseled regarding the risk for fetal heart block and neonatal cutaneous lupus, respectively. Hydroxychloroquine may reduce the risk for recurrent fetal heart block in patients with a previously affected infant, and this is indicated in pregnancy in women with lupus nephritis.53 There is debate as to the optimum monitoring for congenital heart block with variable recommendations for fetal heart rate monitoring and echocardiography in the second trimester. Even if surveillance detects earlystage fetal heart block, the optimum treatment is unclear.

Reflux Nephropathy

Pregnancy outcomes in women with reflux nephropathy depend predominantly on preexisting kidney function and BP control as for other kidney diseases. An analysis of contemporary data (2000–2016) including 434 women with 879 pregnancies showed an increased risk of pregnancy-related hypertension (OR, 5.55) and preeclampsia (OR, 6.04), but no difference in preterm delivery compared with unmatched control pregnancies. A higher incidence of stillbirth has been reported, which warrants further analysis.

Women with reflux are more predisposed to urinary tract infection (UTI) throughout pregnancy, as are women who have had surgically corrected reflux in childhood. Around 20% of women with reflux nephropathy will develop UTI in pregnancy, with a 6% incidence of pyelonephritis in historical studies. Urine culture should be performed throughout pregnancy in those with underlying reflux nephropathy and treatment offered for confirmed bacteriuria. In the absence of evidence of harm, antibiotic prophylaxis is recommended to those with reflux nephropathy after a single confirmed infection, informed by urine culture, antimicrobial sensitivities, and patient preference.49 Management of UTI in pregnancy is further discussed in Chapter 44.

Vesicoureteric reflux may be a familial disorder, estimated to affect 20% of infants with a positive parental family history, compared with a 1% to 2% frequency in the general population.54 However, not all vesicoureteric reflux results in kidney parenchymal damage, and 80% of mild cases resolve in childhood (see Chapter 62).55 Data are inadequate to define an evidence-based screening strategy for the offspring of women with reflux nephropathy. Expert consensus, based on observational data, is that infants of mothers with urinary tract abnormalities who had normal urinary tracts on antenatal ultrasound scans do not need further follow-up unless features of UTI are identified in childhood.49

Inherited Kidney Disorders

Although chronic hypertension is a risk factor for adverse pregnancy outcomes in autosomal dominant polycystic kidney disease (ADPKD),56 normotensive women with ADPKD have comparable pregnancy outcomes to those of unaffected family members. A study of 54 women with ADPKD compared with 92 women with simple cysts showed increased rates of hypertension and preeclampsia but no difference in neonatal outcome.57 Case reports suggest that there is no change in kidney volume in ADPKD because of pregnancy and uterine growth is not compromised.

Very few pregnancies have been described in women with Alport syndrome, but substantial gestational proteinuria with clinical nephrosis is recognized.58

Inherited kidney disorders are likely to have been diagnosed before pregnancy, and specific implications for the offspring should be discussed. For single-gene disorders, preimplantation diagnosis may be available, and referral for specialist counseling is recommended.

HEMODIALYSIS IN PREGNANCY

Significant improvements in outcomes of pregnant patients requiring dialysis during pregnancy have occurred over the past two decades, with fetal survival rising from less than 50% to almost 85%.59 Pregnancy rates have also risen, with a 71% increase in delivery rate among women of reproductive age undergoing hemodialysis reported in the United States60 from 2002 to 2015. Pregnancy rates in non-White women

treated with maintenance dialysis are also reported to be higher.61 Improved outcomes have been associated with more intensive hemodialysis regimens, and advances in neonatal care have enabled survival for premature and growth-restricted infants. A Canadian cohort study reported significant improvement in birth weight and length of gestation in women who received prolonged dialysis (43 ± 6 hr/wk) compared with those with a more modest increment (17 ± 5 hr/wk).62 A meta-analysis of 574 pregnancies in 543 patients reported that fewer dialysis hours per week was strongly associated with preterm delivery before 37 weeks.63 Recommendations for managing hemodialysis during pregnancy are listed in Box 45.6

Women of childbearing age undergoing dialysis have low rates of conceiving,59 but increments in dialysis dose, such as nocturnal home hemodialysis, appear to be associated with increased fertility.62 Women of childbearing age on maintenance dialysis who do not wish to conceive should therefore have access to safe and effective contraception (progesterone-only pill, progesterone implant, intrauterine device).

Initiating Dialysis for Progressive Chronic Kidney Disease

Dialysis should be commenced in pregnancy for the standard indications of hyperkalemia, acidosis, uremic symptoms and/or fluid overload. However, it is more common to initiate dialysis in pregnancy because of potential fetotoxicity of urea. The optimum serum urea concentration at which dialysis offers benefit in pregnancy is unknown and practice varies from routine commencement of dialysis at maternal blood urea nitrogen (BUN) 48 mg/dL64 (or urea > 17 mmol/L) to dialysis only when BUN is consistently greater than 56 mg/dL (or urea > 20 mmol/L). We recommend that in progressive kidney disease, BUN greater than 42 mg/dL (or serum urea > 15 mmol/L) should initiate conversations about the risks, benefits, and logistics of hemodialysis in pregnancy, weighed with the risks of preterm delivery before dialysis initiation if the gestation is approaching or exceeds 34 weeks.49

Dialysis initiated during pregnancy is probably associated with greater likelihood of successful pregnancy than for those on maintenance dialysis, perhaps because of the benefits of residual kidney function,65 although this is not a consistent finding.62

Dialysis Regimens in Pregnancy

Differences in residual kidney function means that intensification of dialysis may not show the same benefit for women initiating dialysis in pregnancy as it does for women established on hemodialysis before pregnancy. Meta-analysis data demonstrating improved outcomes with intensification of dialysis do not include women starting dialysis after 20 weeks' gestation.63 In a study of intensive dialysis in pregnancy, a very small subgroup analysis of women starting hemodialysis after conception showed no significant difference in gestational age at delivery between those receiving 33 ± 6 hours per week (n = 4) compared with 15 ± 4 hours per week (n = 13).62

A graded increase in dialysis guided by residual kidney function and biochemical parameters has been described with initial weekly hours of hemodialysis determined according to residual urine output and time on dialysis before pregnancy, with dialysis provision then adjusted according to midweek predialysis serum urea, BP, weight gain, and polyhydramnios. In this cohort, linear regression identified a midweek predialysis BUN 35 mg/dL (or serum urea 12.5 mmol/L) as discriminatory in determining successful pregnancy outcome.66 We therefore recommend initiating hemodialysis at 2 to 3 hours, 3 times per week in women newly starting dialysis in pregnancy for a fetal rather than maternal indication, and adjusting provision to achieve midweek pre dialysis urea less than 12.5 mmol/L (BUN 35 mg/dL).

BOX 45.6

Pregnancy[49]

Managing Hemodialysis During

Prepregnancy
Discuss risks of pregnancy (miscarriage, fetal death, fetal growth restriction, preterm delivery, preeclampsia)
Ensure all medications are safe in pregnancy
Aspirin: 75–150 mg daily
Folic acid: 5 mg daily
During Pregnancy
Dialysis
- Aim for midweek predialysis BUN <35 mg/dL (serum urea 12.5 mmol/L)
- Heparin requirement may increase because of hypercoagulability of pregnancy

Anemia
- Intravenous iron to maintain iron stores
- Dose ESA to achieve hemoglobin 10–11 g/dL

Bicarbonate
- Adjust dialysate bicarbonate to achieve normal serum bicarbonate for pregnancy (18–22 mmol/L)

Nutrition
- Dietician advice to ensure adequate protein and nutrient intake.
- Supplement oral or dialysate phosphate to maintain postdialysis serum phosphate in normal range.

Calcium
- Maintain normal serum calcium with vitamin D/vitamin D analogues and appropriate dialysate calcium.

Phosphate
- Supplement oral or dialysate phosphate to maintain postdialysis serum phosphate in normal range.

After Pregnancy
Return to usual dialysis schedule.
Readjust dry weight and antihypertensives weekly for 6–12 weeks.
BUN, Blood urea nitrogen; ESA, erythropoiesis-stimulating agents.

In addition to augmentation of dialysis dose as practically possible, ensuring the aforementioned biochemical goals are achieved, and weekly surveillance, the following also should be considered:

✓ • ✓ Control of maternal BP, generally to less than 110 to 140/70 to 90 mm Hg. This is difficult to achieve in many cases. Volume expansion is often evident in women on maintenance hemodialysis who become pregnant, as evidenced by anemia and fall in serum albumin. There are no data supporting assessment of volume status in pregnant patients on dialysis using ultrasound measurement of inferior vena cava diameter or bioimpedance.

✓ • ✓ IV iron and erythropoiesis-stimulating agents aiming for a hemoglobin level of 10 to 11 g/dL. No adverse consequences in pregnancy have been reported with either IV iron or erythropoiesis-stimulating agents, although there is a paucity of data on IV iron preparation use in the first trimester and a theoretic risk for exacerbation of hypertension with the latter agents. Transfusion should be avoided to minimize sensitization but may be required if hemoglobin levels are low, especially before delivery.

✓ • ✓ Phosphate monitoring and supplementary phosphate in the dialysate if required.

✓ • ✓ Fetal monitoring with at least 2- to 4-weekly ultrasound scanning from the time of fetal viability, around 24 weeks of gestation.

Peritoneal Dialysis and Pregnancy

There is little information concerning specific requirements of women on peritoneal dialysis (PD) during pregnancy. A systematic review and meta-analysis compared pregnancy outcomes in women on hemodialysis (HD) with PD and reported a higher incidence of infants who are small for gestational age in those receiving PD.63 Pregnancy rates in Medicare-insured women with ESKD (2000–2015) were only 2.8% (0.5–1.4 deliveries per 1000 patient-years), and, unlike the number of pregnancies in women receiving hemodialysis or kidney transplants, have not increased over the last 2 decades.60 A major risk is that PD peritonitis may provoke premature labor or preterm rupture of membranes. Although some women have had successful outcomes remaining on PD throughout pregnancy, we recommend switching to HD to allow augmentation of dialysis dose in a controlled manner. This recommendation is predicated on the greater available evidence for HD in pregnancy and may change when more data emerge about PD in pregnancy.

KIDNEY TRANSPLANTATION AND PREGNANCY

Successful kidney transplantation is an excellent way of restoring fertility in women with ESKD. It is surprising therefore that the pregnancy rate among female transplant recipients more than halved between 1990 and 2003, which is unexplained by a change in the age of women being transplanted but may be related to the introduction of MMF, which is teratogenic.67 Women with transplants appear less likely to conceive if ESKD is caused by diabetes compared with women without diabetes and overall pregnancy rates among kidney transplant recipients are only one-third of the general population.2

Timing of Pregnancy

Women are recommended to wait at least 12 months after a successful kidney transplant before embarking on pregnancy to ensure stable transplant function and maintenance immunosuppression,49 although evidence is conflicting. A meta-analysis of pregnancy outcomes in women with kidney transplants reported that cesarean section rate was higher and live birth rate lower in those who conceived in the interval of 2 to 3 years than greater than 3 years and less than 2 years (68% vs. 75% vs. 74%, and 73% vs. 65% vs. 42%, respectively). Maternal complications of preeclampsia were higher in the 2- to 3-year interval, and the greater than 3-year interval compared to the less than 2-year interval (24% vs. 23% vs. 13%). Spontaneous abortion rates were highest in the greater than 3-year interval followed by the 2- to 3-year interval, and the less than 2-year interval (16% vs. 14% vs. 10%).68 However, in a study in the United States, rates of preeclampsia, gestational diabetes, cesarean section, and preterm delivery also were higher than for the general population in those who conceived within 2 years.69 One to 2 years after transplantation seems a practical time for ensuring clinical stability and having optimal BP control, absence of cytomegalovirus (CMV) viremia, and stable immunosuppression.

Immunosuppression in Pregnancy

There are usually opportunities to ensure that conception is carefully planned, immunosuppression and vaccination status optimized, and folic acid commenced, but, unfortunately, many pregnancies in women with kidney transplants are still unplanned. Discussion regarding restoration of fertility with transplantation and contraception should take place before transplantation.70 Immunosuppressive drugs considered safe in pregnancy include prednisolone, azathioprine, cyclosporine, and tacrolimus. Tacrolimus has been associated with neonatal hyperkalemia, but overall data support its safety. MMF is associated with teratogenic effects and should be avoided in pregnancy, as should sirolimus and everolimus. We suggest ceasing such drugs 3 to 6 months before pregnancy to ensure clinical stability on an alternative agent (usually azathioprine).

Gestational diabetes occurs in 3% to 12% of pregnancies of patients with kidney transplants but no more frequently in tacrolimus-treated patients than in those receiving cyclosporine. Screening for gestational diabetes is recommended for all transplant recipients at 12 and 28 weeks.

Dosing of tacrolimus in pregnancy remains problematic until assays for free tacrolimus become readily available. During pregnancy, tacrolimus shows increased metabolism but altered protein binding.71 Our practice is to change dose from prepregnancy doses when trough levels are less than normal, with increments targeting the lower end of the prepregnancy range, but with return to prepregnancy doses immediately after delivery, with ongoing close monitoring.

Azathioprine, tacrolimus, cyclosporine, and prednisone appear safe to use for patients who are breastfeeding, but the decision to breastfeed remains an individual one. Patients can be informed that breastfeeding may have considerable advantages, particularly in preterm and growth-restricted babies.

Pregnancy Outcomes

A favorable view of pregnancy in patients who have undergone successful kidney transplantation was supported by observations in over 3000 pregnancies from 2000 women mostly receiving azathioprine and prednisone.72 About 15% of these pregnancies miscarried spontaneously, and of those going past the first trimester, pregnancy was successful in over 90% of cases, provided that hypertension or a decline in GFR had not occurred before 28 weeks of gestation, in which case successful pregnancy outcome was reduced to about 70%. Patients with preconception serum creatinine of 1.4 mg/dL (125 µmol/L) had 96% pregnancy success, whereas those with higher serum creatinine had a 75% success rate. In keeping with the data for all women with CKD, long-term decline in kidney function occurred significantly more often (27%) in those with preconception serum creatinine greater than 1.4 mg/dL (125 µmol/L).

A recent systematic review of 78 studies reporting 6712 pregnancy outcomes in 4174 kidney transplant recipients reported the following pregnancy outcomes: live birth rate of 72.9%, miscarriage rate of 15.4%, termination of pregnancy in 12.4%, stillbirth rate of 5.1%, and ectopic pregnancies in 2.4%. Maternal complications included preeclampsia in 21.5%, cesarean section in 62.6%, gestational diabetes in 5.7% (US mean, 9.2%), and gestational hypertension in 24.1%. Neonatal outcomes included preterm birth (<37 weeks) in 43.1% with mean gestational age at delivery of 34.9 weeks; neonatal mortality was 3.8%.68

Graft and patient survival are similar in those with and without any pregnancy over a follow-up as long as 15 to 20 years, based on 577 pregnancies in the Australian and New Zealand Data registry, most of whom had GN or reflux nephropathy as their primary diagnosis.73 A more recent meta-analysis including 2453 recipients with pregnancies confirmed stable serum creatinine postpartum, with no differences in rates of graft loss compared with nulliparous controls,74 and a Norwegian population study has confirmed reduced rates of graft loss and death in women with kidney transplants after pregnancies compared with nonpregnant women despite adjustment for possible confounders.75

More recently, small studies have also reported longer-term outcomes for children of women with kidney transplants with normal development at 12 and 24 months in 94%, despite low birth weights and prematurity76 (Box 45.7).

BOX 45.7

Maternal and Fetal Outcomes in Kidney Transplant Pregnancies

BOX 45.8

Maternal

- Decline in glomerular filtration if preconception serum creatinine >1.4 mg/dL (125 µmol/L); rate of decline not usually different from female transplant recipients who have not given birth
- Graft loss in 5% to 10% at 2 years postpartum
- Hypertension in about two-thirds
- Rejection reported in 2% to 9% (risk not thought to be increased by pregnancy)
- Infection in 20% to 35%
- Gestational diabetes mellitus in 6%

Prepregnancy

- Stable graft function at least 1 year after transplantation
- Discuss risks with transplant recipient and partner
- Best pregnancy outcome will occur if:
- Prepregnancy serum CKD stage 1 to 2
- Proteinuria < 1 g/day
- Blood pressure < 130/80 mm Hg
- Replace all medications that are not safe in pregnancy
- Eradicate UTI before pregnancy; consider prophylactic antibiotics if there has been recurrent UTI in the past year or a single confirmed UTI in pregnancy
- Stable cyclosporine or tacrolimus blood levels
- Test for and control diabetes

Fetal

- Overall live birth rate: 75% to 80%
- Spontaneous miscarriage: 15%
- Preterm delivery: 45%
- Growth restriction: 50%
- Birth defects in about 5%, comparable to the general population
- Long-term consequences of preterm delivery, although most infants have normal postnatal growth and development

Transplant Rejection

Acute transplant rejection is uncommon—reported in fewer than 1 in 20 cases in older series,[69] but a recently systematic review reported the overall acute rejection rate during pregnancy among 822 kidney transplant recipients to be 9.4% (95% confidence interval [CI], 6.4–13.7), which is comparable to the U.S. mean of 9.1%. The clinical presentation of acute graft dysfunction is not different in pregnancy but differentiation from preeclampsia may be challenging. A recent case control study using Transplant International Pregnancy Registry data identified that acute rejection is associated with higher creatinine concentrations, whereas patients with preeclampsia had much higher levels of proteinuria.[77] Kidney biopsy is required to confirm the diagnosis. Treatment is limited to IV methylprednisolone and increments in oral immunosuppression because safety of more potent agents (e.g., antithymocyte globulin) is unproven in pregnancy and likely to cause harm to the developing fetus. Delivery may need to be considered at more advanced gestations to facilitate therapies with unknown fetal safety.

Infection in Pregnant Transplant Recipients

Management of Kidney Transplant Patients During Pregnancy

During Pregnancy
- Aspirin (75–150 mg daily) for all women with kidney transplant unless contraindicated.
- Assess fetal growth by ultrasound at least every 4 weeks from 28 weeks of gestation.
- Consider increase in CNI dose during pregnancy if drug level is significantly lower than the nonpregnant target range.
- Screen for gestational diabetes according to local protocol with additional early screening if taking steroids or calcineurin inhibitor.
- At each visit, assess BP (goal 110–135/70–85 mm Hg), proteinuria (dipstick, then uPCR or uACR if dipstick result is positive), urine culture, electrolytes, creatinine, full blood count, predose CNI level, and fetal growth.
- Reassess at each visit whether there is an impending indication for delivery (see Box 45.5).

During Delivery
- Vaginal delivery is generally possible, and indications for caesarean delivery are usually obstetric.
- Prophylactic antibiotics are not required.

Postpartum
- Control blood pressure.
- Monitor CNI and serum creatinine levels.
- CNI drugs, azathioprine, and corticosteroids are safe in breastfeeding.
- Higher level of clinical surveillance for the first 3 months.

BP, Blood pressure; CKD, chronic kidney disease; CNI, calcineurin inhibitor; uACR, urinary albumin/creatinine ratio; uPCR, urine protein/creatinine ratio; UTI, urinary tract infection.

There is an increased risk for infection (20%–35%), particularly UTI but also CMV infection, with attendant maternal and fetal risks. The consequences of any infection can include preterm labor and preterm rupture of membranes. CMV can cause congenital malformations and fetal demise, but delay in conception to after at least 1 year posttransplantation makes new infection or reactivation unlikely. Valganciclovir prophylaxis is not advised because of teratogenicity in animals, but there are case reports of successful use in women with severe CMV infection in pregnancy.
Recommendations for management of pregnancy in patients with a kidney transplant are summarized in Box 45.8

and the manufacturers have advised switching to a different agent before conception. However, these recommendations are largely theoretical, and should be balanced against the risk for inadequate immunosuppression for a prolonged period in males with higher risk transplants. A recent French survey reported no increased risk of congenital malformations in offspring of males with kidney transplants compared with the general population.78 Similarly, the ANZDATA registry recently reported no increase in congenital abnormalities in offspring of fathers taking MMF or derivatives.79

Male Transplant Recipients

PREGNANCY IN THE KIDNEY DONOR

Outcomes of pregnancies fathered by male transplant recipients showed mean gestational age and mean birth weight similar to those of the general population. There have been recent concerns about teratogenicity of MMF in the offspring of fathers with kidney transplants,

It is usually stated that being a kidney donor does not adversely affect future pregnancy outcomes in terms of fetal birth weight, stillbirth, or prematurity, although recent studies suggest there may be an increased risk for preeclampsia in pregnancy after organ donation, and some reports suggest that fetal outcomes also may be slightly worse.80 81 A large Canadian study also reported a higher incidence of preeclampsia and gestational hypertension in women after donation compared with controls but there were no differences in neonatal outcomes, including gestation at delivery or birth weight, and thus placental insufficiency is unlikely to be severe.82

More recently, a U.S. case-control study also demonstrated an increased risk of preeclampsia in primiparous kidney donors compared with age- and race-matched primiparous controls, but this was only significant for women up to 30 years old,83 and in keeping with preexisting studies there were no differences in neonatal outcomes. These studies have some limitations in their design, and pregnancy should not be discouraged in women who have been kidney donors; rather, the key message is that all such women should be treated as atrisk pregnancies and have a higher number of clinical reviews, focusing on maternal BP and urinalysis and fetal growth, than in low-risk pregnancies. Aspirin prophylaxis may be considered, especially if women have additional risk factors for preeclampsia.

SUMMARY

A summary of factors to be considered in managing a pregnant patient with kidney disease is shown in Box 45.9. Attention to these issues from preconception to postpartum can result in good pregnancy outcomes with preservation of maternal health. These patients and, in many cases, their offspring require lifelong assessment for progressive kidney and/or cardiovascular disease.

Managing Women With Preexisting Kidney Disease During Pregnancy

BOX 45.9

- Women with chronic kidney disease (CKD) should be managed by a team made up of the obstetrician, nephrologist or expert physician, and experienced midwife or specialty nurse, preferably in a high-risk pregnancy clinic.
- Main determinants of pregnancy outcome are prepregnancy GFR, proteinuria, blood pressure (BP), medication, and previous obstetric history. These should be the focus in counseling.
- Kidney function should be monitored using serum creatinine in pregnancy.
- Proteinuria is quantified using spot uPCR or uACR.
- Low-dose aspirin should be given to reduce the risk for preeclampsia.
- Low-molecular-weight heparin for VTE prophylaxis if uPCR > 300 (uACR > 200). Assess VTE risk if uPCR > 100 (uACR > 30); may need dose adjustment for kidney function.
- Primary issues during pregnancy are BP control, surveillance for preeclampsia, and regular assessment of fetal well-being.
- Fetal assessment by ultrasound
- At 20 weeks: Uterine artery pulsatility index
- Monthly from 28 weeks: fetal growth, blood flow, amniotic fluid index
- Plans for obstetric, nephrology, and neonatal review determined at postpartum discharge. Increased nephrology surveillance recommended for 3 months. Pre-pregnancy counseling recommended in advance of a future pregnancy.

GFR, Glomerular filtration rate; uACR, urinary albumin/creatinine ratio; uPCR, urine protein-to-creatinine ratio; VTE, venous thromboembolism.

SELF-ASSESSMENT QUESTIONS

1. A 32-year-old woman with ADPKD wishes to become pregnant. Her GFR is 110 mL/min/1.73 m2. Her BP is 142/89 mm Hg, and she has no proteinuria. She is taking amlodipine 5 mg once daily. Which of the following is correct advice about a future pregnancy?

A. Her pregnancy will be low risk.
B. She should be offered preimplantation genetic testing.
C. She should take aspirin daily in advance of pregnancy.
D. She should stop amlodipine when she becomes pregnant.

2. A 39-year-old woman with ESKD secondary to lupus nephritis received a kidney transplant from her partner 9 months ago and wishes to conceive. She has had no episodes of rejection. Her GFR is 84 mL/min/1.73 m2, and her BP is 124/77 mm Hg. She is currently taking prednisolone, tacrolimus, MMF, and aspirin. What would you recommend to achieve the best outcome?

A. She should not conceive until at least 24 months after transplantation.
B. Breastfeeding is not recommended with immunosuppressant medication.

C. MMF should be stopped.
D. Anti-Ro and La antibody should be assessed to inform fetal monitoring.

3. A 28-year-old woman with IgA nephropathy is at 32 weeks of gestation. Her prepregnancy GFR is 45 mL/min/1.73 m2 and uPCR is 120 mg/mmol. She presents with headache and peripheral edema; her BP is 166/100 mm Hg and uPCR is 245 mg/mmol. Her serum creatinine has increased from 70 µmol/L 4 weeks ago to 84 µmol/L. What is the best approach to management?

A. Admit for BP control and assess by fetal artery Doppler to determine timing of delivery.
B. Admit for BP control and urgent cesarean section delivery to preserve kidney function.
C. Give IV magnesium sulfate to prevent eclampsia, then plan delivery within 24 hours.
D. Start aspirin 75 mg daily and labetalol 200 mg three times daily with escalation to IV antihypertensives if no response.

REFERENCES

1. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88:950–957.

2. Hewawasam Erandi, Davies Christopher E, Gulyani Aarti, et al. Factors influencing fertility rates in Australian women receiving kidney replacement therapy: analysis of linked ANZDATA registry and perinatal data over 22 years. Nephrol Dial Transplant. 2021:gfab157.

3. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. Nephrol Dial Transplant. 2020:gfaa247.

✓ 4. ✓ Piccoli GB, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. J Am Soc Nephrol. 2015;26:2011–2022.

5. Harel Ziv, Park Alison L, McArthur Eric, et al. Pre-pregnancy renal function and risk of preterm birth and related outcomes. CMAJ. 2020;192(30):E851–E857.

6. Bramham K, Briley AL, Seed PT, et al. Pregnancy outcome in women with chronic kidney disease: a prospective cohort study. Reprod Sci. 2011;18:623–630.

7. Bramham K, Parnell B, Nelson-Piercy C, et al. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014;348:g2301.

8. Kilby M. Management of hypertension in renal disease in pregnancy. In: Davison JM, Nelson-Piercy C, Kehoe S, Baker P, eds. Renal Disease and Pregnancy. London: RCOG Press; 2008:149–165.

✓ 9. ✓ Piccoli GB, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. J Am Soc Nephrol. 2015;26:2011–2022.

✓ 10. ✓ Piccoli GB, Fassio F, Attini R, et al. Pregnancy in CKD: whom should we follow and why? Nephrol Dial Transplant. 2012;27(suppl 3):iii111–iii118.

11. Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for preeclampsia in patients with established hypertension and chronic kidney disease. Kidney Int. 2016;89:874–885.

✓ 12. ✓ Wang GC, Zheng JH, Xu LG, et al. Measurements of serum pituitarygonadal hormones and investigation of sexual and reproductive functions in kidney transplant recipients. Int J Nephrol. 2010;2010:612126.

13. Wiles K, Anckaert E, Holden F, et al. Anti-Müllerian hormone concentrations in women with chronic kidney disease. Clin Kidney J. 2019;14(2):537–542.

✓ 14. ✓ Watnick S. Pregnancy and contraceptive counseling of women with chronic kidney disease and kidney transplants. Adv Chronic Kidney Dis. 2007;14:126–131.

✓ 15. ✓ Galdo T, Gonzalez F, Espinoza M, et al. Impact of pregnancy on the function of transplanted kidneys. Transplant Proc. 2005;37:1577–1579.

16. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372:407–417.

17. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. Obstet Gynecol. 2017;129:174–184.

✓ 18. ✓ Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. BJOG. 2013;120:412–427.

19. Wiles Kate, Chappell Lucy C, Lightstone Liz, Bramham Kate. Updates in diagnosis and management of preeclampsia in women with CKD. Clin J Am Soc Nephrol. 2020;15(9):1371–1380.

✓ 20. ✓ Rolfo A, Attini R, Nuzzo AM, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. Kidney Int. 2013;83:177–181.

21. Coomarasamy A, Honest H, Papaioannou S, et al. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. Obstet Gynecol. 2003;101:1319–1332.

✓ 22. ✓ Spencer K, Enofe O, Cowans NJ, Stamatopoulou A. Is maternal renal disease a cause of elevated free beta-hCG in first trimester aneuploidy screening? Prenat Diagn. 2009;29:1045–1049.

23. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. N Engl J Med. 1996;335:226–232.

24. Imbasciati E, Gregorini G, Cabiddu G, et al. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. Am J Kidney Dis. 2007;49:753–762.

2✓ 5.✓ Spaan JJ, Brown MA. Can we protect the kidneys after hypertensive pregnancy? Can Med Assoc J. 2013;185:199–200.

26. Vikse BE, Hallan S, Bostad L, et al. Previous preeclampsia and risk for progression of biopsy-verified kidney disease to end-stage renal disease. Nephrol Dial Transplant. 2010;25:3289–3296.

2✓ 7.✓ Ronkainen J, Ala-Houhala M, Autio-Harmainen H, et al. Long-term outcome 19 years after childhood IgA nephritis: a retrospective cohort study. Pediatr Nephrol. 2006;21:1266–1273.

2✓ 8.✓ Jarrick S, Lundberg S, Stephansson O, et al. Pregnancy outcomes in women with immunoglobulin A nephropathy: a nationwide populationbased cohort study. J Nephrol. 2021.

29. Liu Y, Ma X, Lv J, et al. Risk factors for pregnancy outcomes in patients with IgA nephropathy: a matched cohort study. Am J Kidney Dis. 2014;64:730–736.

3✓ 0.✓ Fan W, Da LJ, Ying Z, Ting WT, Jun T. Renal outcomes of pregnant patients with immunoglobulin a nephropathy: a systematic review and meta-analysis. Am J Nephrol. 2019;49(3):214–224.

3✓ 1.✓ Su Xiaole, Lv Jicheng, Liu Youxia, et al. Pregnancy and kidney outcomes in patients with IgA nephropathy: a cohort study. Am J Kidney Dis. 2017;70(2):262–269.

3✓ 2.✓ Shimizu A, Takei T, Moriyama T, et al. Effect of kidney disease stage on pregnancy and delivery outcomes among patients with immunoglobulin A nephropathy. Am J Nephrol. 2010;32:456–461.

33. Oh HJ, Han SH, Yoo DE, et al. Reduced Pre-pregnancy proteinuria is associated with improving postnatal maternal renal outcomes in IgA nephropathy women. Clin Nephrol. 2011;76:447–454.

3✓ 4.✓ Park S, Yoo KD, Park JS, et al. Pregnancy in women with immunoglobulin A nephropathy: are obstetrical complications associated with renal prognosis? Nephrol Dial Transplant. 2018;33(3):459–465.

3✓ 5.✓ National Pregnancy in Diabetes Audit Report 2018.

3✓ 6.✓ Bell R, Glinianaia SV, Tennant PW, et al. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. Diabetologia. 2012;80:445–452.

37. Klemetti MM, Laivuori H, Tikkanen M, et al. Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988-2011. Diabetologia. 2015;58:678–686.

38. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? Diabetes Care. 2009;32:38–44.

39. Bomback AS, Rekhtman Y, Whaley-Connell AT, et al. Gestational diabetes mellitus alone in the absence of subsequent diabetes is associated with microalbuminuria: results from the kidney early evaluation program (KEEP). Diabetes Care. 2010;33:2586–2591.

4✓ 0.✓ Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and metaanalysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5:2060–2068.

4✓ 1.✓ Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League against Rheumatism and European renal association-European dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71:1771–1782.

42. Clowse MEB, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum. 2006;54:3640–3647.

4✓ 3.✓ Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus

erythematosus in adults. Rheumatology (Oxford). 2018;57:e1–e45.
4✓ 4.✓ Moroni G, Doria A, Giglio E, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century. A prospective multicenter study. J Autoimmun. 2016;74:6–12.
45. Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. Lupus. 2012;21:1271–1283.
4✓ 6.✓ Ritchie J, Smyth A, Tower C, et al. Maternal deaths in women with lupus nephritis: a review of published evidence. Lupus. 2012;21(5):534–541.

References

47. Webster P, Wardle A, Bramham K, et al. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus. 2014;23:1192–1196.

48. Chakravarty E, Murray E, Kelman A, et al. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117:1499–1506.

✓49. ✓ Datapharm. MabThera 100 mg Concentrate for Solution for Infusion. https://www.medicines.org.uk/emc/product/3801/smpc#PREGNANCY.

50. Kumthekar A, Danve A, Deodhar A. Use of belimumab throughout 2 consecutive pregnancies in a patient with systemic lupus erythematosus. J Rheumatol. 2017;44:1416–1417.

51. Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med. 2015;163:153–163.

52. Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. J Rheumatol. 2011;38:1906–1913.

53. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent antiSSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation. 2012;126:76–82.

✓54. ✓ Scott JE, Swallow V, Coulthard MG, Lambert HJ, Lee RE. Screening of newborn babies for familial ureteric reflux. Lancet. 1997;350:396–400.

55. Elder JS, Peters CA, Arant BS, et al. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol. 1997;157:1846–1851.

56. Chapman AB, Johnson AM, Gabow PA. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994;5:1178–1185.

57. Wu M, et al. Pregnancy outcomes in autosomal dominant polycystic kidney disease: a case-control study. J Matern Fetal Neonatal Med. 2016;29:807–812.

✓58. ✓ Brunini F, Zaina B, Gianfreda D, Ossola W, Giani M, Fedele L, et al. Alport syndrome and pregnancy: a case series and literature review. Arch Gynecol Obstet. 2018;297:1421–1431.

59. Hladunewich M, Hercz AE, Keunen J, et al. Pregnancy in end stage renal disease. Semin Dial. 2011;24:634–639.

60. Oliverio Andrea L, Bragg-Gresham Jennifer L, Admon Lindsay K, et al. Obstetric deliveries in US women with ESKD: 2002-2015. Am J Kidney Dis. 2020;75(5):762–771.

✓61. ✓ Shah S, Christianson AL, Meganathan K, et al. Racial differences and factors associated with pregnancy in ESKD patients on dialysis in the united states. J Am Soc Nephrol. 2019;30(12):2437–2448.

62. Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and united states cohort comparison. J Am Soc Nephrol. 2014;25:1103–1109.

✓63. ✓ Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. Nephrol Dial Transplant. 2016;31(11):1915–1934.

✓64. ✓ Sato JL, De Oliveira L, Kirsztajn GM, et al. Chronic kidney disease in pregnancy requiring first-time dialysis. Int J Gynaecol Obstet. 2010;111:45–48.

✓65. ✓ Jesudason S, Grace BS, McDonald SP. Pregnancy outcomes according to dialysis commencing before or after conception in women with ESRD. Clin J Am Soc Nephrol. 2014;9:143–149.

66. Luders C, Titan SM, Kahhale S, Francisco RP, Zugaib M. Risk factors for adverse fetal outcome in hemodialysis pregnant women. Kidney Int Rep. 2018.

✓67. ✓ Gill JS, Zalunardo N, Rose C, Tonelli M. The pregnancy rate and live birth rate in kidney transplant recipients. Am J Transplant. 2009;9:1541–1549.

✓68.✓ Shah, et al. Pregnancy outcomes in women with kidney transplant: metaanalysis and systematic review. BMC Nephrology. 2019;20(1):24.

69. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. Am J Transplant. 2011;11:2388–2404.
70. Klein CL, Josephson MA. Post-transplant pregnancy and contraception. Clin J Am Soc Nephrol. 2022;17(1):114–120.
7✓ 1.✓ Songmao Zheng BS, Thomas R, Easterling MD, et al. Pharmacokinetics of tacrolimus during pregnancy. Ther Drug Monit. 2012;34(6):660–670.
72. Davison JM. Pregnancy in renal allograft recipients: problems, prognosis and practicalities. Baillieres Clin Obstet Gynaecol. 1994;8:501–525.
73. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. J Am Soc Nephrol. 2009;20:2433–2440.
74. van Buren Marleen C, Schellekens Anouk, Katrien T, Groenhof J, et al. Long-term graft survival and graft function following pregnancy in kidney transplant recipients: a systematic review and meta-analysis. MetaAnalysis. 2020;104(8):1675–1685.
7✓ 5.✓ Majak Guri B, Varberg Reisæter Anna, Weedon-Fekjær Harald, Henriksen Tore, Michelsen Trond M. The effect of pregnancy on the long-term risk of graft loss, cardiovascular disease, and death in kidney transplanted women in norway: a retrospective cohort study. Transplantation. 2018;102(9):e391–e396.
7✓ 6.✓ Bachmann Friederike, Budde Klemens, Gerland Marie, et al. Pregnancy following kidney transplantation: impact on mother and graft function and focus on childrens’ longitudinal development. BMC Pregnancy Childbirth. 2019;19(1):376.
7✓ 7.✓ Yin Ophelia, Kallapur Aneesh, Coscia Lisa, Constantinescu Serban, Moritz Michael, Afshar Yalda. Differentiating acute rejection from preeclampsia after kidney transplantation. Obstet Gynecol. 2021;137(6):1023–1031.
78. Boyer Annabel, Lobbedez Thierry, Ouethrani Mohamed, et al. Paternity in male kidney transplant recipients: a French national survey, the paternal study. BMC Nephrol. 2020;21(1):483.
7✓ 9.✓ Jesudason Shilpanjali, Fitzpatrick Alyssa, Gulyani Aarti, et al. Fatherhood and Kidney Replacement Therapy: analysis of the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry. Am J Kidney Dis. 2020;76:444–446.
80. Ibrahim HN, Akkina SK, Leister E, et al. Pregnancy outcomes after kidney donation. Am J Transplant. 2009;9:825–834.
8✓ 1.✓ Reisaeter AV, Roislien J, Henriksen T, et al. Pregnancy and birth after kidney donation: the norwegian experience. Am J Transplant. 2009;9:820–824.
8✓ 2.✓ Garg AX, Nevis IF, McArthur E, et al. Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med. 2015;372:124–133.
8✓ 3.✓ Davis Scott, Dylewski James, Shah Pratik B, et al. Risk of adverse maternal and fetal outcomes during pregnancy in living kidney donors: a matched cohort study. Clin Transplant. 2019;33(1):e13453.
84. Brown MA, Magee LA, Kenny LC, et al. International society for the study of hypertension in pregnancy ISSHP: hypertensive disorders of pregnancy: iSSHP classification, diagnosis, and management recommendations for International Practice. Hypertension. 2018;72:24–43.
8✓ 5.✓ American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin No. 222: gestational hypertension and preeclampsia. Obstet Gynecol. 2020;135:e237–e260.
86. Wiles K, Bramham K, Seed PT, Brockbank A, et al. Placental and endothelial biomarkers for the prediction of superimposed pre-eclampsia in chronic kidney disease. Pregnancy Hypertension. 2021;24:58–64.
87. Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for preeclampsia in patients with established hypertension and

chronic kidney disease. Kidney Int. 2016;89:874–885.
88. Wiles K, Chappell L, Clark K, et al. Clinical practice guideline on pregnancy and renal disease. BMC Nephrol. 2019;20(1):401.

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Autosomal Dominant Polycystic Kidney Disease

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DEFINITION

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by multiple, bilateral kidney cysts and associated with cysts in other organs, such as the liver, pancreas, and arachnoid membranes.1 It is a genetic disorder caused mainly by mutations in either of two major genes and inherited in an autosomal dominant pattern, with variable expression. Although benign (nongenetic) kidney cysts are common with aging, an underlying inherited disease should be suspected in patients with multiple bilateral kidney cysts, even if the kidney function is normal.

ETIOLOGY AND PATHOGENESIS

The common ADPKD proteins, polycystin-1 and polycystin-2, play a critical role in the normal function of the primary cilium that is essential to maintaining the differentiated phenotype of tubular epithelium.2

Genetic Mechanisms

ADPKD is genetically heterogeneous with two common genes identified (Fig. 46.1): PKD1 (chromosome 16p13.3) and PKD2 (4q21). Recently, three additional genes have been identified in pedigrees with an atypical ADPKD presentation: GANAB,3 DNAJB11,4 and ALG95; the encoded proteins are involved in the maturation and processing of polycystins. Autosomal dominant polycystic liver disease (ADPLD) also exists as an independent entity and is genetically heterogeneous; the first two genes identified (PRKCSH in chromosome 19 and SEC63 in chromosome 6) account for about one-third of isolated ADPLD cases. More recently, mutations to GANAB, ALG8, SEC61B, and LRP5 have also been shown to cause ADPLD.6

Evidence from animal models of ADPKD and analysis of cystic epithelia have shown that kidney cysts may develop from loss of functional polycystin with somatic inactivation of the normal allele. However, cysts can develop even if the protein is not completely lost, as demonstrated by animal models expressing incompletely penetrant alleles.7

Polycystic Kidney Disease Proteins

Polycystin-1 (PC1; PKD1 protein) and polycystin-2 (PC2; PKD2 protein) belong to a subfamily of transient receptor potential (TRP) channels. PC1 (~440 kDa) has the structure of a receptor or adhesion molecule and contains a large extracellular N region, 11 transmembrane regions, and a short intracellular C region (see Fig. 46.1). PC1

interacts with PC2 through a coiled-coil domain in the C-terminal portion and with multiple other proteins at different extracellular and intracellular sites. PC1 is found in the primary cilia, plasma membrane at focal adhesions, desmosomes, adherens junctions, and possibly endoplasmic reticulum (ER) and nuclei. PC2 (TRPP2; ~110 kDa) contains a short N-terminal cytoplasmic region, six transmembrane domains, and a short C-terminal portion. PC2 is localized predominantly to the ER but also to the plasma membrane, primary cilium, centrosome, and mitotic spindles in dividing cells.2 A cryo-EM structure indicates 1 PC1 to 3 PC2 molecules.8 PC1 and PC2 are also found at high concentrations in exosomes, which are shed into the urine and physically interact with primary cilia, possibly exerting an effect on other cells in the nephron.

Mechanisms of Cyst Formation

Experimental data indicate that the timing of ciliary loss or Pkd1 inactivation determines the rate of development of cystic disease. Inactivation in the developing kidney results in rapid progression.9 Interestingly, the loss of Pkd1 and cilia results in less severe polycystic kidney disease (PKD) than loss of Pkd1 alone.10

The polycystins are involved in the detection of extracellular cues at primary cilia, cell-cell contacts, and cell-matrix contacts and are essential to maintain the differentiated phenotype of the tubular epithelium. Reduction in one of the polycystins to below a critical threshold results in inability to maintain planar polarity, increased rates of proliferation, expression of a secretory phenotype, and remodeling of the extracellular matrix.2 PC1 and PC2 in the primary cilium may be required for the increase in cytosolic calcium that occurs in response to ciliary bending.11 PC2 is a TRP channel (TRPP2) and functions as a calcium release channel in the ER.12 PC1 interacts with and modulates the maturation and function of PC2, and vice versa.13 PC1 and PC2 also interact with additional calcium channel proteins. Precisely how intracellular calcium homeostasis is altered in ADPKD remains uncertain, but many studies show reduced resting intracellular calcium, ER calcium stores, and store-operated calcium entry in primary cell cultures or microdissected samples from human and rodent polycystic tissues2 (Fig. 46.2).

A common finding in animal models of PKD is increased levels of cyclic adenosine monophosphate (cAMP), not only in the kidney but also in the liver and vascular smooth muscle.14 Tissue levels of cAMP are determined by the activities of membrane-bound and soluble adenylyl cyclases and cAMP phosphodiesterases (PDEs), themselves subject to complex regulatory mechanisms. Reduced intracellular calcium

Polycystins
PKD2

PKD1
Intron–exon
sequences
1

5

10

20

25

30

35 40 45

2

3 4

5 6

7 8 910111213

p

16
15.3
15.2
15.1
14
13
12
11
11
12
13

q

21

Key

13.2
13.1

Signal sequence

12
11.2
11.1
11.1
11.2

q

1

NH2

13.3

p

15

12.1
12.2
13
21

Leucine-rich repeats

WSC domain

PKD repeat

C-type lectin

LDL-A related

REJ module

GPS domain

Transmembrane
region
G protein binding

PLAT domain
Coiled coil

TRP channel
homology

22

EF hand
ER retention
signal

23

Polycystin-2

24

Chromosome
16

?
Polycystin-1

141516

22
23
24
25

26
27
28
31.1
31.2
31.3
32
33
34
35

Chromosome
4
?
COOH

COOH

NH2

Fig. 46.1 Polycystins: Genes, Messenger RNAs, and Proteins. Diagrammatic representation of chromosome 16 (left) and chromosome 4 (right). Intron-exon sequences of PKD1 (upper left) and PKD2 (upper right). Diagram of proposed structural features of the polycystin-1 and polycystin-2 proteins (center). ER, Endoplasmic reticulum; GPS, G-protein-coupled receptor proteolytic site; LDL, low-density lipoprotein; PKD, polycystic kidney disease; PLAT, polycystin-1, lipoxygenase, alpha-toxin; REJ, receptor for egg jelly; TRP, transient receptor potential; WSC, wall integrity and stress response component.

in PKD may activate calcium inhibitable AC6 or AC5, directly inhibit calcium/calmodulin-dependent PDE1, and indirectly inhibit cGMP inhibitable PDE3, thereby accounting for the accumulation of cAMP and activation of protein kinase A (PKA), which, in turn, contributes to the development and progression of PKD by stimulating cystic fibrosis transmembrane conductance regulator (CFTR)-driven chloride and fluid secretion and cell proliferation (see Fig. 46.2).

Chloride enters across basolateral Na^+-K^+-2Cl cotransporters, driven by the sodium gradient generated by basolateral Na^+,K^+ ATPase, and exits across apical PKA-stimulated CFTR. Basolateral recycling of potassium occurs through the KCa3.1 channel.

cAMP exerts opposite effects on cell proliferation in different cell types. cAMP and PKA signaling enhance several proproliferative pathways (extracellular signal–regulated kinase [ERK]) in cells derived from polycystic kidneys and inhibit proliferation in cells derived from normal human kidney cortex.[15,16] Treatment of normal human kidney or murine collecting duct cells with calcium channel blockers replicates the proliferative response of the ADPKD cells to cAMP, thus linking this response to the reduction in intracellular calcium that results from disrupting the polycystin pathway.[17] Conversely, treatment of ADPKD cyst–derived cells with calcium channel activators or calcium ionophores restores the normal antimitogenic response to cAMP (see Fig. 46.2).

Liver Cyst Development

Liver cysts arise by excessive proliferation and dilation of biliary ductules and peribiliary glands. Estrogen receptors, insulin-like growth factor 1 (IGF-1), IGF-1 receptors, and growth hormone receptors are expressed in the epithelium lining the hepatic cysts, and estrogens and IGF-1 stimulate hepatic cyst–derived cell proliferation. Cyst growth is also promoted by growth factors and cytokines secreted into the cyst fluid.

Hypertension

Hypertension is a major clinical manifestation and predictor of outcome in ADPKD (see Clinical Manifestations). Several factors contribute to the development of hypertension in ADPKD. Activation of the intrarenal renin-angiotensin system (RAS) likely plays an important role, but whether the circulating RAS is inappropriately activated is controversial. The expression of PC1 and PC2 in vascular smooth muscle and endothelium, along with enhanced vascular smooth muscle contractility and impaired endothelium-dependent vasorelaxation in ADPKD, suggest that disruption of polycystin function directly contributes to hypertension. Other factors include increased sympathetic nerve activity and plasma endothelin-1 levels and insulin resistance.[1]

Endothelial vasodilation and constitutive nitric oxide synthase activity are reduced in subcutaneous resistance vessels from patients with ADPKD and normal glomerular filtration rate (GFR). Flowinduced vasodilation of the brachial artery is inconsistently impaired, whereas pulse wave reflection is amplified, suggesting a predominant involvement of small resistance vessels. Reduced coronary flow velocity reserve and increased carotid intima-media thickness in normotensive patients with normal GFR suggest that atherosclerosis starts early in the course of ADPKD.

Signaling Pathways in Polycystic Kidney Disease
Reduced in PKD

Fluid secretion

Increased in PKD

PC1

Cl–

PC2
CFTR

K+

PKA
PC2

2Cl–
Na+

Src
Ca^{2+}

MAPK
mTOR

cAMP
Cell proliferation

ATP
TKR

V2R
AVP

PDE1
AMP

Gs AC6 Gi

SSTR
SST

Fig. 46.2 Signaling Pathways in Polycystic Kidney Disease (PKD). Pathways that are upregulated or downregulated in PKD and the rationale for potential therapies. Dysregulation of intracellular calcium homeostasis leads to intracellular accumulation of cyclic adenosine monophosphate (cAMP), activation of protein kinase A (PKA), cystic fibrosis transmembrane conductance regulator (CFTR) phosphorylation, and stimulation of chloride-driven fluid secretion. In the setting of reduced intracellular calcium, PKA activates Src, mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK), and mammalian target of rapamycin (mTOR) signaling. Activation of tyrosine kinase receptors (TKR) for several growth factors contributes to the activation of Src and downstream proproliferative pathways. Therapies currently under clinical investigation target G protein–coupled receptors (modulating activity of adenylyl cyclase 6 [AC6] and

generation of cAMP), Src, mTOR, and TKRs. AVP, Arginine vasopressin; PDE1, phosphodiesterase-1; SST, somatostatin; SSTR, somatostatin receptor.

Reduced nitric oxide endothelium-dependent vasorelaxation in ADPKD may be caused by increased plasma levels of asymmetric dimethylarginine, a mechanism common to all hypertension associated with kidney disease.

Altered polycystin function in cardiac fibroblasts likely accounts for the increased frequency of valvular heart disease in ADPKD.

EPIDEMIOLOGY

ADPKD occurs worldwide and in all races, with a prevalence of genetically affected individuals at birth estimated at 1 in 400 to 1 in 1000. In most patients the diagnosis is made decades later, and some patients are never diagnosed. Therefore, at any point in time, only a fraction of genetically affected individuals are aware of having the disease. Clinical registry data suggest point prevalence rates of diagnosed cases ranging from 1 in 543 to 1 in 4000. The proportion of end-stage kidney disease (ESKD) caused by ADPKD is less among Blacks than among Whites because of a higher incidence of other causes of ESKD. Yearly incidence rates for ESKD caused by ADPKD in males and females, respectively, are 8.7 and 6.9 per 1 million (1998–2001, United States), 7.8 and 6.0 per million (1998 and 1999, Europe), and 5.6 and 4.0 per million (1999 and 2000, Japan). Age-adjusted sex ratios greater than unity (1.2–1.3) and recent genotype/phenotype studies suggest more progressive disease in males than in females.18–20 In recent studies, the age of onset of ESKD has increased in both sexes, and all-cause mortality has decreased, possibly because of improved detection and control of hypertension.1

PHENOTYPIC VARIABILITY

Genic, allelic, and gene-modifier effects contribute to the high phenotypic variability of ADPKD. PKD1-associated disease is more severe than PKD2-associated disease (age at ESKD, 58 years vs. 79 years for PKD1 and PKD2, respectively).21 The greater severity of PKD1 is caused by development of more cysts at an early age, not faster cyst growth.1 Both PKD1 and PKD2 can be associated with severe polycystic liver disease (PLD) and vascular abnormalities.22 Because of the lesser severity of the kidney involvement, the prevalence of PKD2-associated disease has likely been underestimated in clinical studies.

Mutations in PKD1 and PKD2 are highly variable and often “private” (unique to a kindred). The ADPKD Mutation Database (http://pkdb.mayo.edu) lists 1621 likely pathogenic PKD1 mutations identified in 2417 families with a total of 2905 variants, including silent polymorphisms. Also, 256 likely pathogenic PKD2 mutations are listed in 553 families, with a total of 358 different variants. A much smaller number of patients with mutations to GANAB, DNAJB11, and ALG9 have been described.3

Allelic factors have an effect on the severity of ADPKD. Recent studies in large cohorts have shown that the type of PKD1 mutation, but not its position, correlates strongly with kidney survival. The median age at onset of ESKD was 55 years for carriers of a truncating mutation and 67 years for carriers of a nontruncating mutation.21 Hypomorphic or incompletely penetrant PKD1 or PKD2 alleles have been described. These alleles alone may result in mild cystic disease; two such alleles cause typical to severe disease and, in combination with an inactivating allele, may be associated with early-onset disease that mimics autosomal recessive PKD (ARPKD).1 A prognostic score (PRO-PKD score) based on the gene mutated and type of mutation helps predict kidney outcomes and enable the personalization of therapeutic management in patients with ADPKD.2 23

The large intrafamilial variability of ADPKD highlights a role for genetic background in disease presentation. Age at onset of clinical manifestations in ADPKD is less variable within than between families, which suggests a common familial modifying background for early and severe disease expression (e.g., mutations or variants in genes encoding other cystoproteins). The contiguous deletion of the adjacent PKD1 and TSC2 is characterized by childhood PKD with additional clinical signs of tuberous sclerosis complex. Other modifying loci are likely to account for more common and subtle intrafamilial variability.

DIAGNOSIS

Only individuals who have been properly informed about the advantages and disadvantages of screening should be offered presymptomatic screening. If ADPKD is diagnosed, the patient should receive appropriate genetic counseling, and risk factors such as hypertension can be identified and treated early. If ADPKD is absent, the patient can be reassured. Disadvantages of presymptomatic screening relate to insurability and employability. Presymptomatic screening of children is not recommended until more effective therapy for the disease becomes available.

Kidney Imaging

Kidney ultrasound is used for presymptomatic testing because of cost and safety. Revised criteria have been proposed to improve the diagnostic performance of ultrasound in ADPKD (Table 46.1). At least three (unilateral or bilateral) kidney cysts are sufficient for diagnosis of at-risk individuals 15 to 39 years of age; two cysts in each kidney are sufficient for diagnosis for ages 40 to 59 years.24 For at-risk individuals age 60 and older, four or more cysts in each kidney are required. The specificity and positive predictive value (PPV) of ultrasound are close to 100% using these criteria, but their sensitivity and negative predictive value (NPV) when applied to PKD2 patients age 15 to 59 years are low. This is a problem in the evaluation of potential kidney donors, in which exclusion of the diagnosis is important. Different criteria have therefore been proposed to exclude a diagnosis of ADPKD in an individual at risk from a family with an unknown genotype. An ultrasound finding of normal kidneys or one kidney cyst in an individual aged 40 years or older has an NPV of 100%. The absence of any kidney cysts provides near certainty that ADPKD is absent in at-risk individuals aged 30 to 39 years, with a false-negative rate of 0.7% and NPV of 98.7%. A normal or indeterminate ultrasound scan does not exclude ADPKD with certainty in an at-risk individual younger than 30 years. A study of 73 affected and 82 nonaffected individuals suggested that finding fewer than five cysts by magnetic resonance imaging (MRI) is sufficient to exclude the diagnosis of ADPKD in potential living related kidney donors.25 Contrast-enhanced computed tomography (CT) scanning with thin slices likely provides similar information, but this has not been proven.

Ultrasound Criteria for the Diagnosis of Autosomal Dominant Polycystic Kidney Disease

TABLE 46.1

Age (y)

Criteria

PPV

NPV

Original Ravine’s PKD1 Diagnostic Criteria
15–29
≥2 cysts, unilateral or bilateral
99
30–39
≥2 cysts in each kidney
100
40–59
≥2 cysts in each kidney
100
≥60
≥4 cysts in each kidney
100

88
88
95
100

Revised Unified Diagnostic Criteria
15–29
≥3 cysts, unilateral or bilateral
30–39
≥3 cysts, unilateral or bilateral
40–59
≥2 cysts in each kidney
≥60
≥4 cysts in each kidney

86
86
95
100

100
100
100
100

Revised Diagnostic Criteria (when diagnosis needs to be excluded)
15–29
≥1 cyst
97
91
30–39
≥1 cyst
94
98
40–59
≥2 cysts
97
100

≥60
≥3 cysts in each kidney
100
100
NPV, Negative predictive value; PPV, positive predictive value.

made for broader screening to obtain a firm diagnosis. Molecular diagnosis of ADPKD is complicated by duplication of the PKD1 gene, which means it may not be efficiently screened by whole-exome sequencing. For diagnostic purposes, next-generation sequencing panels of PKD genes are now generally employed that allow for higher throughput screening and lower costs.26 Molecular testing by direct DNA sequencing is now informative in at least 90% of patients. However, because many mutations are unique and up to one-third of PKD1 changes are missense, the pathogenicity of some changes is difficult to prove. De novo mutations and mosaicism also can complicate interpretation of results.27

In preimplantation genetic diagnosis (PGD), genetic analysis is performed on single blastomeres from preimplantation embryo biopsy specimens obtained after in vitro fertilization (IVF), and only embryos unaffected by the disease are selected for transfer. PGD for ADPKD is complicated by the genetic heterogeneity of the disease and the large size and complex structure of the PKD1 gene but has been performed for ADPKD. PGD should be included in the discussion of reproductive choices with patients with ADPKD, but it is only available in certain countries and the acceptance of this technique is influenced by personal values and by the severity of the disease.1

DIFFERENTIAL DIAGNOSIS

Kidney cysts can be a manifestation of many other systemic diseases. Conditions to consider when presentation is not typical of ADPKD include ARPKD, tuberous sclerosis complex, von Hippel–Lindau disease, kidney cysts and diabetes from HNF1B mutations, and oro-faciodigital syndrome type I, as well as medullary sponge kidney and simple kidney cysts. These are discussed further, including differential diagnosis, in Chapter 47. If the patient has ESKD, acquired cystic disease also should be considered (see Chapter 92).

Genetic Testing

CLINICAL MANIFESTATIONS

Genetic testing can be performed when a precise diagnosis is needed and the results of imaging are indeterminate, although a case can now be

ADPKD is a multisystem disorder. Multiple kidney and extrarenal manifestations of ADPKD can cause significant complications.

Kidney Manifestations of Autosomal Dominant Polycystic Kidney Disease

BOX 46.1

Functional Manifestations
- Concentrating defect
- Reduced kidney blood flow

Hypertension → Target Organ Damage
- Cardiac
- Cerebrovascular
- Arteriolosclerosis and glomerulosclerosis
- Peripheral vascular disease

Pain, Caused by
- Cyst hemorrhage
- Gross hematuria
- Nephrolithiasis
- Infection
- Kidney enlargement

Reduced Glomerular Filtration Rate, Possibly Caused by
- Interstitial inflammation
- Apoptosis of tubular epithelial cells
- Hypertensive glomerulosclerosis
- Compression atrophy

Kidney Manifestations

A number of clinical features that result from kidney damage can be identified (Box 46.1). Reduction in urinary concentrating capacity and glomerular hyperfiltration are early functional abnormalities that can be observed in some children and adolescents with ADPKD.

Kidney Size

Kidney size increases with age, and kidney enlargement eventually occurs in 100% of patients with ADPKD. The severity of the structural abnormality correlates with the manifestations of ADPKD, such as pain, hematuria, hypertension, and kidney impairment.1 Massive kidney enlargement can lead to compression of local structures, resulting in such complications as inferior vena cava (IVC) compression and digestive symptoms. Most manifestations are directly related to the development and enlargement of kidney cysts. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), a prospective study of 241 patients by annual MRI, has shown that total kidney volume (TKV) and cyst volumes increased exponentially.28 Rates of growth were relatively constant, averaging 5.3% per year, but were highly variable from patient to patient. Baseline TKV predicted the subsequent rate of increase in kidney volume and decline in GFR.29 An imaging classification of ADPKD based on height-adjusted TKV and age may facilitate the selection of patients with rapidly progressive disease (class 1C–E) for enrollment into clinical trials and for diseasemodifying treatments.30

Pain

Episodes of acute kidney pain are seen frequently; causes include cyst hemorrhage, infection, stone, and, rarely, tumor, and these must be investigated thoroughly. A few patients with ADPKD with kidney enlargement and structural distortion develop chronic flank pain without an identifiable cause.

Hematuria and Cyst Hemorrhage

Visible hematuria may be the initial presenting symptom and occurs in up to 40% of patients with ADPKD over the course of the disease. Many have recurrent episodes. Differential diagnosis includes cyst hemorrhage, stone, infection, and tumor. Cyst hemorrhage is a frequent complication and produces gross hematuria when the cyst communicates with the collecting system. Frequently, the cyst does not communicate with the collecting system, and flank pain without hematuria occurs. It can manifest with fever, raising the possibility of cyst infection. On occasion, a hemorrhagic cyst will rupture, resulting in a retroperitoneal bleed that can be significant, potentially requiring transfusion. In most patients, cyst hemorrhage is self-limited, resolving within 2 to 7 days. If symptoms of hematuria or flank pain last longer than 1 week or if the initial episode of hematuria occurs after age 50 years, neoplasm should be excluded.

Urinary Tract Infection and Cyst Infection

Urinary tract infection (UTI) is common in ADPKD, but its incidence may have been overestimated because sterile pyuria is common in these patients. UTI presents as cystitis, acute pyelonephritis, cyst infection, and perinephric abscesses. As in the general population, females are affected more frequently than males. Most infections are caused by Escherichia coli, Klebsiella and Proteus species, and other Enterobacteriaceae. The route of infection in acute pyelonephritis and cyst infection is usually retrograde from the bladder; therefore cystitis should be promptly treated to prevent complicated infections.

Both CT and MRI are sensitive to detect complicated cysts and can provide anatomic definition, but the findings are not specific for infection. Nuclear imaging, especially indium-labeled white blood cell scanning, is useful, but false-negative and false-positive results are possible. F-Labeled fluorodeoxyglucose (FDG) positron emission tomography (PET) has recently been used for detection of infected cysts.[1] FDG is taken up by inflammatory cells because of their high metabolic rate but is filtered by the kidneys, is not reabsorbed, and appears in the collecting system, which may limit its use in diagnosis of kidney cyst infections; its present role is for diagnosis of infected liver cysts. FDG-PET is expensive and not widely available, but it provides rapid imaging with high spatial resolution, high targetto-background ratio, low radiation burden, and high interobserver agreement.

When there is fever and flank pain with suggestive diagnostic imaging but blood and urine cultures are negative, cysts should be aspirated under ultrasound or CT guidance to culture the organism and inform the selection of antimicrobial therapy.

Nephrolithiasis

Kidney stone disease occurs in about 20% of patients with ADPKD. Most stones are composed of uric acid, calcium oxalate, or both. Uric acid stones are more common in ADPKD than in stone formers without ADPKD. Urinary stasis secondary to distorted kidney anatomy may play a role in the pathogenesis of nephrolithiasis. Predisposing metabolic factors include decreased ammonia excretion, low urinary pH, and low urinary citrate concentration.

Stones can be difficult to diagnose on imaging in ADPKD because of cyst wall and parenchymal calcification. The distorted anatomy can cause difficulty in localizing stones to the collecting system on plain radiographs. Intravenous (IV) urography has the advantage of specifically localizing stone material to the collecting system and may provide clues to stone composition. IV urography also can detect precalyceal tubular ectasia, found in 15% of patients with ADPKD. CT urography has replaced IV urography in many centers; it is more sensitive in detecting small or radiolucent stones and for differentiating stones patients with ADPKD with estimated GFR (eGFR) >60 mL/min/1.73 m2 and with the rate of decline in kidney function in those with eGFR between 25 and 60 mL/min/1.73 m2 32

Several mechanisms account for loss of GFR. The CRISP study confirmed that kidney and cyst volumes are the strongest predictors of declining GFR29 and also found that kidney blood flow (or vascular resistance) is an independent predictor.33 The latter suggests that vascular remodeling may account for cases in which the decline of kidney function seems disproportionate to the severity of the cystic disease, particularly in patients reaching ESKD in the seventh decade of life or later.34 Other factors, such as heavy use of analgesics, may contribute to chronic kidney disease (CKD) progression in some patients.

Probability of kidney survival

Effect of Blood Pressure on
Kidney Survival in Autosomal
Dominant Polycystic Kidney Disease
100
80
60
40
Normotensive n = 12
Hypertensive n = 22

20
0
0

5

10

15

20

25

30

Years from diagnosis

Fig. 46.3 Patients with polycystic kidney disease and hypertension at diagnosis have less probability of kidney survival than those with normal blood pressure.

from tumor, clot, and cyst wall or parenchymal calcification. Dualenergy CT is increasingly used to distinguish between calcium and uric acid stones.

Hypertension

Hypertension is the most common manifestation of ADPKD and a major contributor to kidney disease progression and cardiovascular morbidity and mortality (Fig. 46.3). Albuminuria and hematuria are more common in hypertensive patients with ADPKD and correlate with the rate of kidney function loss. Hypertension also may increase morbidity from valvular heart disease and intracranial aneurysms, which are common in ADPKD.

Ambulatory blood pressure (BP) monitoring of children or young adults without diagnosed hypertension often reveals elevated BP, attenuated nocturnal BP dipping, and exaggerated BP response during exercise. A study stratified 65 children by BP into three cohorts: hypertensive (≥95th percentile), borderline hypertensive (75th to 95th percentile), and normotensive (≤75th percentile).31 Both the hypertensive and the borderline hypertensive children had significantly higher left ventricular (LV) mass indices than the normotensive children. Among normotensive children, indices were significantly higher in those within the upper quartile of normal BP. These observations suggest that target organ damage develops early in ADPKD and that antihypertensive treatment may be indicated in children with ADPKD and borderline hypertension.

End-Stage Kidney Disease

In most patients, kidney function is maintained within the normal range, despite relentless growth of cysts, until the fourth to sixth decade of life. By the time kidney function starts declining, the kidneys usually are greatly enlarged and distorted with little recognizable parenchyma on imaging studies. At this stage, the average rate of GFR decline is 4.4 to 5.9 mL/min per year. Nevertheless, ESKD is not inevitable in ADPKD. Up to 77% of patients are alive with preserved GFR at age 50 years and 52% at age 73 years. Males tend to progress to kidney failure more rapidly and require kidney replacement therapy at a younger age than females. Other risk factors for kidney failure include Black race, diagnosis of ADPKD before age 30 years, first episode of hematuria before age 30 years, onset of hypertension before age 35 years, hyperlipidemia, low level of high-density lipoprotein cholesterol, sickle cell trait, and PKD1 truncating mutations. Recently, a post hoc analysis of the HALT PKD clinical trials showed an association of dietary sodium with the rate of kidney growth in

Extrakidney Manifestations

Polycystic Liver Disease

PLD is the most common extrarenal manifestation of ADPKD. PLD is associated with both PKD1 and PKD2 genotypes. In contrast to the kidney phenotype, the ADPKD genotype is not associated with the severity or growth rate of PLD in patients with ADPKD.22 In addition, PLD also occurs as a genetically distinct disease in the absence of kidney cysts (ADPLD). Most simple hepatic cysts are solitary, and PLD should be suspected when four or more cysts are present in the hepatic parenchyma. The liver in PLD contains multiple microscopic or macroscopic cysts that result in hepatomegaly (Fig. 46.4), but typically there is preservation of normal hepatic parenchyma and liver function. Hepatic cysts are exceedingly rare in children with ADPKD. Their frequency increases with age and may have been underestimated by ultrasound and CT studies. Their prevalence by MRI in the CRISP study was 58%, 85%, and 94%, respectively, in participants age 15 to 24, 25 to 34, and 35 to 46 years. Females develop more cysts at an earlier age than males. Females who have multiple pregnancies or who have used oral contraceptives (OCs) or estrogen replacement therapy (ERT) in the postmenopausal period may have worse disease. After menopause, the volume of polycystic livers often remains stable or may even decrease.22 Typically, PLD is asymptomatic, but reported symptoms have become more frequent as the life span of patients with ADPKD is prolonged with dialysis and transplantation. Symptoms result from mass effect or from complications related to the cysts themselves.35 Symptoms include dyspnea, orthopnea, early satiety, gastroesophageal reflux, mechanical low back pain, uterine prolapse, and even rib fracture. Other complications caused directly by mass effect include hepatic venous outflow obstruction, IVC compression, portal vein compression, and bile duct compression presenting as obstructive jaundice. Hepatic venous outflow obstruction is an uncommon condition caused by severe extrinsic compression of the intrahepatic IVC and hepatic veins by cysts, rarely with superimposed thrombosis. Symptomatic cyst complications include cyst hemorrhage, which occurs less frequently than kidney cyst hemorrhage, cyst infection, and the rare occurrence of torsion or rupture of cysts. Hepatic cyst infection can be a serious complication and typically presents with localized pain, fever, leukocytosis, elevated sedimentation rate, and often elevated alkaline phosphatase. Enterobacteriaceae are the most common microorganisms causing cyst infection. The same imaging techniques discussed for the investigation of kidney cyst infections may be useful for the localization of infected cysts in the liver.

Congenital hepatic fibrosis, always found in association with ARPKD, can rarely coexist with ADPKD. Contrary to PKD, which affects members of several generations in these families, congenital hepatic fibrosis is seen in only one generation and is not transmitted vertically, suggesting the importance of modifier genes. These patients present with manifestations of portal hypertension, but hepatocellular function is normal.

A

B

C

Fig. 46.4 Variable Presentation of Symptomatic Polycystic Liver Disease. (A) Hepatomegaly caused by a very large, isolated, dominant cyst. (B) Hepatomegaly caused by several large cysts. (C) Hepatomegaly caused by multiple smaller cysts throughout the hepatic parenchyma.

Clinical Manifestations and Classification
of Intracranial Aneurysms
Intracranial
aneurysm

Unruptured

Asymptomatic
Incidental
Concurrent

Symptomatic
Cranial nerve
compression
Compression of other
CNS structures
Distal embolization (TIAs)
Seizures
Headache

Ruptured
Thunderclap headache
Neck stiffness
Lower back pain
Loss of consciousness
Focal neurologic signs
Preretinal/subhyaloid
hemorrhage

Fig. 46.5 Clinical manifestations and classification of intracranial aneurysms. CNS, Central nervous system; TIAs, transient ischemic attacks.

Intracranial Aneurysms

Intracranial aneurysms occur in about 8% of patients with ADPKD. There is some familial clustering; intracranial aneurysms occur in 6% of patients with a negative family history and 16% of those with a positive family history. Most are asymptomatic. Focal findings, such as cranial nerve palsy and seizure, may result from compression of local structures by an enlarging aneurysm (Fig. 46.5). Yearly rupture rates increase with size, ranging from less than 0.5% for aneurysms <5 mm in diameter to 4% for aneurysms >10 mm. Rupture carries a 35% to 55% risk for combined severe morbidity and mortality. The mean age at rupture in ADPKD is 39 years (vs. 51 years in the general population), with a range of 15 to 69 years. Most patients have normal kidney function, and up to 29% have normal BP at rupture.

Although still controversial, the largest follow-up study of asymptomatic, unruptured intracranial aneurysms discovered by presymptomatic imaging and a review of the literature suggest that widespread screening is not indicated for all patients with ADPKD because most intracranial aneurysms found by presymptomatic imaging are small, have a low risk for rupture, and require no treatment because the risks of intervention exceed any risk for rupture.36 Indications for targeted imaging in patients with a good

life expectancy include family history of intracranial aneurysm or subarachnoid hemorrhage, previous aneurysmal rupture, preparation for elective surgery with potential hemodynamic instability, high-risk occupations (e.g., airline pilots), and significant patient anxiety despite adequate information about the risks. Magnetic resonance angiography is the modality of choice for presymptomatic imaging because it is noninvasive and does not require IV contrast administration. CT angiography is a satisfactory alternative if there is no contraindication to IV contrast. Repeated imaging of patients with a strong family history of intracranial aneurysms or aneurysmal rupture after 5 to 10 years is recommended.

Other Vascular Abnormalities

In addition to intracranial aneurysms, ADPKD is associated with other vascular abnormalities, such as thoracic aortic and cervicocephalic arterial dissections, coronary artery aneurysms, and retinal artery and vein occlusions (Fig. 46.6). Thoracic aortic dissection is seven times more common in ADPKD than in the general population in autopsy series, but reported cases are rare. Rare patients with coronary aneurysms can present with cardiac ischemia and thrombus in the aneurysm in the absence of atherosclerotic disease. Several case reports describe abdominal aortic aneurysms in ADPKD. However, a prospective ultrasound study showed neither a wider aortic diameter nor a higher prevalence of abdominal aortic aneurysms in patients with ADPKD compared with an unaffected kindred in any age group.

Valvular Heart Disease and Other Cardiac Manifestations

Mitral valve prolapse is the most common valvular abnormality and has been demonstrated in up to 25% of patients with ADPKD by echocardiography. Mitral regurgitation, tricuspid regurgitation, and tricuspid prolapse also occur more frequently in ADPKD than in unaffected kindreds. Aortic regurgitation may be associated with dilation of the aortic root. On histologic examination, valvular tissue shows myxoid degeneration with disruption of collagen, as seen in Marfan and Ehlers-Danlos syndromes. Although the lesions may progress with time, they rarely require valve replacement. Echocardiography is not indicated unless a murmur is detected on physical examination. Coexistence of ADPKD and idiopathic cardiomyopathies (dilated, hypertrophic, and LV noncompaction) appears to be higher than expected by chance.37 Small, hemodynamically insignificant pericardial effusion can be detected by CT scanning in up to 35% of patients with ADPKD.

A

A

B

Fig. 46.6 Vascular Manifestations of Autosomal Dominant Polycystic Kidney Disease (ADPKD). (A) Gross specimen demonstrating bilateral aneurysms of the middle cerebral arteries (arrows). (B) Gross specimen demonstrating a thoracic aortic dissection extending into the abdominal aorta in a patient with ADPKD.

Other Associated Conditions

Cyst formation has been described in such diverse organs as the pancreas, seminal vesicles, and arachnoid membrane (Fig. 46.7). Seminal vesicle cysts, usually multiple and bilateral, are found in 40% of ADPKD compared with 2% of nonaffected males. Ovarian cysts are not associated with ADPKD. Pancreas and arachnoid membrane cysts are present in 5% and 8% of patients, respectively. Pancreatic cysts are almost always asymptomatic, with rare occurrences of recurrent pancreatitis and possibly chance associations of intraductal papillary mucinous tumor or carcinoma. Epididymal and prostate cysts also may occur with increased frequency. Sperm abnormalities with defective motility are common in ADPKD and rarely may be a cause of male infertility. Spinal meningeal diverticula may occur with increased frequency and rarely manifest with intracranial hypotension (orthostatic headache, diplopia, hearing loss, ataxia) caused by cerebrospinal fluid leak. The prevalence of colonic and duodenal diverticula also may be increased.

PATHOLOGY

Polycystic kidneys are diffusely cystic and enlarged (Fig. 46.8). Size varies from normal to weighing more than 4 kg. The outer and cut surfaces show numerous spherical cysts of varying size, which are distributed evenly between cortex and medulla. The epithelium lining the cysts is characterized by hyperplastic changes, including flat nonpolypoid hyperplasia, polypoid hyperplasia, and microscopic adenomas (Fig. 46.9), as well as increased rates of cell proliferation and apoptosis. Despite the frequency of hyperplastic lesions and microscopic adenomas, the incidence of renal cell carcinoma is not increased.

B

Fig. 46.7 Extrakidney Manifestations of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Computed tomography (A) and magnetic resonance imaging (B) scans demonstrate cysts in the arachnoid membrane (arrows) in ADPKD.

Fig. 46.8 Polycystic Kidneys. Greatly enlarged polycystic kidneys from a patient with autosomal dominant polycystic disease compared with a normal kidney (middle).

Cysts arise from all segments of the nephron and collecting ducts. As they grow, cysts dissociate from the parent tubule and eventually become isolated, fluid-filled sacs. There is no agreement on whether

A

B

Fig. 46.9 Kidney Cyst Histology in Autosomal Dominant Polycystic Kidney Disease (ADPKD). (A) Papillary hyperplasia of cyst epithelium. (B) Papillary microscopic adenoma in kidney of patient with ADPKD. (Magnification ×200.)

the cysts originate preferentially from particular tubular segments. Most studies indicate that cysts are predominantly of distal nephron and collecting duct origin. Studies in advanced kidney disease showing proximal tubular cysts may be confounded by the effects of obstruction and acquired kidney cystic disease.

Polycystic kidneys demonstrate advanced sclerosis of preglomerular vessels, interstitial fibrosis, and tubular epithelial hyperplasia, even in patients with normal GFR or early kidney failure. Sclerosis involves both afferent arterioles and interlobular arteries. Interstitial fibrosis is also prominent, even in early disease. It is associated with an interstitial infiltrate of macrophages and lymphocytes.

TREATMENT

Therapy is directed toward the kidney and extrarenal complications of ADPKD in an effort to limit morbidity and mortality. Advances in the understanding of the genetics of ADPKD and mechanisms of cyst development and growth have raised hopes for treatments specifically directed toward limiting the development and progression of the disease, and some of these treatments are now being evaluated in clinical trials, with one treatment now approved (see Novel Therapies).

Flank Pain

Causes of flank pain that may require intervention, such as infection, stone, and tumor, should be excluded. Care should be taken to avoid long-term administration of nephrotoxic agents, such as combination analgesics and nonsteroidal anti-inflammatory drugs. Narcotic analgesics should be reserved for the management of acute pain. Patients with chronic kidney pain are at risk for narcotic and analgesic dependence, and a psychological evaluation and a supportive attitude by the physician are essential. Reassurance, lifestyle modification, and avoidance of aggravating activities may be helpful. Tricyclic antidepressants are helpful as in other chronic pain syndromes, with a generally welltolerated side effect profile. Splanchnic nerve blockade with local anesthesia or corticosteroids results in pain relief prolonged beyond the duration of the local anesthetic.

When distortion of the kidneys by large cysts is deemed responsible for the pain and conservative measures fail, cyst decompression should be considered. Cyst aspiration, under ultrasound or CT guidance, is a relatively simple procedure. To prevent the reaccumulation of cyst fluid, sclerosing agents such as 95% ethanol, acidic solutions of minocycline, sodium tetradecyl sulfate, and, more recently, sodium tetradecyl sulfate mixed with room air (foam sclerotherapy),[38] may be used. Minor complications include microhematuria, localized pain, transient fever, and systemic absorption of the alcohol. More serious complications, such as pneumothorax, perirenal hematoma, arteriovenous fistula, urinoma, and infection, are rare. Complications from aspiration of centrally located cysts are more common, and the morbidity of the procedure is proportional to the number of cysts treated.

If multiple cysts are contributing to pain, laparoscopic or surgical cyst fenestration may be of benefit. Surgical decompression is effective in 80% to 90% of patients at 1 year, and 62% to 77% have sustained pain relief for over 2 years (Fig. 46.10A). Surgical intervention does not accelerate the decline in kidney function but does not appear to preserve declining GFR either (see Fig. 46.10B). Laparoscopic fenestration is as effective as open surgical fenestration in short-term follow-up in patients with limited disease, and there is a shorter, less complicated recovery period compared with open surgery. Previous abdominal surgery with possible adhesion formation is a relative contraindication.

Other interventions are available for the management of pain in ADPKD whose roles have not been fully defined. Laparoscopic kidney denervation has been used in combination with cyst fenestration and may be considered, particularly in polycystic kidneys without large cysts. Thoracoscopic sympatho-splanchnicectomy is effective in some patients but has significant morbidity. Catheter-based kidney denervation has been reported to be successful in a few patients, but a prospective protocolized evaluation of this approach is needed. Laparoscopic and retroperitoneoscopic nephrectomy and arterial embolization have been used to treat symptomatic polycystic kidneys in patients with ESKD.

Cyst Hemorrhage

Episodes of cyst hemorrhage are self-limited, and patients respond well to conservative management with bed rest, analgesics, and increased fluid intake to prevent obstructing clots. Rarely, bleeding is more severe, with extensive subcapsular or retroperitoneal hematoma causing significant decrease in hematocrit and hemodynamic instability. This requires hospitalization and transfusion. The antifibrinolytic agent tranexamic acid has been successfully used in some patients, but no controlled studies have been performed.[39] The dose should be reduced at lower levels of eGFR. Potential adverse effects of tranexamic acid therapy include glomerular thrombosis and ureteral obstruction from clots. In patients with unusually severe or persistent hemorrhage, segmental arterial embolization can be successful. If not, surgery may be required to control bleeding.

Urinary Tract and Cyst Infection

Because most kidney cyst infections begin as cystitis, prompt treatment of symptomatic cystitis and asymptomatic bacteriuria is indicated to prevent retrograde seeding of the kidney parenchyma. Antibiotics that require glomerular filtration, such as highly polar aminoglycosides, are

1.0

0.7
1/creatinine (dL/mg)

Probability of pain relief

Surgical Fenestration of Kidney Cysts

0.8
0.6
0.4
0.2
0

0.5
0.4
0.3
0.2
0.1

No surgery

0
0

A

0.6

3

6

9

12 15 18 21 24
Months

−24

B

−18

−12

−6
0
Months

6

12

Fig. 46.10 Surgical Cyst Fenestration for Symptomatic Autosomal Dominant Polycystic Kidney Disease. (A) Effects on relief of pain. (B) Rate of decline of kidney function. Orange lines indicate the course of kidney function in individual patients who underwent cyst fenestration at month 0. The green line represents

the mean rate of decline for all patients in the study.

not effective for upper UTI in severe kidney impairment. Cyst infection is often difficult to treat despite prolonged therapy with an antibiotic to which the organism is susceptible. Treatment failure occurs if antibiotics do not penetrate the cyst epithelium and achieve therapeutic concentrations within the cysts. Lipophilic agents have been shown to penetrate cysts reliably and have an acid dissociation constant (pKa) that allows for favorable electrochemical gradients into acidic cyst fluid. Therapeutic agents of choice include trimethoprimsulfamethoxazole and fluoroquinolones, both of which have favorable intracystic therapeutic concentration gradients at physiologic pH in gradient and nongradient cysts.

If fever persists after 1 to 2 weeks of appropriate antimicrobial therapy, infected cysts should be drained percutaneously or surgically. In the case of end-stage polycystic kidneys, nephrectomy should be considered. If fever recurs after stopping antibiotics, complicating features such as obstruction, perinephric abscess, and stone should be excluded. If no such complicating features are identified, the antibiotic course should be extended and may require several months to fully eradicate infection.

Nephrolithiasis

Treatment of nephrolithiasis in patients with ADPKD is the same as that in patients without ADPKD (see Chapter 60). Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid lithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects. Extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy are reported to be 82% and 80% successful, respectively, without increased complications compared with patients without ADPKD.[1] Flexible ureterorenoscopy with laser fragmentation also has been used safely and effectively and cannot cause traumatic nephron loss.[1]

Hypertension

Control of hypertension is essential because uncontrolled hypertension accelerates the decline in kidney function and aggravates extrarenal complications. Antihypertensive agents of choice and optimal BP targets in ADPKD have not been established. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) increase kidney blood flow in ADPKD, have a favorable side effect profile, and may have renoprotective properties that go beyond BP control. The HALT PKD study, a recent double-blind, placebo-controlled randomized clinical trial (RCT), examined the role of RAS blockade in both early and advanced ADPKD.[40] [41] Monotherapy with ACE inhibitors gave good BP control in the majority of patients. In early ADPKD (15–49 years of age, GFR >60 mL/min/1.73 m^2), rigorous BP control (target range 95–110/60–75 mm Hg) was associated with slower increase in TKV, faster eGFR decline during the first 4 months of treatment followed by a slower eGFR decline thereafter without an overall eGFR effect, a lesser increase in kidney vascular resistance, and a greater decline in LV mass index, after 8 years of follow-up.[42]

Patients with more severe ADPKD, determined by age-adjusted kidney volume, were more likely to benefit from rigorous BP control.[42]

Dual RAS blockade with lisinopril and telmisartan had no beneficial effect compared with lisinopril alone in these patients, nor in more advanced ADPKD (aged 18–64 years with GFR between 25 and 60 mL/min/1.73 m^2). The HALT PKD study therefore supports the use of an ACE inhibitor or ARB as the antihypertensive medication of choice in most patients with ADPKD and a rigorous BP target (95–110/60–75 mm Hg) in young patients with ADPKD with normal kidney function and without other significant comorbidities.

Progressive Kidney Failure

General strategies to delay progression of CKD are discussed in Chapter 82. Hypertension plays an important role in the progression of ADPKD to ESKD. In addition to the HALT PKD clinical trials, longterm follow-up of participants in the Modification of Diet in Kidney Disease (MDRD) study suggested that individuals with ADPKD randomized to a low BP target (mean arterial pressure [MAP] < 92 mm Hg) experienced significantly less ESKD and combined ESKD/death than those randomized to the usual BP target (MAP < 107 mm Hg).1 Preclinical studies, and evidence suggesting the increased vasopressin effect on the kidney and cAMP levels are involved in cyst progression, have led to the ingestion of supplemental water sufficient to achieve a urinary osmolality below 250 mOsm/kg H_2O (~3 L in most patients) being recommended for patients with ADPKD with eGFR >30 mL/min, although no RCTs support this approach.43 Exclusions would include severe protein or sodium restriction, reduced effective intravascular volume, taking diuretics or drugs enhancing the release of arginine vasopressin (AVP), or abnormal voiding. Serum sodium concentration should be monitored.

Patients with ADPKD have reduced morbidity and mortality on dialysis compared with patients with ESKD from other causes. Females appear to do better than males. The good outcome in ADPKD may result from higher endogenous erythropoietin production, better maintenance of hemoglobin, or lower comorbidity. Rarely, hemodialysis can be complicated by intradialytic hypotension if there is IVC

10 years
before

3 years
before

Immediately
before

Immediately
after

4 years
after

Liver resection and
cyst fenestration

Fig. 46.11 Hepatic Resection in Autosomal Dominant Polycystic Kidney Disease (ADPKD). Computed tomography scans of the abdomen from two patients with ADPKD obtained are 10 years before (column 1), 3 years before (column 2), immediately before (column 3), immediately after (column 4), and 4 years after (column 5) liver resection and cyst fenestration, demonstrating long-term, sustained reduction in liver size after the procedure.

compression by a medially located kidney cyst. Despite kidney size, peritoneal dialysis can usually be performed in ADPKD, although there is increased risk for inguinal and umbilical hernias, which require surgical repair.

Polycystic Liver Disease

Usually asymptomatic, PLD requires no treatment. When symptomatic, therapy is directed toward reducing cyst volume and hepatic size. Noninvasive measures include avoiding excessive use of ethanol, other hepatotoxins, and possibly cAMP agonists (e.g., excessive caffeine), which have been shown to stimulate cyst fluid secretion in vitro. Histamine-2 blockers and somatostatin may reduce secretion of secretin and secretory activity of cyst walls. Estrogens are likely to contribute to cyst growth, but the use of OCs and postmenopausal ERT are contraindicated only if the liver is significantly enlarged and the risk for further hepatic cyst growth outweighs the benefits of estrogen therapy. Rarely, symptomatic PLD may require invasive measures to reduce cyst volume and hepatic size. Options include percutaneous cyst aspiration and sclerosis, laparoscopic fenestration, and open surgical fenestration. Cyst aspiration is the procedure of choice if symptoms are caused by one or a few dominant cysts or by cysts that are easily accessible to percutaneous intervention. To prevent the reaccumulation of cyst fluid, sclerosis with minocycline, 95% ethanol, or foam sclerotherapy with sodium tetradecyl sulfate is often successful. Laparoscopic fenestration can be considered for large cysts that are more likely to recur after ethanol sclerosis, or if several cysts are present that would require multiple percutaneous passes to be treated adequately. Partial hepatectomy with cyst fenestration is an option because PLD often spares a part of the liver with adequate preservation of hepatic parenchyma and liver function[44] (Fig. 46.11). In the rare case in which no segments are spared, liver transplantation may be necessary. When no better options are available, long-acting somatostatin analogs can be effective in reducing, and in some cases, reversing the growth of polycystic livers (see under Novel Therapies).

When a hepatic cyst infection is suspected, any cyst with unusual appearance on an imaging study should be aspirated for diagnostic purposes. The best management is percutaneous cyst drainage in combination with antibiotic therapy. Long-term oral antibiotic suppression or prophylaxis should be reserved for relapsing or recurrent cases.

As for kidney cyst infection, antibiotics of choice are trimethoprimsulfamethoxazole and the fluoroquinolones.

Intracranial Aneurysm

Ruptured or symptomatic intracranial aneurysm requires surgical clipping of the neck of the aneurysm. Asymptomatic aneurysms measuring <5 mm, diagnosed by presymptomatic screening, can be observed with repeated magnetic resonance angiography at 6 months, then annually and less frequently after stability of the aneurysm has been established. If the size increases, surgery is indicated. Definitive management of aneurysms between 6 and 9 mm remains controversial.

Surgical intervention is usually indicated for all unruptured aneurysms that are at least 10 mm in diameter. For patients with high surgical risk or technically difficult lesions, endovascular treatment with detachable platinum coils may be indicated.[45]

NOVEL THERAPIES

A better understanding of the pathophysiology and the availability of animal models have facilitated the development of promising candidate drugs for clinical trials (see Fig. 46.2). Of the candidates, only tolvaptan has so far been approved by regulatory agencies for the treatment of rapidly progressive ADPKD[46] and has entered clinical practice.

Vasopressin Antagonists

The effect of vasopressin, through V2 receptors, on cAMP levels in the collecting duct, the major site of cyst development in ADPKD, and the role of cAMP in cystogenesis provided the rationale for successful preclinical trials of vasopressin V2 receptor antagonists.[2] High water intake by itself also exerted a protective effect on the development of PKD in a rat model of PKD (PCK rat), probably because of suppression of vasopressin. Genetic elimination of AVP in these rats yielded animals born with normal kidneys that remained relatively free of cysts unless an exogenous V2 receptor agonist was administered.47

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 trial, a phase III, double-blind, 3-year RCT of a split daily dose of tolvaptan in 1445 patients with rapidly progressive disease and relatively preserved GFR (18–50 years old, estimated creatinine clearance > 60 mL/min, TKV > 750 mL), showed a reduction in the rates of kidney growth (from 5.5% to 2.8% per year) and of eGFR decline (from 3.70 to 2.72 mL/min/1.73 m2 per year), and in the frequency of ADPKDrelated adverse events (kidney pain, hematuria, UTI).48 However, tolvaptan was associated with a higher frequency of aquaresis-related adverse events (polyuria, thirst, urinary frequency, nocturia) that led to drug discontinuation in 8.3% of tolvaptan-treated patients. In addition, clinically significant increases in liver enzymes (>2.5 times the upper limit of normal) were seen in 4.9% of tolvaptan-treated versus 1.2% of placebo-treated patients, and two patients had severe hepatocellular toxicity. Small increases in serum sodium and uric acid levels were also seen more frequently in the patients taking tolvaptan. The Replicating Evidence of Preserved Renal function: an Investigation of Tolvaptan Safety and Efficacy (REPRISE) trial, a phase III, randomized withdrawal, double-blind, 1-year trial, in 1370 18- to 55-year-old or 56- to 65-year-old patients with eGFR of 25 to 65 or 25 to 44 mL/min per 1.73 m2, respectively, showed a reduction in the rate of eGFR decline (from 3.61 to 2.34 mL/min/1.73 m2).49 Reversible elevations in the alanine aminotransferase of more than three times the upper limit of normal occurred in 5.6% in the tolvaptan group and 1.2% in the placebo group. No patients had severe hepatocellular toxicity, likely because of more frequent monitoring and earlier discontinuation of tolvaptan. An analysis of 97 patients continuously treated with tolvaptan at a single center for 4.6 (range, 1.1–11.2) years showed that the effect on the rate of eGFR decline was sustained and cumulative over time.50

Tolvaptan is approved for the treatment of rapidly progressive ADPKD in the United States, Japan, Canada, the European Union, Switzerland, Norway, South Korea, and Australia. Criteria of rapid progression vary widely among countries, using a combination of age, baseline GFR, GFR slope, baseline TKV, and TKV rate of growth. Height-adjusted TKV (HtTKV) adjusted by age (image classification) is a practical and validated method to identify risk of rapid progression (Class 1C–1E) at early stages of the disease when the GFR is still normal.51 Because of the potential hepatocellular toxicity, the Food and Drug Administration (FDA) in the United States requires a risk evaluation and mitigation strategy (REMS) program, including liver function testing before initiation and at specific intervals (after 2 and 4 weeks, then monthly for 18 months, and every 3 months thereafter) after initiation of treatment. A clinical trial of lixivaptan, a vasopressin V2 receptor antagonist predicted by a quantitative systems toxicology mathematical model to have a lower risk of hepatotoxicity compared with tolvaptan, is ongoing.

Somatostatin Analogs

Somatostatin acting on somatostatin receptors inhibits cAMP accumulation not only in the kidney but also in the liver. Somatostatin has a half-life of approximately 3 minutes, so more stable synthetic peptides (octreotide, lanreotide, pasireotide) have been developed for clinical use, which vary in stability and receptor affinity. In preclinical studies, these drugs reduced cAMP levels and proliferation of cholangiocytes in vitro, expansion of liver cysts in three-dimensional collagen culture, and development of kidney and liver cysts and fibrosis in animal models orthologous to ARPKD and ADPKD. Three initial small RCTs of octreotide or lanreotide52–54,55–57 showed similar results. Kidney growth was halted during the first year of treatment and then resumed, possibly at a lower rate than without treatment. Liver volume decreased by 4% to 6% during the first year of treatment, and this reduction was sustained during the second year. Similar results were obtained in a larger RCT of patients (A Long-Acting Somatostatin on Disease Progression in Nephropathy Due to Autosomal Dominant Polycystic Kidney Disease [ALADIN]), in which a trend toward stabilization of GFR was observed after the first year.58 The results of three additional RCTs have been recently reported. The Developing Interventions to Halt Progression of Autosomal Dominant Polycystic Kidney Disease-1 (DIPAK-1) trial, an open-label, 2.5-year RCT of lanreotide-LAR, 120 mg intramuscularly every 28 days, in 309 patients with eGFR 30 to 60 mL/min/1.73 m2, confirmed a significant reduction in liver and kidney cyst growth, but no attenuation of eGFR decline.59 ALADIN-2, a double-blind, placebo-controlled 3-year RCT of octreotide-LAR, 40 mg intramuscularly every 28 days, in 100 patients with eGFR between 15 and 40 mL/min/1.73 m2 showed a significant effect on kidney growth and no effect on the rate of eGFR decline but a significant reduction in the rate of progression to ESKD, particularly in the patients with most advanced disease.60 A doubleblind, 1-year RCT of pasireotide (60 mg subcutaneously every 28 days) in 48 patients aged older than 18 years, with eGFR greater than 30 mL/min/1.73 m2 and liver volume greater than 4000 mL, showed a reduction in liver volume and total kidney growth rates but no effect on eGFR.61

Octreotide and lanreotide are generally well tolerated. Selfresolving abdominal cramps and loose stools are common in the first few days after the injections. Other adverse effects include injection site granuloma and pain, cholelithiasis, steatorrhea, weight loss, and, rarely, hair loss. In DIPAK-1, an increased frequency of liver cyst infection in patients with a past history of a similar episode was observed. A high incidence of diabetes and hyperglycemia was observed in patients treated with pasireotide.

Mammalian Target of Rapamycin Inhibitors

The mammalian target of rapamycin (mTOR) is activated in animal models of PKD. Patients with the contiguous PKD1/TSC2 gene syndrome have more severe PKD than those with ADPKD alone. This observation suggests a convergence of signaling pathways downstream from PC1 and the TSC proteins tuberin and hamartin that control the activity of mTOR. Studies in rodent models of PKD showed that the mTOR inhibitors sirolimus and everolimus significantly prevent cyst expansion and protect kidney function. However, two large RCTs using everolimus and sirolimus for 18 to 24 months have shown no benefit.62,63

Other Investigational Therapies

Pravastatin, an HMG-CoA reductase inhibitor, slowed the rate of kidney growth in a small RCT in children and young adults with ADPKD.64 A phase II, multicenter, double-blind RCT of the Src inhibitor bosutinib reduced the rate of kidney growth, with a trend to worsen GFR (ClinicalTrials.gov NCT01233869). Clinical trials of the glycosylceramide synthase inhibitor venglustat, Nrf2 activator bardoxolone, vasopressin V2 receptor antagonist lixivaptan, multikinase inhibitor KD019, metformin, pioglitazone, nicotinamide, and triptolide are ongoing (see Fig. 46.2).

TRANSPLANTATION

Transplantation is the treatment of choice for ESKD in patients with ADPKD. There is no difference in patient or graft survival between patients with ADPKD and other ESKD populations. Living donor transplants also have graft survival no different from that of nonADPKD populations. However, living related transplantation has only recently been widely practiced in the ADPKD population. In 1999, 30% of kidney transplants for patients with ADPKD were from living donors in the United States, compared with 12% in 1990.

Complications after transplantation are no greater in the ADPKD population than in the general population, and specific complications directly related to ADPKD are rare. Cyst infection is not increased after transplantation, and there is no significant increase in the incidence of symptomatic mitral valve prolapse or hepatic cyst infection. One study showed an increased rate of diverticulosis and bowel perforation in ADPKD. Whether ADPKD increases the risk for development of newonset diabetes mellitus after transplantation is controversial.

Although practiced routinely in the past, pretransplantation nephrectomy has fallen out of favor. By 1 and 3 years after kidney transplantation, kidney volumes decrease by 37.7% and 40.6%, whereas liver volumes increase by 8.6% and 21.4%, respectively.65 Indications for nephrectomy include a history of infected cysts, frequent bleeding, severe hypertension, and massive kidney enlargement with extension into the pelvis. There is no evidence of an increased risk for development of kidney cell carcinoma in native ADPKD kidneys after transplantation. When nephrectomy is indicated, hand-assisted laparoscopic nephrectomy is associated with less intraoperative blood loss, less postoperative pain, and faster recovery compared with open nephrectomy and is increasingly being used.

SELF-ASSESSMENT QUESTIONS

1. Age of ESKD onset in the patient with ADPKD depends on:
A. mutated gene (PKD1 vs. PKD2).
B. type of mutation.
C. modifier genes.
D. environmental factors.
E. all of the above.

2. Which one of the following statements about ADPKD and intracranial aneurysm is true?
A. All ADPKD patients should be evaluated for intracranial aneurysms.
B. Most intracranial aneurysms rupture.
C. The risk for rupture of an intracranial aneurysm depends on its size and location.
D. Magnetic resonance angiography to screen for intracranial aneurysms is contraindicated in advanced CKD because it requires the administration of gadolinium.
E. None of the above.

3. Which one of the following is the most common risk factor for nephrolithiasis in ADPKD?
A. Low urine citrate
B. Hypercalciuria
C. Hyperuricosuria
D. Hyperoxaluria
E. Renal tubular acidosis

4. Which of the following statements about ADPKD and hypertension is true?
A. ACE inhibitors have been shown to be superior to β-blockers to treat hypertension and protect kidney function in patients with ADPKD.

B. Rigorous BP control has been shown to be superior to standard BP control in prospective studies to protect kidney function in patients with ADPKD and CKD stage 3.
C. Both A and B are true.
D. Both A and B are false.

REFERENCES

1. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015;88:17–27.
2. Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. J Clin Invest. 2014;124:2315–2324.
3. Porath B, Gainullin VG, Cornec-Le Gall E, et al. Mutations in GANAB, encoding the glucosidase iialpha subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet. 2016;98:1193–1207.
4. Cornec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. Am J Hum Genet. 2018;102:832–844.
5. Besse W, Chang AR, Luo JZ, et al. ALG9 mutation carriers develop kidney and liver cysts. J Am Soc Nephrol. 2019;30:2091–2102.
6. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. J Clin Invest. 2017;127:1772–1785.
7. Hopp K, Ward CJ, Hommerding CJ, et al. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. J Clin Invest. 2012;122:4257–4273.
8. Su Q, Hu F, Ge X, et al. Structure of the human PKD1-PKD2 complex. Science. 2018:361.
9. Piontek K, Menezes LF, Garcia-Gonzalez MA, et al. A critical developmental switch defines the kinetics of kidney cyst formation after loss of Pkd1. Nat Med. 2007;13:1490–1495.
10. Ma M, Tian X, Igarashi P, et al. Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease. Nat Genet. 2013;45:1004–1012.
11. Nauli SM, Alenghat FJ, Luo Y, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet. 2003;33:129–137.
12. Koulen P, Cai YQ, Geng L, et al. Polycystin-2 is an intracellular calcium release channel. Nature Cell Biology. 2002;4:191–197.
13. Gainullin VG, Hopp K, Ward CJ, et al. Polycystin-1 maturation requires polycystin-2 in a dose-dependent manner. J Clin Invest. 2015;125:607–620.
14. Wallace DP. Cyclic AMP-mediated cyst expansion. Biochim Biophys Acta. 2011;1812:1291–1300.
15. Yamaguchi T, Pelling JC, Ramaswamy NT, et al. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. Kidney Int. 2000;57:1460–1471.
16. Hanaoka K, Guggino WB. cAMP regulates cell proliferation and cyst formation in autosomal polycystic kidney disease cells. J Am Soc Nephrol. 2000;11:1179–1187.
17. Yamaguchi T, Wallace DP, Magenheimer BS, et al. Calcium restriction allows cAMP activation of the B-Raf/ERK pathway, switching cells to a cAMP-dependent growth-stimulated phenotype. J Biol Chem. 2004;279:40419–40430.
18. Heyer CM, Sundsbak JL, Abebe KZ, et al. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2016;27:2872–2884.
19. Hwang YH, Conklin J, Chan W, et al. Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2015;27:1861–1868.
20. Lavu S, Vaughan LE, Senum SR, et al. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. JCI Insight. 2020;5:e138724.
21. Cornec-Le Gall E, Audrezet MP, Chen JM, et al. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol. 2013;24:1006–1013.
22. Chebib FT, Jung Y, Heyer CM, et al. Effect of genotype on the severity

and volume progression of polycystic liver disease in autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2016;31:952–960.

23. Cornec-Le Gall E, Audrezet MP, Rousseau A, et al. The PROPKD Score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2016;27:942–951.
24. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20:205–212.
25. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2015;26:746–753.
26. Eisenberger T, Decker C, Hiersche M, et al. An efficient and comprehensive strategy for genetic diagnostics of polycystic kidney disease. PLoS One. 2015;10:e0116680.
27. Hopp K, Cornec-Le Gall E, Senum SR, et al. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. Kidney Int. 2020;97:370–382.
28. Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. N Engl J Med. 2006;354:2122–2130.
29. Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012;7:479–486.
30. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol. 2015;26:160–172.
31. Cadnapaphornchai MA, McFann K, Strain JD, et al. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. Kidney Int. 2008;74:1192–1196.
32. Torres VE, Abebe KZ, Schrier RW, et al. Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. Kidney Int. 2017;91:493–500.
33. Torres VE, King BF, Chapman AB, et al. Magnetic resonance measurements of renal blood flow and disease progression in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2007;2:112–120.
34. Shukoor SS, Vaughan LE, Edwards ME, et al. Characteristics of patients with end-stage kidney disease in ADPKD. Kidney Int Rep. 2021;6:755–767.
35. Drenth JP, Chrispijn M, Nagorney DM, et al. Medical and surgical treatment options for polycystic liver disease. Hepatology. 2010;52:2223–2230.
36. Sanchis IM, Shukoor S, Irazabal MV, et al. Presymptomatic Screening for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2019;14:1151–1160.
37. Chebib FT, Hogan MC, El-Zoghby ZM, et al. Autosomal dominant polycystic kidney patients may be predisposed to various cardiomyopathies. Kidney Int Rep. 2017;2:913–923.
38. Iliuta IA, Shi B, Pourafkari M, et al. Foam sclerotherapy for cyst volume reduction in autosomal dominant polycystic kidney disease: a prospective cohort study. Kidney Med. 2019;1:366–375.
39. Peces R, Aguilar A, Vega C, et al. Medical therapy with tranexamic acid in autosomal dominant polycystic kidney disease patients with severe haematuria. Nefrologia. 2012;32:160–165.
40. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. N Engl J Med. 2014;371:2255–2266.
41. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. N Engl J Med. 2014;371:2267–2276.
42. Irazabal MV, Abebe KZ, Bae KT, et al. Prognostic enrichment design in clinical trials for autosomal dominant polycystic kidney disease: the HALT-PKD clinical trial. Nephrol Dial Transplant. 2017;32:1857–1865.
43. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. Clin J Am Soc Nephrol. 2009;4:1140–1150.
44. Chebib FT, Harmon A, Irazabal Mira MV, et al. Outcomes and durability of hepatic reduction after combined partial hepatectomy and

cyst fenestration for massive polycystic liver disease. J Am Coll Surg. 2016;223:118–126.e111.
45. Irazabal MV, Huston 3rd J, Kubly V, et al. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6:1274–1285.

References

46. Chebib FT, Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for diseasemodifying therapy. Am J Kidney Dis. 2021.
47. Wang X, Wu Y, Ward CJ, et al. Vasopressin directly regulates cyst growth in polycystic kidney disease. J Am Soc Nephrol. 2008;19:102–108.
48. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367:2407–2418.
49. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in laterstage autosomal dominant polycystic kidney disease. N Engl J Med. 2017;377:1930–1942.
50. Edwards ME, Chebib FT, Irazabal MV, et al. Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2018;13:1153–1161.
51. Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrol Dial Transplant. 2016;31:337–348.
52. Caroli A, Antiga L, Cafaro M, et al. Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. Clin J Am Soc Nephrol. 2010;5:783–789.
53. van Keimpema L, Nevens F, Vanslembrouck R, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2009;137:1661–1668. e1661-1662.
54. Hogan MC, Masyuk T, Page LJ, et al. Randomized clinical trial of longacting Somatostatin therapy for autosomal dominant polycystic kidney and liver disease. J Am Soc Nephrol. 2010;21:1052–1061.
55. Chrispijn M, Nevens F, Gevers TJ, et al. The long-term outcome of patients with polycystic liver disease treated with lanreotide. Aliment Pharmacol Ther. 2012;35:266–274.

56. Hogan MC, Masyuk TV, Page L, et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. Nephrol Dial Transplant. 2012;27:3532–3539.
57. Pisani A, Sabbatini M, Imbriaco M, et al. Long-term effects of octreotide on liver volume in patients with polycystic kidney and liver disease. Clin Gastroenterol Hepatol. 2016;14:1022–1030.e1024.
58. Caroli A, Perico N, Perna A, et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet. 2013;382:1485–1495.
59. Meijer E, Visser FW, van Aerts RMM, et al. Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: the DIPAK 1 randomized clinical trial. JAMA. 2018;320:2010–2019.
60. Perico N, Ruggenenti P, Perna A, et al. Octreotide-LAR in laterstage autosomal dominant polycystic kidney disease (ALADIN 2): a randomized, double-blind, placebo-controlled, multicenter trial. PLoS Med. 2019;16:e1002777.
61. Hogan MC, Chamberlin JA, Vaughan LE, et al. Pansomatostatin agonist pasireotide long-acting release for patients with autosomal dominant polycystic kidney or liver disease with severe liver involvement: a randomized clinical trial. Clin J Am Soc Nephrol. 2020;15:1267–1278.
62. Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363:820–829.
63. Walz G, Budde K, Mannaa M, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363:830–840.
64. Cadnapaphornchai MA, George DM, McFann K, et al. Effect of

pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2014;9:889–896.
65. Yamamoto T, Watarai Y, Kobayashi T, et al. Kidney volume changes in patients with autosomal dominant polycystic kidney disease after renal transplantation. Transplantation. 2012;93:794–798.

47

Other Cystic Kidney Diseases

Lisa M. Guay-Woodford

Numerous disorders share kidney cysts as a common feature (Box 47.1).1 These disorders may be inherited or acquired; their manifestations may be confined to the kidney or expressed systemically. They may present at a wide range of ages, from the perinatal period to old age (Fig. 47.1). The kidney cysts may be single or multiple, and the associated kidney morbidity may range from clinical insignificance to progressive parenchymal destruction with resultant kidney insufficiency.

The clinical context often helps distinguish these kidney cystic disorders from one another. Echogenic, enlarged kidneys in a neonate or infant should raise suspicion about autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD, see Chapter 46), tuberous sclerosis complex (TSC), or one of the many congenital syndromes associated with kidney cystic disease. Reduced kidney function in an adolescent suggests ARPKD or nephronophthisis (NPHP) as possible etiologies. The finding of a solitary cyst in a 5-year-old may indicate a calyceal diverticulum, whereas this finding in a 50-year-old is most compatible with a simple kidney cyst. Kidney stones occur in ADPKD and medullary sponge kidneys (MSKs). For those disorders with systemic manifestations, such as ADPKD, TSC, and von Hippel-Lindau (VHL) disease, the associated extrarenal features may provide other important differential diagnostic clues.

For an increasing number of the single-gene disorders, genetic testing is available in expert laboratories around the world. Genetic testing resources are listed at the National Institutes of Health (NIH) Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Definition

ARPKD is a severe, typically early-onset form of cystic disease that primarily involves the kidneys and biliary tract. Affected patients have a spectrum of clinical phenotypes that correlate in part with the age at presentation.

Etiology and Pathogenesis

Genetic Basis

All typical forms of ARPKD are caused by mutations in a single gene, PKHD1, that encodes multiple alternatively spliced isoforms predicted to form both membrane-bound and secreted proteins. The largest protein product of PKHD1, the fibrocystin/polyductin complex (FPC), contains one membrane-spanning domain and an intracellular C-terminal tail. FPC localizes, at least in part, to the primary cilium and the centrosome in kidney epithelial cells. The basic defects observed in ARPKD suggest that FPC mediates the terminal differentiation of the collecting duct and biliary tract. However, the exact function of the numerous isoforms has not been defined, and the widely varying clinical spectrum of ARPKD may depend in part on the nature and number of splice variants that are disrupted by specific PKHD1 mutations.2

Although ARPKD is generally considered to be a genetically homogeneous disease, recent reports describe a few patients with atypical forms of ARPKD that result from mutations in either the DZIP1L gene or CYS1, the human orthologue of the gene disrupted in the cpk mouse, the most widely studied experimental model of ARPKD.3 4 These children presented with hypertension and large, cystic kidneys; some progressed to end-stage kidney disease (ESKD). Distinguishing features of the disease phenotype in these children include more moderate kidney disease and the absence of clinically apparent liver disease.

Pathogenesis

ARPKD typically begins in utero, and the kidney cystic lesion appears to be superimposed on a normal developmental sequence. The tubular abnormality involves nonobstructive, fusiform, and/or saccular dilation of the kidney collecting ducts. In the liver, defective remodeling of the ductal plate in utero results in persistence of primitive bile duct configurations and the evolution of progressive portal tract fibrosis.5 The remainder of the liver parenchyma develops normally. The defect in ductal plate remodeling is accompanied by abnormalities in the branching of the portal vein. The resulting histopathologic pattern is referred to as congenital hepatic fibrosis.
ARPKD is one of several kidney cystic diseases that are associated with congenital hepatic fibrosis, prompting these disorders to be described as hepatorenal fibrocystic diseases.6 The primary cilium appears to play a central role in the pathogenesis of ARPKD and other hepatorenal fibrocystic diseases, so the broader term “ciliopathies” is used for these disorders, in which dysfunction of the cilia-centrosome complex appears to underpin the development of a wide array of phenotypes, including kidney cystic disease.5

Epidemiology

The estimated incidence of ARPKD is 1 per 20,000 live births. It occurs more frequently in Whites than in other ethnic populations. A recent U.S.-based study using electronic health record (EHR) data calculated an annualized incidence of 1 in 26,485 live births.7

Clinical Manifestations

The clinical spectrum of ARPKD is variable. Most cases are identified either in utero or at birth. The most severely affected fetuses have enlarged echogenic kidneys and oligohydramnios because of poor fetal urine output. These fetuses develop the Potter phenotype, with pulmonary hypoplasia, a characteristic facies, and deformities of the spine and limbs. Pulmonary hypoplasia continues to pose a severe clinical challenge and often dictates postnatal survival.8 A recent EHRbased analysis estimated perinatal mortality to be about 21%.7 Kidney function, although frequently compromised, is rarely a cause of neonatal death. For those who survive the first month of life, the reported mean 5-year patient survival rate is 85% to 90%. Morbidity and mortality result from severe systemic hypertension, reduced kidney function, and portal hypertension because of portal tract hyperplasia and fibrosis.9 Hypertension usually develops in the first few months and ultimately affects 70% to 80% of patients. ARPKD patients have defects in both urinary-diluting capacity and concentrating capacity. Newborns can have hyponatremia, presumably resulting from defects in free water excretion. Although net acid excretion may be reduced, metabolic acidosis is not a significant clinical feature. Retrospective studies have noted an increased incidence of pyuria on urinalysis and cultureconfirmed urinary tract infections (UTI).2

BOX 47.1

Kidney Cystic Disorders

Disorders
Nongenetic
Developmental
Medullary sponge kidney (MSK)a
Kidney cystic dysplasia
- Multicystic dysplasia
- Cystic dysplasia associated with lower urinary tract obstruction
- Diffuse cystic dysplasia: syndromal and nonsyndromal

Acquired
Simple cysts
Solitary multilocular cysts
Hypokalemic cystic disease
Acquired cystic disease (in advanced kidney failure)
Geneticb

Autosomal Dominant
Autosomal dominant polycystic kidney disease
Autosomal dominant tubulointerstitial kidney disease
Tuberous sclerosis complex
von Hippel-Lindau syndrome
Autosomal Recessive
Autosomal recessive polycystic kidney disease
Nephronophthisis and nephronophthisis-like disorders (Meckel-Gruber syndrome, Joubert syndrome, Bardet-Biedl syndrome)
X-Linked
Oro-facio-digital syndrome type I

In the first 6 months of life, ARPKD infants may have a transient improvement in glomerular filtration rate (GFR) because of kidney maturation. Subsequently, a progressive but variable decline in GFR occurs, with patients presenting in the first month of life progressing more rapidly to ESKD than those presenting at more than 1 month of age.10 11 With advances in effective therapy for ESKD, prolonged survival is common and for many patients, the hepatic complications become the predominant clinical issue.

On average, those infants with serum creatinine values greater than 2.2 mg/dL (200 µmol/L) progress to ESKD within 5 years, but this is highly variable. In longitudinal studies, the probability of freedom from ESKD is approximately 85% at 1 year, approximately 70% at 10 years, approximately 65% at 15 years, and approximately 40% at 20 years.12

In children who present later in childhood or in adolescence, portal hypertension is frequently the predominant clinical abnormality, with hepatosplenomegaly and bleeding esophageal or gastric varices, as well as hypersplenism with consequent thrombocytopenia, anemia, and leukopenia. Hepatocellular function is usually preserved. Ascending suppurative cholangitis is a serious complication and can cause fulminant hepatic failure.13 14

Other associated features include growth retardation, although the mechanism is not yet defined, and, very rarely, vascular aneurysms (intracranial and extracranial).15 16

Pathology

aMSK

is generally considered to be a sporadic disorder, but recent studies provide evidence for familial clustering, involving autosomal dominant inheritance with reduced disease penetrance and variability in disease expression.

bMendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM)

Kidney

The kidney involvement is invariably bilateral and largely symmetric. The histopathology varies depending on the age of presentation and the extent of cystic involvement (Fig. 47.2AB).

In the affected neonate, the kidneys can be 10 times normal size but retain the typical kidney contour. Dilated, fusiform collecting ducts

Age Distribution of Cystic Kidney Diseases

Neonates

Infants/children

Adolescents

Autosomal dominant polycystic kidney disease (ADPKD)

Autosomal recessive polycystic kidney disease (ARPKD)

Nephronophthisis (NPHP)

Medullary sponge kidney (MSK)

Tuberous sclerosis complex (TSC)

von Hippel–Lindau disease (VHL)

Simple cysts

Fig. 47.1 Age distribution of patients with kidney cystic disorders.

Adults

A

B

C

Fig. 47.2 Pathologic Features of Autosomal Recessive Polycystic Kidney Disease. (A) Cut section of autosomal recessive polycystic kidney disease (ARPKD) kidney from a 1-year-old child shows discrete medullary cysts and dilated collecting ducts. (B) Light microscopy shows later-onset ARPKD kidney with prominent medullary ductal ectasia (H&E stain; magnification ×10). (C) Light microscopy of congenital hepatic fibrosis shows extensive fibrosis of the portal area with ectatic, tortuous bile ducts and hypoplasia of the portal vein (H&E stain; ×40).

extend radially through the cortex. On histopathologic sections, the dilated medullary collecting ducts are often cut tangentially or transversely, resulting in a more spheroid appearance. Up to 90% of the collecting ducts are involved. Associated interstitial fibrosis is minimal in neonates and infants but increases with progressive disease.

In patients diagnosed later in childhood, the kidney size and extent of cystic involvement tend to be more limited. Cysts can expand to as large as 2 cm in diameter and may become more spherical. Progressive interstitial fibrosis is probably responsible for secondary tubular obstruction.

In older children, medullary ductal ectasia is the predominant finding. Cysts are lined with a single layer of nondescript cuboidal epithelium. The glomeruli and nephron segments proximal to the collecting ducts are initially structurally normal but are often crowded between ectatic collecting ducts or displaced into subcapsular wedges. The presence of cartilage or other dysplastic elements indicates a diagnosis other than ARPKD, such as cystic dysplasia.

Liver

The liver lesion in ARPKD is characterized by ductal plate malformation. The liver can be either normal in size or somewhat enlarged. Bile ducts are dilated (biliary ectasia) and marked cystic dilation of the entire intrahepatic biliary system (Caroli syndrome) is well described.13 In neonatal ARPKD, the bile ducts are increased in number, tortuous in configuration, and often located around the periphery of the portal tract. In older children, the biliary ectasia is accompanied by increasing portal tract fibrosis and hypoplasia of the small portal vein branches (see Fig. 47.2C). The hepatic parenchyma may be intersected by delicate fibrous septa that link the portal tracts, but the hepatocytes themselves are seldom affected.

Diagnosis

Imaging

A number of other hepatorenal fibrocystic diseases can resemble or “phenocopy” ARPKD (Table 47.1).6 Although most of these disorders are characterized by large, echogenic kidneys in the fetus and neonate, these can usually be distinguished by ultrasound. ARPKD kidneys in utero are hyperechogenic and display decreased corticomedullary differentiation because of the hyperechogenic medulla (Fig. 47.3A). With high-resolution ultrasound, the radial array of dilated collecting ducts may be imaged. In comparison, ADPKD kidneys in utero tend to be moderately enlarged with a hyperechogenic cortex and relatively hypoechogenic medulla causing increased corticomedullary differentiation

Kidney size typically peaks at 1 to 2 years of age, then gradually declines relative to the child’s body size and stabilizes by 4 to 5 years. With age, there is increased medullary echogenicity with scattered small cysts, measuring less than 2 cm in diameter. These cysts and progressive fibrosis can alter the usual kidney contour, causing ARPKD in some older children to be mistaken for ADPKD. Magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) scanning can be useful in delineating the kidney architecture (see Fig. 47.3B). Bilateral pelvicaliectasis and kidney calcifications have been reported in 25% and 50% of ARPKD patients, respectively. In adults with medullary ectasia alone, the cystic lesion may be confused with MSK.

The liver may be either normal in size or enlarged. It is usually less echogenic than the kidneys. Prominent intrahepatic bile duct dilation suggests associated Caroli syndrome. With age, the portal fibrosis tends to progress and in older children, ultrasound typically shows hepatosplenomegaly and a patchy increase in hepatic echogenicity.13 14

Genetic Testing

With the identification of PKHD1 as the principal disease gene, genetic testing is available as a clinical diagnostic tool. The mutation detection rate is 80% to 87%. Current diagnostic approaches include genespecific analysis and multigene testing panels using next-generation sequencing technologies.17 Genetic testing is primarily applied in the context of prenatal testing and preimplantation genetic diagnosis. Patients with two truncating mutations typically have a severe phenotype leading to perinatal or neonatal mortality, whereas missense mutations are typically associated with neonatal survival.17 18

The European ARegPKD Consortium recently reported that the position of PKHD1 variants is important in determining the phenotype.

Patients with two missense variants affecting FPC amino acids 709 to 1837 or a missense variant in this region combined with a null variant less frequently develop ESKD. Patients with missense variants affecting FPC amino acids 1838 to 2624 have less severe liver disease, whereas variants affecting amino acids 2625 to 4074 are associated with poorer hepatic outcome.19 These findings may facilitate genetic counseling, but caution is warranted because about 20% of ARPKD siblings have discordant clinical phenotypes, perhaps because of the modulating effect of genetic and environmental factors.17

Treatment

The survival of neonates with ARPKD has improved significantly in the last two decades because of advances in mechanical ventilation and

Features of Kidney Cystic Disease in Children

TABLE 47.1

Clinical Characteristics
ARPKD
Clinical onset
(years)
Enlarged kidneys

Perinatal

Kidney pathology

Multiple cysts

Cyst infection
BP

Uncommon
Normal/
increased
Normal/impaired

Kidney function
(glomerular
filtration rate)
Nephrocalcinosis/
nephrolithiasis
Congenital
hepatic fibrosis
Pancreas lesions
CNS involvement

Yes

NPHP
NPHP2/3/13: 0–5 y
NPHP: 10–18 y
NPHP2: yes
NPHP3/13: some cases
NPHP: no
NPHP2/3/13: multiple
cysts
NPHP: few cysts at
C-M junction
No
NPHP2/13: increased
NPHP: normal
Normal/impaired

Meckel-Grubera

GCKDb

ADPKD

TSC

Infancy and older

children
Variable

Infancyc

and older
children
Occurs

Infancyc and older
children
Occurs

Multiple cysts

Multiple cortical
cysts

Multiple cysts

Few to multiple cysts
angiomyolipoma

Uncommon
Normal

No
Normal/increased

Occurs
Normal/increased

Uncommon
Normal/increased

Normal/ impaired

Normal

Normal

Normal

No

TSC1
TSC2
Yes

Perinatal infancy
Yes

Nephrocalcinosis
up to 25%
Yes

No

No

No

Rare

Yes

No

No
No

No
(Joubert)d

No
Encephalocele;
cognitive disability

MODY5
No

Nephrolithiases
occur
10%–15% infantile
ADPKD
No
No

Genetics
Disease gene

PKHD1

NPHP1-NPHP20

MKS1-MKS12

Genetic testinge

Yes

Most

Most

PKD1
HNF1B
Yes

PKD1
PKD2
Yes

No
No
Seizures, cognitive
disability

aMeckel-Gruber

syndrome is a severe, often lethal, autosomal recessive disorder characterized by bilateral kidney cystic dysplasia, biliary ductal dysgenesis, bilateral postaxial polydactyly, and variable CNS malformations. The triad of kidney cystic disease, occipital encephalocele, and polydactyly is most common. Genes disrupted in Meckel-Gruber syndrome have also been identified in NPHP and Joubert patients, suggesting a phenotypic spectrum.
bGCKD can occur as the infantile manifestation of ADPKD. Familial hypoplastic GCKD, because of mutations in HNF1B, the gene encoding hepatocyte nuclear factor

(HNF1β), can be associated with MODY5.

[c] A contiguous germline deletion of both the PKD1 and TSC2 genes (the PKDTS contiguous gene syndrome) occurs in a small group of patients with features of TSC, as well as massive kidney cystic disease reminiscent of ADPKD, severe hypertension, and a progressive decline in kidney function with the onset of ESKD in the second or third decade of life.

[d] Joubert syndrome is a genetically heterogeneous, autosomal recessive disorder characterized by developmental defects in the cerebellum (cerebellar vermis aplasia) and the eye (coloboma), as well as retinitis pigmentosa, congenital hypotonia, and either ocular motor apraxia or irregularities in breathing patterns during the neonatal period. The disease can be associated with NPHP, and mutations in several NPHP genes have been described in Joubert patients.

[e] Genetic testing listed on the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

ADPKD, Autosomal dominant polycystic kidney disease; BP, blood pressure; C-M, corticomedullary; CNS, central nervous system; GCKD, glomerulocystic kidney disease; MODY5, maturity-onset diabetes of the young, type 5; NIH, National Institutes of Health; NPHP, nephronophthisis; PKDTS, polycystic kidney disease with tuberous sclerosis; TSC, tuberous sclerosis complex.

other supportive measures. Aggressive interventions such as unilateral or bilateral nephrectomies and continuous hemofiltration have been advocated in neonatal management, but prospective, controlled studies have yet to be performed.[9]

For children who survive the perinatal period, blood pressure (BP) control is a major clinical issue. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), adrenergic antagonists, and loop diuretics are effective antihypertensive agents. The management of ARPKD children with declining GFR should follow the standard guidelines established for chronic kidney disease (CKD) in children.[9]

Given the relative urinary concentrating defect, children with ARPKD should be monitored for dehydration during intercurrent illnesses associated with fever, tachypnea, nausea, vomiting, or diarrhea.

In those infants with severe polyuria, thiazide diuretics may be used to decrease distal nephron solute and water delivery. Acid-base balance should be closely monitored and supplemental bicarbonate therapy initiated as needed.

Close monitoring for portal hypertension is warranted in all patients with ARPKD. There is no correlation between the severity of the kidney and liver disease.[14] Recent studies suggest that the platelet count combined with serial abdominal ultrasound (assessing liver and splenic size) and Doppler flow studies provide good surrogate markers for the portal hypertension severity.[14] Medical management may include sclerotherapy or variceal banding.[13] Surgical approaches such as portocaval or splenorenal shunting may be indicated in some patients. Although hypersplenism is fairly common, splenectomy is seldom warranted. Unexplained fever with or without elevated

NEPHRONOPHTHISIS: AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE

Definitions

A

NPHP and autosomal dominant tubulointerstitial kidney disease (ADTKD; formerly known as medullary cystic kidney disease [MCKD]) share a triad of histopathologic features: tubular basement membrane irregularities, tubular atrophy with cyst formation, and interstitial cell infiltration with fibrosis. These histopathologically similar disorders differ in their mode of transmission, age of onset, and genetic defects. NPHP is an autosomal recessive disorder that manifests in childhood, whereas ADTKD occurs in adults. NPHP is more common than ADTKD and has been reported as an isolated kidney disease and also in association with systemic manifestations, including retinitis pigmentosa, congenital hepatic fibrosis, oculomotor apraxia, and skeletal anomalies.

Nephronophthisis

NPHP is an autosomal recessive tubulointerstitial nephropathy and one of the most frequent inherited causes of ESKD in children and adolescents.[23] The term nephronophthisis derives from the Greek, meaning “progressive loss of nephrons.”

Genetic Basis

B

Fig. 47.3 Radiologic Findings Associated With Autosomal Recessive Polycystic Kidney Disease. (A) Autosomal recessive polycystic kidney disease (ARPKD) in a neonate. High-resolution ultrasound reveals radially arrayed dilated collecting ducts. (B) ARPKD in a symptomatic 4-year-old girl. Contrast-enhanced computed tomography shows striated nephrogram and prolonged corticomedullary differentiation.

transaminase levels suggests bacterial cholangitis and requires meticulous evaluation to make the diagnosis and guide aggressive antibiotic therapy.

Effective management of systemic and portal hypertension, coupled with successful kidney replacement therapy (KRT), has allowed long-term patient survival. Therefore, the prognosis in ARPKD, particularly for those children who survive the first month of life, is far less bleak than popularly thought and aggressive medical therapy is warranted.

Although current treatment of ARPKD is entirely supportive, preclinical studies suggest future benefit from new, targeted therapies.[2]

Transplantation

A prolonged period of dialysis in childhood has been associated with both cognitive and educational impairment.[20] Therefore, kidney transplantation is the treatment of choice for ESKD in ARPKD patients.

ARPKD is a recessive disorder, and therefore either parent may be a suitable kidney donor. However, the identification of subtle kidney and liver abnormalities on ultrasound in ARPKD parents[21] mandates more extensive posttransplant follow-up. Native nephrectomies may be warranted in patients with massively enlarged kidneys to allow allograft placement.

In some patients, combined kidney-liver transplantation may be appropriate.[22] Indications include the combination of kidney failure and either recurrent cholangitis or significant complications of portal hypertension (e.g., recurrent variceal bleeding, refractory ascites, and the hepatopulmonary syndrome). In addition, liver transplantation may be a consideration for patients with a single episode of cholangitis in the context of Caroli syndrome.13

Multiple disease-causing genes have been identified. Defects in NPHP1 account for 20% of NPHP with large, homozygous deletions detected in 80% of affected family members and in 65% of sporadic cases. Mutations in each of the remaining NPHP genes cause 1% to 4% of NPHP-related disease, meaning that almost two-thirds of cases remain genetically unsolved.24–26

Clinical disease expression appears to be exacerbated by oligogenic inheritance, in which patients carry two mutations in a single NPHP gene as well as a single-copy mutation in an additional NPHP gene.

In addition, multiple allelism, or distinct mutations in a single gene, appears to explain the continuum of multiorgan phenotypic abnormalities observed in NPHP-related disorders, which include MeckelGruber syndrome, Joubert syndrome, and Bardet-Biedl syndrome.25 27

Most of the protein products of the NPHP-associated genes are expressed in the cilia-centrosome complex5; NPHP is considered a ciliopathy.25

Clinical Manifestations

Kidney disease. Three distinct forms of NPHP (infantile, juvenile, and adolescent) were initially described, based on the age of onset of ESKD. In the infantile form, ESKD occurs before 5 years of age, whereas in juvenile NPHP (the most common form), ESKD occurs at a mean age of 13 years. However, recent studies have demonstrated that there is no clear genotype-phenotype correlation for this spectrum of presentations, and these disorders should be referred to with the single designation of NPHP.

Decreased urinary concentrating capacity is invariable in NPHP and usually precedes the decline in GFR, with typical onset between 4 and 6 years of age. Polyuria, polydipsia, and secondary enuresis are common. Salt wasting develops in most patients with kidney impairment, and sodium supplementation is often required until the onset of ESKD. One-third of patients become anemic before GFR is overtly reduced, perhaps because of impaired regulation of erythropoietin production by peritubular fibroblasts. Growth retardation (out of proportion to the degree of GFR reduction) is common.

Slowly progressive decline in GFR is typical of NPHP, with progression to ESKD at a median age of 13 years. Although symptoms can begin after the age of 2 years, they may progress insidiously, so that

15% of affected patients present with ESKD. There is no specific treatment. The disease is not known to recur in kidney allografts. Unlike patients with PKD or MSK, those with NPHP rarely develop flank pain, hematuria, hypertension, UTI, or kidney calculi.

Children with the relatively rare infantile NPHP variant develop symptoms in the first few months of life and rapidly progress to ESKD, usually before the age of 2 years, but invariably by 5 years of age. Severe hypertension is common in this disorder.28

Associated extrarenal abnormalities. Extrarenal abnormalities have been described in approximately 15% to 20% of patients with NPHP,23 the most frequent of which is retinal dystrophy because of tapetoretinal degeneration (Senior-Loken syndrome). Severely affected patients present with coarse nystagmus, early blindness, and a flat electroretinogram (Leber amaurosis), whereas those with moderate retinal dystrophy typically have mild visual impairment and retinitis pigmentosa. Other extrarenal anomalies include oculomotor apraxia (Cogan syndrome), cerebellar vermis aplasia (Joubert syndrome), and cone-shaped epiphyses of the bones. Congenital hepatic fibrosis occurs on occasion in patients with NPHP, but the associated bile duct proliferation is mild and qualitatively different from that observed in ARPKD.

Pathology

In classic NPHP, the kidneys are moderately contracted with parenchymal atrophy causing a loss of corticomedullary demarcation.

Histopathologic findings include tubular atrophy with thickened tubular basement membrane, diffuse and severe interstitial fibrosis, and cysts of variable size distributed in an irregular pattern at the corticomedullary junction and in the outer medulla. However, up to 25% of NPHP kidneys have no grossly visible cysts.

In the typical NPHP kidney lesion, clusters of atrophic tubules alternate either with groups of viable tubules showing dilation or marked compensatory hypertrophy. Multilayered thickening of tubular basement membranes is a prominent histopathologic feature (Fig. 47.4). This pattern is not unique, but the abrupt transition from one type of tubular profile to another suggests NPHP. Moderate interstitial fibrosis, usually without a significant inflammatory cell infiltrate, is interspersed among the atrophic tubules. Spherical, thin-walled cysts lined with a simple cuboidal epithelium may be evident at the corticomedullary junction, in the medulla, and even in the papillae. Microdissection studies indicate that these cysts arise from the loop of Henle, distal convoluted tubules, and collecting ducts. Glomeruli may be normal, although some may be completely sclerosed; others show periglomerular fibrosis, and still others have dilation of Bowman’s space, suggestive of glomerulocystic kidney disease.29

In comparison, infantile NPHP has features of both classic NPHP (such as tubular cell atrophy, interstitial fibrosis, and tubular cysts) and PKD, including enlarged kidneys and widespread cystic involvement.

Diagnosis

In a child with NPHP and reduced GFR, ultrasound typically reveals normal-sized or small kidneys with increased echogenicity and loss of corticomedullary differentiation. On occasion, cysts can be detected at the corticomedullary junction or in the medulla. Thin-section CT scanning may be more sensitive than ultrasound in detecting these cysts.

The pathologic findings in NPHP are not unique; hence in the early stages of the disease, neither imaging nor histopathology can confirm the clinical diagnosis. Molecular testing can be useful; current strategies using multigene panels and next-generation sequencing technologies allow high-throughput mutation detection for known NPHP genes, but to date defects in these genes only explain disease in only up to 40% of patients with NPHP-related disorders.24 25 27

Fig. 47.4 Kidney Pathology in Nephronophthisis. Light microscopy shows tubulointerstitial nephropathy. Atrophic tubules with irregularly thickened basement membranes are surrounded by interstitial fibrosis. Dilated tubules are evident at the corticomedullary junction. (H&E stain; ×40.)

A recent Dutch study of more than 5500 patients with adult-onset ESKD found that 0.5% of the cohort were homozygous for NPHP1 deletions.30 A subsequent study in 18 adult patients with kidney biopsies consistent with NPHP found disease-causing mutations in seven patients (39%) involving the NPHP1, NPHP3, NPHP4, or CEP164 genes.31 These data extend the phenotypic spectrum of NPHP into adulthood and reinforce the utility of genetic testing for patients with ESKD of undetermined etiology.

Treatment

Current treatment of NPHP is supportive but preclinical studies suggest that targeted therapies may be beneficial. For example, treatment with a vasopressin receptor 2 antagonist remarkably attenuated kidney cystic disease progression in a mouse model of NPHP-related disease.32 Others have proposed that therapeutic strategies should target the kidney fibrosis rather than cystic disease in NPHP and note that low-dose paclitaxel has shown promising results in rodent models of kidney fibrosis.33

Autosomal Dominant Tubulointerstitial Kidney Disease

The term autosomal dominant tubulointerstitial kidney diseases (ADTKD) has recently been proposed for the set of disorders previously described as MCKD, UMOD-related kidney disease, familial juvenile hyperuricemic nephropathy (HNFJ1; MIM 162000), and familial glomerulocystic disease with hyperuricemia (MIM 609886).34

ADTKD is less common than NPHP and the kidney pathologic findings are indistinguishable, although the progressive tubulointerstitial fibrosis resulting in ESKD is slower in ADTKD. Some patients have phenotypically unaffected parents but an affected second- or thirddegree relative, suggesting that disease is poorly recognized in affected family members and/or there is variable penetrance.

ADTKD typically manifests in adults, with familial kidney disease characterized by bland urinalysis (i.e., little or no proteinuria or hematuria) and slowly progressive loss of GFR. There may be hyperuricemia or gout. Ultrasound shows normal or small kidneys, sometimes with medullary cysts.

Disease-causing mutations in four genes, MUC1, UMOD, REN, and HNF1B, are responsible for most cases, with mutations in SEC61A1 reported in a handful of families.34 Hyperuricemia is a key feature of disease related to mutations in the UMOD and REN genes.

Uremia typically occurs after 60 years of age in ADTKD-MUC1 (MCKD1, MIM 174000). In ADTKD-UMOD (MCKD2, MIM 603860) and ADTKD-REN, progression to ESKD occurs between the fourth and seventh decades of life. However, disease progression within families can be highly variable, with rare individuals reaching ESKD in their teens, whereas other individuals in the same family may not develop kidney failure until past age 80 years.35

MEDULLARY SPONGE KIDNEY

Definition

MSK is characterized by dilated medullary and papillary collecting ducts that give the kidney medulla a spongy appearance. It is associated with nephrocalcinosis, recurrent calcium nephrolithiasis, abnormalities in renal tubular acidification and urinary concentration, bone mineralization defects, and an increased risk for UTI.36

Etiology and Pathogenesis

Histopathologic observations of embryonal tissue in the affected papillae, coexistence of kidney tubular defects, and evidence of defects in the genes encoding the RET proto-oncogene and the glial cell linederived neurotrophic factor (GDNF)37 suggest that MSK results from a developmental defect in the ureteric bud-metanephric mesenchyme interaction. In addition, MSK occurs more frequently in individuals with other developmental anomalies and/or tumors (e.g., congenital hemihypertrophy, Beckwith-Wiedemann syndrome, congenital anomalies of the kidney and urinary tract [CAKUT] syndrome, and Wilms tumor).38

MSK is usually a sporadic disorder, but familial clustering with autosomal dominant inheritance39 and evidence for genetic alteration in the RET-GDNF axis suggest a genetic basis for MSK in at least a subset of patients.

Epidemiology

In the general population, the frequency of MSK may be underestimated because some affected individuals remain asymptomatic. Up to 20% of patients with nephrolithiasis have at least a mild degree of MSK, but excretory urography in unselected patients indicates a disease frequency of approximately 1 in 5000 individuals.

A

B

Clinical Manifestations

MSK is asymptomatic unless complicated by nephrolithiasis, hematuria, or infection. Symptoms typically begin between the fourth and fifth decade of life, but adolescent presentations have been reported. Stones or granular debris in patients with MSK are composed of either pure apatite (calcium phosphate) or a mixture of apatite and calcium oxalate. Several factors appear to contribute to stone formation, including urinary stasis within the ectatic ducts, hypercalciuria, and hypocitraturia. Hyperparathyroidism also has been reported.

Hematuria is unrelated to either coexisting stones or infection and may be recurrent. The bleeding is usually asymptomatic unless gross hematuria causes clot-related colic. UTI may occur in association with nephrolithiasis or as an independent event. In patients with stones, infections are more likely to occur in females than in males.

Decreased urinary concentrating ability and impaired urinary acidification are common clinical features. In most patients, the acidification defect is not associated with overt systemic acidosis, but bone mineralization defects are well described.38

Pathology

The pathologic changes are confined to the medullary and intrapapillary collecting ducts. Multiple spherical or oval cysts measuring 1 to 8 mm may be detected in one or more papillae. These cysts may be isolated or may communicate with the collecting system. The cysts are frequently bilateral and often contain spherical concretions composed of apatite. The affected pyramids and associated calyces are usually enlarged, and nephromegaly can result when many pyramids are involved. The kidney cortex, medullary rays, calyces, and pelvis appear normal, unless complications (e.g., pyelonephritis or urinary tract obstruction) are superimposed.

Diagnosis

Abdominal plain radiographs often reveal radio-opaque concretions in the medulla (Fig. 47.5B). Historically, the diagnosis was established

C

Fig. 47.5 Radiologic Findings Associated With Medullary Sponge Kidney. (A) Preliminary radiograph shows medullary nephrolithiasis. (B) Initial radiograph from excretory urography shows clusters of rounded densities in the papillae among discrete linear opacities (paintbrush appearance). (C) Nonenhanced computed tomography reveals densely echogenic foci in the medulla (arrowhead).

by excretory urography (see Fig. 47.5B). Retention of contrast media by the ectatic collecting ducts appears either as spherical cysts or, more commonly, as diffuse linear striations. The latter imparts a characteristic blush-like pattern to the papillae, the so-called bouquet of flowers or paintbrush appearance. Medullary nephrocalcinosis is a common but not invariant finding. Urography has been almost completely replaced by nonenhanced CT, which may help distinguish MSK from papillary necrosis or even ADPKD (see Fig. 47.5C).

Treatment

Asymptomatic patients with MSK require no therapy. Hematuria in the absence of stones or infection requires no intervention. If the tubular ectasia is unilateral and segmental, partial nephrectomy may alleviate recurrent nephrolithiasis and UTI. However, for the majority of patients who have bilateral disease, medical management is sufficient. Hypercalciuria and hypocitraturia are the predominant factors contributing to MSK-related nephrolithiasis. The mainstays of treatment are a well-balanced diet consisting of fruits and vegetables, potassium citrate, and high fluid intake.40 Patients with persistent hypercalciuria and/or recurrent stone formers may benefit from thiazide diuretics. If thiazides are poorly tolerated or contraindicated, inorganic phosphate therapy may be useful. To avoid struvite stone formation, oral phosphates should not be used in patients with previous UTIs caused by urease-producing organisms. Patients who recurrently form and pass stones may require lithotripsy or surgical intervention (see Chapter 60).

UTIs should be treated with standard antibiotic regimens and for some patients, prolonged therapy may be warranted. Ureaseproducing organisms, such as coagulase-negative Staphylococcus, are particularly problematic as urinary pathogens in MSK. Positive urine cultures, even with relatively insignificant colony counts, should be vigorously pursued.

With proper management of the clinical complications, the longterm prognosis is excellent. Progression to kidney impairment is unusual.

TUBEROUS SCLEROSIS COMPLEX

Definition

TSC is an autosomal dominant, tumor-suppressor gene syndrome in which benign focal malformations, called hamartomas, develop in multiple organ systems, including the kidneys, brain, heart, lungs, and skin.

Etiology and Pathogenesis

TSC results from inactivating mutations in one of two genes, TSC1 on chromosome 9q32-q34 and TSC2 on chromosome 16p13, adjacent to the PKD1 gene. Large deletions involving both PKD1 and TSC2 result in the infantile severe polycystic kidney disease with tuberous sclerosis (PKDTS) contiguous gene deletion syndrome.

The focal development of hamartomas and the variability of disease expression even within families suggest that TSC1 and TSC2 function as tumor suppressor genes. The tumor suppressor gene paradigm proposes that two successive mutations are necessary to inactivate a target gene and cause tumor formation. The first mutation, inherited and therefore present in all cells, is necessary but not sufficient to produce tumors. A second mutation occurs after fertilization and is required to induce tumor transformation. The inactivating germ-line mutations identified in TSC1 and TSC2, as well as the loss of heterozygosity detected in TSC2-associated and TSC1-associated hamartomas, support the hypothesis that both TSC1 and TSC2 function as tumor suppressor genes.

The TSC2 gene product, tuberin, interacts with hamartin, the product of the TSC1 gene. The hamartin/tuberin (TSC1/TSC2) complex functions in multiple cellular pathways, primarily by inhibiting the kinase activity of the mammalian target of rapamycin (mTOR), which functions in a protein complex (mTORC1) to integrate nutrient uptake, cell-cycle progression, cell growth, and protein translation41 (Fig. 47.6). The PKD1 gene product, polycystin-1, plays a key role in regulating mTORC1 activity by complexing with tuberin and mTOR, thereby inhibiting the mTOR pathway.42 In a normal adult kidney, mTOR is inactive. With loss of function of either polycystin-1 or tuberin, mTOR activity is upregulated, contributing to dysregulated cell growth and cystogenesis. In addition, hamartin appears to function via TORC1-independent pathways to regulate the structural integrity of the primary cilium, suggesting that ciliary dysfunction is an additional mechanism in TSC pathogenesis.43

Epidemiology

TSC affects 1 in 6800 to 15,000 individuals,44 with approximately 2 million people affected with TSC worldwide.41 The disease penetrance is quite variable. About 70% of TSC patients are sporadic cases with no family history and the disease apparently results from new mutational events. Mutations in TSC2 are detectable in approximately 70% of all patients with TSC, whereas TSC1 mutations can be detected in about 20% of patients. In a substantial fraction of the remaining 10% of patients, the genetic defect may involve genetic mosaicism, whereby a mutational event in either TSC2 or TSC1 occurs after the one-cell stage of embryonic development.41

Clinicopathologic Manifestations

The clinical features of TSC1- and TSC2-linked disease are similar, although TSC2-linked disease tends to be more severe. The most common clinical manifestations include seizures, cognitive disability and/or autism, skin lesions, interstitial lung disease, and tumors in the brain, retina, kidney, and heart. In affected individuals over 5 years of age, the most common skin lesions are facial angiofibromas (Fig. 47.7), hypomelanotic macules, and ungual fibromas.

Kidney involvement occurs frequently in TSC, with kidney lesions that include angiomyolipomas (AMLs; 85%), cysts (30%–47%), and renal cell carcinoma (RCC; 2%–3%).45–47 Other kidney neoplasms, interstitial fibrosis with focal segmental glomerulosclerosis (FSGS), glomerular microhamartomas, and peripelvic and perikidney lymphangiomatous cysts also have been reported. Kidney involvement in TSC often progresses insidiously but can result in considerable morbidity, including retroperitoneal hemorrhage, reduced GFR (~1%), and death. Kidney complications are the most frequent cause of death in TSC.41

Kidney Angiomyolipomas

Angiomyolipomas (AMLs) are benign kidney hamartomas composed of abnormal, thick-walled vessels and varying amounts of smooth muscle-like cells and adipose tissue (Fig. 47.8AB). These are the most common kidney lesion in TSC patients, detected in approximately 20% of children with TSC before 2 years of age and evident in approximately 67% of patients by age 10 years.41 Whereas solitary AMLs are found in the general population, TSC-associated AMLs are multiple and bilateral, rarely occurring before 5 years of age, but increasing in frequency and size with age. They can become locally invasive, extending into the perirenal fat or, more rarely, the collecting system, renal vein, and even the inferior vena cava and right atrium.

Clinical manifestations occur secondary to hemorrhage (intratumoral or retroperitoneal) or mass effects (abdominal or flank masses and tenderness, hypertension, reduced GFR). Females tend to have

TSC1/TSC2 Complex
Receptor
tyrosine kinases
Cell energy
status

AMPK

Growth factors
Cytokines

AKT
ERK / RSK1

Cell cycle

CDK1

TSC1/TSC2

Rheb-GTP

Rapamycin

mTORC1

Ragulator

Amino acids

- Autophagy
- Protein translation
- Invasiveness
- Apoptosis
- Nucleotide synthesis
- Angiogenesis
- Lipid synthesis

Fig. 47.6 The TSC1/TSC2 complex regulates mTORC1 signaling by integrating extracellular and intracellular signals that promote metabolic homeostasis. Hamartin (TSC1) and tuberin (TSC2) integrate signals from extracellular cytokines and growth factors (via AKT and ERK/RSK1), the intracellular energy status (via AMPK), and the cell cycle (via CDK1) to direct signaling pathways that regulate cellular proliferation, differentiation, and migration. Tuberin contains a guanosine triphosphatase (GTPase)-activating protein domain in its carboxy terminus, and when it forms a complex with hamartin, the small GTPase Rheb is converted from its active GTPbound state to an inactive guanosine diphosphate–bound state. Rheb is an activator of the mTORC1 kinase, which regulates a number of processes linked to protein synthesis and cell growth. mTORC1 is activated physiologically in response to growth factor signaling, which causes phosphorylation of tuberin, dissociation of the hamartin/tuberin complex, and increased levels of Rheb-GTP. Inactivation

of the hamartin/tuberin complex through mutations in TSC1 or TSC2 leads to inappropriate activation of mTORC1. AMPK, Adenosine monophosphate–activated protein kinase; CDK1, cyclin-dependent kinase 1; ERK, extracellular signal–regulated kinase; RSK, ribosomal protein S6 kinase α3. (Modified from Lam HC, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: Pathogenesis and therapy. Nat Rev Nephrol. 2018;14[11]:704–716.)

more numerous and larger AML than males. Pregnancy appears to increase the risk for rupture and hemorrhage.47

Kidney Cystic Disease

Fig. 47.7 Facial Angiofibromas in Tuberous Sclerosis Complex. The angiofibromas are small red bumps that give a facial rash in a butterfly distribution and on the chin.

Kidney cysts occur less frequently than AML and are evident in 35% to 50% of patients with TSC. However, like AML, kidney cysts tend to increase in size and number over time. The concurrence of cysts and AML is easily detected by CT and strongly suggests TSC.

The cysts in TSC can develop in any nephron segment. When limited in number and size, TSC-related cysts are predominantly cortical.

In some cases, glomerular cysts predominate.29 The cystic lining epithelia appear to be unique to TSC, with large and acidophilic epithelia containing large hyperchromatic nuclei with occasional mitotic figures (see Fig. 47.8C). Associated papillary hyperplasia and adenomas are common.

A small subset of affected infants can present with massive kidney cystic disease, severe hypertension, and a progressive decline in kidney function with the onset of ESKD in the second or third decade of life.

The majority of these patients have a contiguous germ-line deletion involving both the PKD1 and TSC2 genes, the PKDTS contiguous gene

B

A

C

Fig. 47.8 Kidney Pathology in Tuberous Sclerosis Complex (TSC) (A) Cut section shows multiple kidney angiomyolipomas. (B) Light microscopy shows angiomyolipoma containing adipose tissue and spindle smooth muscle–like cells interspersed between abnormal vessels with thickened walls (H&E stain; ×16). (C) Light microscopy shows TSC cysts lined with distinctive epithelia consisting of large, acidophilic cells with hyperchromatic nuclei (H&E stain; ×65).

syndrome.[48] Early detection, strict BP control, initiation of mTOR1 inhibitor therapy to limit the growth of AML, and surveillance for TSC-associated renal cell carcinoma (RCC) may improve the overall prognosis.[49]

Kidney Neoplasms

Benign epithelial tumors, such as papillary adenomas and oncocytomas, are common in TSC patients and can be multifocal. Malignant transformation is rare, with 2% to 4% lifetime risk of developing RCC.[41] TSC-associated RCCs have a unique constellation of clinic-pathologic features, including female predominance, younger age at diagnosis, association with AML, multiplicity, and slow progression.[50] Three distinct histopathologic patterns predominate, with papillary RCC being most common, followed by hybrid oncocytic/chromophobe tumor and RCC with granular eosinophilic morphology. Although TSC-associated RCCs tend to have an indolent clinical course, the prognosis compared with sporadic RCC in the general population is unknown.

Diagnosis

TSC is a pleiotropic disease in which the size, number, and location of the lesions can be variable, even among affected individuals within the same family. Major and minor criteria have been developed to guide clinical diagnosis (Box 47.2). Two major features, or one major and two minor ones, are required to make the diagnosis of TSC. Imaging is the mainstay for diagnosis of TSC-associated kidney lesions. The presence of small cysts and fat-containing AMLs is strongly suggestive of TSC.

Kidney imaging is advised for monitoring disease progression in patients with TSC.[47] Ultrasound has historically been the preferred modality; it has high sensitivity in detecting the fat-rich AMLs and kidney cysts but is relatively insensitive for detecting fat-poor lesions. Current recommendations are to perform abdominal CT (Fig. 47.9) or MRI every 1 to 3 years for life to assess AML progression and kidney cystic disease.[51] On occasion, the distinction between an AML and RCC cannot be reliably established by imaging and biopsy is indicated. TSC-associated kidney cysts can radiologically mimic simple cysts and, when numerous, ADPKD. In the absence of AML, TSC-related kidney cystic disease is suggested by the limited number of cysts compared with ADPKD and the absence of associated hepatic cysts. Although 10% of patients with TSC have hepatic AML, hepatic cysts are rare.

Gene-based diagnosis is currently available for TSC1- and TSC2 related disease and to detect large-scale deletions associated with the PKDTS contiguous gene syndrome.

Clinical Diagnostic Criteria for Tuberous Sclerosis Complex [a]

BOX 47.2

Major

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypomelanotic macules (>3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber(s)
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma(s) (≥1)
- Lymphangioleiomyomatosis
- Kidney angiomyolipoma

Minor

- Multiple, random dental pits
- Hamartomatous gastrointestinal or rectal polyps
- Bone cysts
- White matter radial migration lines
- Gingival fibromas
- Non-kidney hamartoma
- Retinal achromic patch
- “Confetti” skin lesions
- Multiple kidney cysts

[a] Two major features or one major feature with two minor features indicate definite TSC; one major feature and one minor feature indicate probable TSC; and one major feature or two minor features indicates possible TSC.

From Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13[12]:624–628.

Treatment

Kidney Angiomyolipomas

Kidney AMLs are generally benign and require no treatment. Larger AMLs frequently develop microaneurysms and macroaneurysms and are associated with a risk of serious hemorrhage, particularly in actively growing AML more than 3 cm in diameter or those less than 5 mm in diameter with aneurysms.41 47 Large AMLs require preemptive treatment either with nephron-sparing surgery or embolization.52 In addition to size and complications such as pain or hemorrhage, the inability to exclude an associated RCC should prompt intervention.

VON HIPPEL-LINDAU DISEASE

Definition

VHL disease is a dominantly transmitted, multisystem cancer predisposition syndrome associated with tumors of the eyes, cerebellum, spinal cord, adrenal glands, pancreas, and epididymis, as well as kidney and pancreatic cysts.56

Etiology and Pathogenesis

Fig. 47.9 Contrast-enhanced computed tomography showing bilateral angiomyolipomas associated with tuberous sclerosis complex.

When an associated malignancy cannot be excluded, nephron-sparing surgery, such as enucleation or partial nephrectomy, is preferred.

Defective mTORC1 signaling is a central feature of TSC. Recent international TSC guidelines recommend mammalian target of rapamycin (mTOR1) inhibitors (rapalogs) as the first-line therapy for the treatment of asymptomatic, growing angiomyolipomas more than 3 cm in diameter.47 Sirolimus and everolimus are effective in reducing AML volume and/or postembolization response rates, with an acceptable safety profile,41 although they have a range of adverse events which must be borne in mind (see Chapter 106).53

The increased frequency and size of the AMLs in females and the reports of hemorrhagic complications during pregnancy suggest that female sex hormones may accelerate AML growth. Therefore, it is prudent to caution females with multiple AMLs about the potential risks of pregnancy and estrogen administration.

Kidney Cystic Disease

The mainstay of treatment of TSC-associated kidney cystic disease is strict BP control. Benefit from mTORC1 inhibitors has been suggested by small studies but not definitively demonstrated.41

Kidney Carcinoma

TSC-associated RCC should be suspected in enlarging, fat-poor lesions or when intratumoral calcifications are present and should be confirmed by biopsy. Because TSC-associated RCCs are often slow growing and frequently bilateral, nephron-sparing surgery is the treatment of choice.

Kidney Replacement Therapy

CKD, although rare in tuberous sclerosis, can occur by several different mechanisms, including AML-related parenchymal destruction, progressive kidney cystic disease, interstitial fibrosis, and FSGS. On a large French study, TSC-associated ESKD had a prevalence of 1 per 100 patients with TSC and was more frequent in females (63%), with a mean age diagnosis of 29 years.54

A follow-up French national KRT registry study evaluated 99 patients with TSC, who progressed to ESKD primarily because of nephrectomy or repeated AML embolization. The age at initiation of KRT was 48.4 years. Fifty-four patients underwent kidney transplantation after an average of 23 months on dialysis. None of the patients had been treated with an mTORC1 inhibitor before dialysis, leaving open the possibility that reducing the size of AML with mTORC1 inhibitors may lower the number of patients with TSC requiring KRT.55

VHL disease is a tumor suppressor disorder, with disease resulting from a germ-line mutation and a subsequent somatic mutation in the VHL gene. In approximately 80% of patients, VHL is familial, whereas disease in about 20% of cases results from de novo mutations. Moreover, VHL mutations have been identified in sporadic RCC, implying that VHL plays an important role in the pathogenesis of RCC.56 57

The VHL protein (pVHL) is a central driver in a finely tuned rheostat system that regulates the response to low oxygen levels.57 In the normal physiologic state, pVHL functions as part of a multiprotein E3 ubiquitin ligase complex that directs a number of proteins, most notably the alpha subunits of the transcription factor, hypoxia-inducible factor (HIF-α), for destruction via the ubiquination pathway. In cells that lack pVHL, HIF-α subunits are stabilized and bind to HIF-β. The heterodimer then translocates to the nucleus, leading to overexpression of HIF-target genes, which encode proteins that regulate glucose uptake, metabolism, extracellular pH, erythropoiesis, angiogenesis (vascular endothelial growth factor [VEGF] and platelet-derived growth factor B [PDGFB]), and mitogenesis (transforming growth factor β [TGF-β]).

This transcriptional dysregulation promotes the pathologic growth and survival of endothelial cells, pericytes and stromal cells and, ultimately, their malignant transformation.56 57

Clinical Manifestations

VHL disease has an incidence of 1 in 36,000 live births and has been observed in all ethnic groups. Biallelic VHL inactivation leads to increased risk for central nervous system (CNS) and retinal hemangioblastomas, RCC, pheochromocytomas, pancreatic islet cell tumors, endolymphatic sac tumors, and papillary cystadenomas of the broad ligament (females) and epididymis (males). In addition, cystic changes can occur in the kidney and pancreas.56

VHL-associated disease clusters in two complexes (Table 47.2). In the initial stratification, patients with VHL disease can be subclassified based on a low risk (type 1) or high risk (type 2) of developing pheochromocytoma. Type 1 disease is characterized by large deletions or truncations of the VHL gene, which cause complete inactivation of the gene and result in high levels of HIF activity. Type 2 disease primarily involves missense mutations and is associated with partial activity of pVHL. Type 2 patients can be further subdivided into three subtypes: type 2A, which has a low incidence of kidney lesions; type 2B, which is associated with a high risk for RCC; and type 2C, which is associated only with pheochromocytoma and no other malignancies.56

In patients with VHL disease, the lifetime cumulative RCC risk approaches 70%.58 RCCs are typically multiple and bilateral. Although RCC may manifest with hematuria or back pain, more often detection occurs as an incidental finding on unrelated imaging studies or during a screening protocol. The mean age of symptomatic presentation is 35 to 40 years, although patients have been diagnosed in adolescence. In VHL disease, males and females are equally affected with RCC, in contrast to the male predominance in sporadic RCC. VHL disease-associated RCC metastasizes to the lymph nodes, liver, lungs, and bones and accounts for about 50% of VHL-disease related deaths.

In addition to RCC kidney manifestations of VHL, multiple bilateral kidney cysts are found in 50% to 70% of patients.[56] Kidney cysts arise from tubular cells that have undergone somatic loss of the wildtype allele.

Historically, deterioration in GFR among patients VHL was thought to be unusual. However, a recent international consortium study of 96 patients with VHL and nonmetastatic RCC found that 16% of patients pretreatment and 25% of patients posttreatment (e.g., partial nephrectomy or tissue ablation) had CKD.[59]

Pathology

VHL disease-associated RCCs are mostly of the clear-cell type and usually bilateral and multifocal in distribution. Detailed microscopic examination of VHL disease associated kidney cystic lesions often reveals small foci of carcinoma. VHL disease-associated RCCs tend to have low-grade histology and a better 10-year survival than sporadic RCC. More advanced RCCs can metastasize, and metastatic disease is a major cause of death in patients with VHL.

TABLE 47.2 Classification of von Hippel-Lindau Subtypes

Subtype	Tumor Manifestations
Type 1	hemangioblastoma (CNS, retina), kidney cell carcinoma, pancreatic cysts low risk for pheochromocytoma
Type 2A	hemangioblastoma (CNS, retina), pheochromocytoma, low risk for kidney cell carcinoma
Type 2B	hemangioblastoma (CNS, retina), kidney cell carcinoma, pheochromocytoma, pancreatic cysts
Type 2C	predominantly pheochromocytoma very limited risk of hemangioblastoma and kidney cell carcinoma

CNS, Central nervous system.

From Maher ER, Neumann HP, Richard S. von Hippel–Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617–23; and Wind JJ, Lonser RR. Management of von Hippel-Lindau diseaseassociated CNS lesions. Expert Rev Neurother. 2011;11(10):1433.

TABLE 47.3

Diagnosis

The minimum clinical criteria for the diagnosis of VHL disease in an at-risk individual include the presence of a single retinal or cerebellar hemangioblastoma, or RCC, or pheochromocytoma. Up to 50% of affected individuals with familial VHL disease may manifest only one feature of the syndrome. In presumed sporadic cases (20% of patients), the clinical diagnosis requires two tumors (such as two hemangioblastomas, or a hemangioblastoma and a characteristic visceral tumor).

Molecular analysis of the VHL gene is indicated in patients with known or suspected VHL or in at-risk children from VHL families, given that unsuspected, untreated tumors can cause significant morbidity. Presymptomatic genotyping can be useful in determining the phenotypic classification of VHL and used to direct monitoring for a specific subset of tumors. In addition, genotyping can be useful in distinguishing whether a pheochromocytoma has occurred in the context of a VHL type 2 mutation or multiple endocrine neoplasia (MEN) type 2 or is nonsyndromic.60

In patients with type 2 VHL disease, annual assessment of BP, measurement of urinary catecholamine metabolites, and abdominal ultrasound imaging should be initiated at the age of 2 years. Abdominal MRI and iodine-131 metaiodobenzyl-guanidine (MIBG) scans are indicated if abnormalities are detected. By age 16 years, all patients with VHL disease should have annual MRI scans of the abdomen. Ultrasound is a useful alternative imaging modality in pregnant persons. Annual assessment should be lifelong. Early detection of kidney disease and a multidisciplinary approach to follow-up can substantially improve survival.

Differential Diagnosis

The differential diagnosis of VHL disease–associated kidney lesions includes several conditions, most notably ADPKD and TSC (Table 47.3). As with VHL, ADPKD affects both sexes with a similar mean

Clinical Characteristics of Kidney Cystic Disease in Adults

Simple Cysts

ADPKD

MSK

VHL

TSC

Acquired Cystic Disease

Age at clinical onset
Cysts
Cyst infection
Tumors
BP
GFR
Nephrolithiasis
Liver cysts
Pancreas cysts
CNS involvement
Skin lesions

>30 y
Single/multiple
Uncommon
No
Normal/increased
Normal
No
No
No
No
No

30–40 y
Multiple

Common
Rare
Increased
Normal/impaired
Common
Common
Few
Aneurysms
No

20–40 y
Multiple
Common
No
Normal
Normal
Common
No
No
No
No

30–40 y
Few, bilateral
Uncommon
RCC, often bilateral
Normal/increased
Normal
No
Rare
Multiple
Hemangioblastomas
No

10–30 y
Multiple
Uncommon
AML/RCC
Normal/increased
Normal/impaired
No
No
No
Seizures, cognitive disability
See Fig. 47.9

Chronic kidney disease
Multiple
Uncommon
Common
Normal/increased
Impaired/ESKD
No
No
No
No
No

Genetics
Disease gene

No

No

VHL

No

No

Yes

TSC1
TSC2
Yes

No

Genetic testing[a]

PKD1
PKD2
Yes

[a] Genetic

No

testing is listed at the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).
ADPKD, Autosomal dominant polycystic kidney disease; AML, angiomyolipoma; BP, blood pressure; CNS, central nervous system; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; MSK, medullary sponge kidney; RCC, kidney cell carcinoma; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau disease.

Treatment

Nephron-sparing surgery continues to be the mainstay of treatment for localized RCC in patients with VHL disease.56 Repeated surgical intervention may be required as tumors continue to develop. Percutaneous and laparoscopic radiofrequency ablation therapy is effective in treating smaller tumors (<3 cm) with low complication rates, but frequent posttreatment monitoring is required.56 The role of adjuvant therapy with drugs that inhibit the pVHL-HIF-VEGF pathway, such as the multiple tyrosine kinase inhibitors (TKI; e.g., sunitinib, sorafenib, and pazopanib) and monoclonal antibody VEGF inhibitor (e.g., bevacizumab), remains controversial.58

Bilateral nephrectomy and kidney transplantation may be an acceptable alternative to repeated nephron-sparing surgery in patients with VHL disease–associated RCC. It remains to be determined whether posttransplant immunosuppression enhances the growth of the retinal and CNS hemangioblastomas and other lesions found in patients with VHL disease.

For RCCs that have locally advanced or metastasized, systemic approaches with immunotherapy (checkpoint inhibitors) and molecularly targeted agents (VEGF receptor TKIs, monoclonal antibody VEGF inhibitors, and mTOR inhibitors), as well as radiation therapy, all may have a role depending on the extent of disease, sites of involvement, and patient-specific factors.58

A

SIMPLE CYSTS

Introduction and Definition

Simple kidney cysts are the most commonly acquired cystic lesion and occur twice as frequently in males as in females. Simple cysts are usually unilateral and may be either solitary or multiple. They occur rarely in children but become increasingly common with age.61 In a seminal ultrasound study, unilateral cysts were detected in 1.7% of patients aged 30 to 49 years, 11% of patients aged 50 to 70 years, and 22% to 30% of patients older than 70 years.62 This age-related increase in cyst incidence has been corroborated by MRI studies.

B

Fig. 47.10 Radiologic Findings Associated With von Hippel–Lindau Syndrome. (A) Noncontrast computed tomography shows massive cystic involvement of the pancreas (arrowheads) and bilateral kidney cysts (arrows). (B) Contrast-enhanced magnetic resonance imaging shows a right cerebellar hemangioblastoma with a small enhancing mass (arrow).

age at presentation. However, in VHL disease, kidney involvement is characterized by a few bilateral cysts, RCC, normal kidney size, normal BP, and usually normal GFR. Kidney cyst infection, a frequent finding in ADPKD, is uncommon in VHL disease, and RCC is an infrequent complication of ADPKD. Cysts in the liver are frequent in ADPKD and rare in VHL disease. Pancreatic cysts are rare in ADPKD but can be numerous and scattered through the pancreas in VHL disease (Fig. 47.10A). The CNS in ADPKD is affected by arterial aneurysms, whereas hemangioblastomas are the predominant CNS manifestation in VHL disease (see Fig. 47.10B).

TSC should be considered in the differential diagnosis of multiple kidney tumors. In both TSC and VHL disease, multiple kidney cysts occur. However, the TSC-associated kidney tumor is usually an AML, and extrarenal lesions readily distinguish VHL disease and

TSC.

Etiology and Pathogenesis

Simple kidney cysts likely originate from the distal convoluted tubule or collecting ducts and may arise from kidney tubular diverticula, but the pathogenic mechanisms are unknown. Focal tubular obstruction and kidney parenchymal ischemia have both been suggested as etiologic processes. Less likely is the possibility that simple cysts arise from calyceal diverticuli because simple cysts are often found in the kidney cortex and their frequency increases with age.

Age, smoking, reduced GFR, and hypertension63 have been implicated as risk factors for simple cysts. However, these associations may be coincidental, given that the studies were largely retrospective, the cohorts had variable reasons for diagnostic referral, and the observations were not optimally controlled for patient age.64

Clinical Manifestations

Simple cysts are typically asymptomatic. However, increasing evidence supports a relationship between simple kidney cysts and hypertension,63 which may be associated with increased renalase levels.65 In addition, red blood cell abnormalities (elevated red blood cell mass, hematocrit, and hemoglobin) are well described in patients with simple kidney cysts.66 Patients can also present with hematuria, flank pain, evidence of infection, or obstruction of the collecting system. Clinical symptoms are more common with neoplasms than simple cysts and should therefore prompt evaluation for cyst-associated malignancy.64

Pathology

Whether unilateral or bilateral, simple cysts are usually spherical and unilocular. They may be solitary or multiple. On average, simple cysts measure 0.5 to 1.0 cm in diameter, but 3 to 4 cm cysts are not uncommon. Simple cysts can occur in the cortex, where they can protrude from the cortical surface (exophytic cysts), the corticomedullary junction, or in the medulla. By definition, they do not communicate with the kidney pelvis. The cyst walls are typically thin and transparent, lined with a single layer of flattened epithelium. Cyst fluid is essentially an ultrafiltrate of plasma. In the wake of infection, cyst walls can become thickened, fibrotic, and even calcified.

Diagnosis

Simple cysts are most often detected as incidental findings during abdominal imaging studies. On occasion, they are discovered during radiologic evaluation of palpable abdominal masses, pyelonephritis, or hematuria after abdominal trauma.

The critical clinical challenge is to distinguish single or multiple simple cysts from cysts associated with ADPKD, other cystic diseases, or RCC. This distinction can usually be made on the basis of patient age, family history, and imaging (see Table 47.3).

The ultrasound features of simple cysts include smooth walls, lack of septae, and no intracystic debris. If the ultrasound pattern is indeterminate, CT scanning should be performed. Benign cysts have homogeneous attenuation, no contrast enhancement, thin and smooth cyst walls, and no associated calcifications, unless prior infection has occurred.

A classification system for kidney cysts based on their appearance and enhancement on CT, described by Israel and Bosniak, is widely used and informs management (see Table 63.5).67

Treatment

Simple cysts associated with pain or renin-dependent hypertension can be managed with percutaneous aspiration under radiologic guidance and instillation of a sclerosing agent into the cyst cavity.68 Laparoscopic or retroperitoneoscopic cyst unroofing (marsupialization) may be more appropriate for large cysts containing volumes in excess of 100 mL. Cyst infection with Enterobacteriaceae, Staphylococci, and Proteus has been reported and operative or percutaneous drainage is often required in addition to antibiotic treatment.

SOLITARY MULTILOCULAR CYSTS

Solitary multilocular cysts are generally benign neoplasms that arise from the metanephric blastema. These solitary cysts also have been designated multilocular cystic nephroma, benign cystic nephroma, and papillary cystadenoma. By definition, the cystic structures are unilateral, solitary, and multilocular. The cystic locules do not communicate with each other or with the kidney pelvis. These locules are lined with a simple epithelium and the interlocular septa do not contain differentiated kidney epithelia structures.

There is a spectrum of multilocular cysts; at one end is cystic nephroma (CN) and at the other end is cystic partially differentiated nephroblastoma (CPDN), in which the septa contain foci of blastemal cells. It is not clear whether a multilocular cyst represents a congenital abnormality in nephrogenesis, a hamartoma, a partially or completely differentiated Wilms tumor, or a benign variant of Wilms tumor.

There is a bimodal age distribution69; approximately half the cases occur in children younger than 4 years and half the cases are detected in adults. The childhood cases (mostly CPDN) are usually found in males, whereas multilocular cysts presenting in adulthood

Fig. 47.11 Solitary Multilocular Cyst. Contrast-enhanced computed tomography shows a solitary, septated, and well-circumscribed kidney cystic lesion in the right kidney.

(mostly CN) occur more commonly in females. An abdominal or flank mass is the most common clinical feature because these cysts are typically quite large and often replace an entire pole. Associated hematuria, calculi, urinary tract obstruction, and infection occur in rare instances. Diagnosis can be made either by ultrasound or CT (Fig. 47.11).

Almost all multilocular cysts are Bosniak class III (see Table 63.5), complex kidney cysts suspicious for malignancy.67 CPDN in children may contain blastema and incompletely differentiated metanephric tissue but usually has a benign course. In adults, associated foci of kidney cell carcinoma or sarcoma must be excluded. For both diagnostic accuracy and treatment, partial nephron sparing surgery is usually required.

The typical prognosis of solitary multilocular cysts is excellent.

KIDNEY LYMPHANGIOMATOSIS

Kidney lymphangiomatosis is a rare, generally benign disorder characterized by developmental malformation of kidney lymphatic channels.

Synonyms include kidney lymphangioma, peripelvic lymphangiectasia, or kidney hygroma.70

The cystic phenotype is widely variable and the underlying pathogenesis is unclear. Dilation may involve a single lymphatic channel or multiple channels. The lymphangiectasis may be unilateral or bilateral, may be limited to the hilar region, or may extend into the kidney parenchyma to the corticomedullary junction. On occasion, kidney lymphangiomatosis may be very extensive and simulate either ADPKD or ARPKD.71 72 The distinguishing features include cyst lining by lymphatic endothelium and cyst fluid–containing lymphatic constituents such as albumin and lipid.

The characteristic ultrasound or CT findings include multiple, bilateral small peripelvic cysts that splay the renal hilum, as well as capsular cysts in the perirenal space, both separated by thin septations.

Kidney lymphangiomas are most often asymptomatic and require no treatment. However, the condition may be exacerbated by pregnancy, resulting in large perinephric lymph collections and ascites that can require percutaneous drainage.

GLOMERULOCYSTIC KIDNEY DISEASE

Glomerular cysts occur in three different clinical contexts: (1) isolated glomerulocystic kidney disease (GCKD); (2) glomerulocystic kidneys associated with heritable malformation syndromes, such as TSC, Meckel syndrome, autosomal dominant tubulointerstitial kidney disease (ADTKD), oro-facio-digital syndrome type I; trisomies 9, 13 and 18; short-rib polydactyly syndromes; and Zellweger cerebrohepatorenal syndrome; and (3) glomerular cystic changes in dysplastic kidneys.29

Isolated GCKD can occur as a sporadic condition, a familial disorder, or as the infantile manifestation of ADPKD. Pathologically, the kidney architecture is normal, with no dysplastic elements in the cortex and no evidence of urinary tract obstruction. Cystic dilation predominantly involves Bowman's space and the initial proximal tubule.

GCKD is defined as a twofold to threefold dilation of Bowman's space compared with the normal glomerular dimension. Glomerular cysts can be distributed from the subcapsular zone to the inner cortex. The typical ultrasound pattern in GCKD involves increased echogenicity of the kidney cortex with minute cysts, smaller than those evident in ADPKD. T2-weighted MRI typically reveals numerous, uniformly small, cortical cysts.73 Young infants with either familial or sporadic forms of GCKD may also have kidney medullary dysplasia and biliary dysgenesis.29

Heritable GCKD is usually transmitted as an autosomal dominant trait, often occurring as the infantile expression of ADPKD. In these infants, the kidneys are bilaterally enlarged and diffusely cystic. In non–ADPKD-associated GCKD families, the kidneys are typically normal in size, although on occasion, enlarged kidneys are observed. Finally, several sporadic cases of nonsyndromal GCKD have been described, suggesting either new spontaneous mutations or a recessively transmitted disorder.29

Familial hypoplastic GCKD (MIM 137920) appears to be a distinct form of GCKD that results from mutations in HNF1B, the gene encoding hepatocyte nuclear factor 1β 74 The kidneys are smaller than normal and often associated with medullocalyceal abnormalities. Tubular abnormalities include hyperuricemia with or without gout, hypokalemia, hypomagnesemia, and polyuria.75 This multisystem disease is pleiotropic among affected family members with variable associations of hypoplastic GCKD, gynecologic abnormalities, and maturity-onset diabetes of the young, type V (MODY5).

ACQUIRED CYSTIC DISEASE

Hypokalemic Cystic Disease

Kidney cysts are often seen in association with chronic hypokalemia secondary to primary hyperaldosteronism or other kidney potassiumwasting disorders. Nearly 50% of patients with idiopathic adrenal hyperplasia and 60% of patients with adrenal tumors are reported to have kidney medullary cysts, which typically regress after adrenalectomy. Medullary cysts have been reported in children with type I RTA, and patients with mutations involving subunits of the H+-ATPase can also have radiologic findings of medullary sponge kidney. Whether these abnormalities and/or the severity of nephrocalcinosis alter the progression of CKD in these patients is not known.76

Hilar Cysts

Hilar cysts are spherical accumulations of clear, fat droplet-containing fluid within the kidney sinus. These cystic structures are not lined by epithelia. They are most commonly seen in debilitated patients and may represent atrophy of the kidney sinus fat.

Perinephric Pseudocysts

Perinephric pseudocysts are also unlined cavities. They typically occur under the kidney capsule or in the perirenal fascia as a result of urine extravasation from traumatic or spontaneous rupture of a kidney cyst or as the posterior extension of a pancreatic pseudocyst. Surgical intervention is indicated for associated urinary tract obstruction. Otherwise, treatment is directed to the underlying cause.

Acquired Cystic Disease in Kidney Failure

Acquired cystic disease is a significant complication of prolonged kidney failure (see Table 47.3), occurring as the result of progressive structural end-stage kidney remodeling and may be associated with kidney cell carcinoma. Acquired kidney cystic disease is discussed further in Chapter 92

SELF-ASSESSMENT QUESTIONS

1. Extrarenal complications of ARPKD can include which of the following?
A Congenital hepatic fibrosis
B. Caroli syndrome
C. Growth retardation
D. Intracranial aneurysms
E. All of the above
2. Which kidney cystic disease is distinguished by small, contracted kidneys?
A. ARPKD
B. NPHP
C. MSK
D. von Hippel–Lindau disease
E. None of the above
3. Which phenotypic feature most accurately distinguishes tuberous sclerosis complex from von Hippel–Lindau disease?

A. Systemic hypertension
B. Kidney cysts
C. Kidney angiomyolipomas
D. Kidney cell carcinoma
E. Liver cysts
4. Gene-based testing is a clinically informative tool for which of the following disorders?
A. ARPKD
B. NPHP
C. MSK
D. von Hippel–Lindau disease
E. All of the above
5. Medullary sponge kidney is a single-gene disorder in a subset of patients.
A. True
B. False

REFERENCES

1. Cramer MT, Guay-Woodford LM. Cystic kidney disease: a primer. Adv Chronic Kidney Dis. 2015;22(4):297–305.
2. Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. Nat Rev Dis Primers. 2018;4(1):50.
3. Lu H, Galeano MCR, Ott E, Kaeslin G, Kausalya PJ, Kramer C, et al. Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease. Nat Genet. 2017;49(7):1025–1034.
4. Yang C, Harafuji N, O’Connor A, Kesterson R, Watts J, Majmundar A, et al. Cystin gene mutations cause autosomal recessive polycystic kidney disease associated with altered Myc expression. Sci Rep. 2021;11:18274.
5. Habbig S, Liebau MC. Ciliopathies - from rare inherited cystic kidney diseases to basic cellular function. Mol Cell Pediatr. 2015;2(1):8.
6. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. Pediatrics. 2014;134(3):e833–e845.
7. Alzarka B, Morizono H, Bollman JW, Kim D, Guay-Woodford LM. Design and implementation of the hepatorenal fibrocystic disease core center clinical database: a centralized resource for characterizing autosomal recessive polycystic kidney disease and other hepatorenal fibrocystic diseases. Front Pediatr. 2017;5:80.
8. Gimpel C, Avni FE, Bergmann C, Cetiner M, Habbig S, Haffner D, et al. Perinatal diagnosis, management, and follow-up of cystic renal diseases: a clinical practice recommendation with systematic literature reviews. JAMA Pediatr. 2018;172(1):74–86.
9. Guay-Woodford LM, Bissler JJ, Braun MC, Bockenhauer D, Cadnapaphornchai MA, Dell KM, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. J Pediatr. 2014;165(3):611–617.
10. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman M, Graf J, Bryant JC, et al. Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. Clin J Am Soc Nephrol. 2010;5(6):972–984.
11. Burgmaier K, Kunzmann K, Ariceta G, Bergmann C, Buescher AK, Burgmaier M, et al. Risk factors for early dialysis dependency in autosomal recessive polycystic kidney disease. J Pediatr. 2018;199:22–28. e6.
12. Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int. 2005;67(3):829–848.
13. Srinath A, Shneider BL. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. J Pediatr Gastroenterol Nutrit. 2012;54(5):580–587.
14. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman Gerstein M, Piwnica-Worms K, Choyke P, et al. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. Gastroenterology. 2013;144(1):112–121. e2.
15. Elchediak DS, Cahill AM, Furth EE, Kaplan BS, Hartung EA. Extracranial aneurysms in 2 patients with autosomal recessive polycystic kidney disease. Case Rep Nephrol Dial. 2017:34–42.
16. Chalhoub V, Abi-Rafeh L, Hachem K, Ayoub E, Yazbeck P. Intracranial aneurysm and recessive polycystic kidney disease: the third reported case. JAMA Neurol. 2013;70(1):114–116.
17. Bergmann C. Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. Front Pediatr. 2018;5:221.
18. Abdul Majeed N, Font-Montgomery E, Lukose L, Bryant J, Veppumthara P, Choyke PL, et al. Prospective evaluation of kidney and liver disease in autosomal recessive polycystic kidney disease-congenital hepatic fibrosis. Molecul Genet Metabol. 2020;131(1-2):267–276.
19. Burgmaier K, Brinker L, Erger F, Beck B, Benz M, Bergmann C, et al. Refining genotype-phenotype correlations in 304 patients with autosomal recessive polycystic kidney disease (ARPKD) and PKHD1 variants. Kidney

international. Kidney Int. 2021;100(3):650–659.
20. Hartung EA, Matheson M, Lande MB, Dell KM, Guay-Woodford LM, Gerson AC, et al. Neurocognition in children with autosomal recessive

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polycystic kidney disease in the CKiD cohort study. Pediatr Nephrol (Berlin, Germany). 2014;29(10):1957–1965.
Gunay-Aygun M, Turkbey BI, Bryant J, Daryanani KT, Gerstein MT, Piwnica-Worms K, et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. Mol Genet Metabol. 2011;104(4):677–681.
Mekahli D, van Stralen KJ, Bonthuis M, Jager KJ, Balat A, Benetti E, et al. Kidney versus combined kidney and liver transplantation in young people with autosomal recessive polycystic kidney disease: data from the European Society for Pediatric Nephrology/European Renal AssociationEuropean Dialysis and Transplant (ESPN/ERA-EDTA) Registry. Am J Kidney Dis. 2016;68(5):782–788.
Wolf MT. Nephronophthisis and related syndromes. Curr Opinion Pediatr. 2015;27(2):201–211.
Halbritter J, Porath JD, Diaz KA, Braun DA, Kohl S, Chaki M, et al. Identification of 99 novel mutations in a worldwide cohort of 1,056 patients with a nephronophthisis-related ciliopathy. Human Genet. 2013;132(8):865–884.
Srivastava S, Molinari E, Raman S, Sayer JA. Many Genes-One Disease? Genetics of Nephronophthisis (NPHP) and NPHP-Associated Disorders. Front Pediatr. 2017;5:287.
Barroso-Gil M, Olinger E, Sayer JA. Molecular genetics of renal ciliopathies. Biochem Soc Trans. 2021;49(3):1205–1220.
Schueler M, Halbritter J, Phelps IG, Braun DA, Otto EA, Porath JD, et al.

Large-scale targeted sequencing comparison highlights extreme genetic heterogeneity in nephronophthisis-related ciliopathies. J Med Genet. 2016;53(3):208–214.
Tory K, Rousset-Rouviere C, Gubler MC, Moriniere V, Pawtowski A, Becker C, et al. Mutations of NPHP2 and NPHP3 in infantile nephronophthisis. Kidney Internatl. 2009;75(8):839–847.
Bissler JJ, Siroky BJ, Yin H. Glomerulocystic kidney disease. Pediatr Nephrol (Berlin, Germany). 2010;25(10):2049–2056. quiz 56–59.
Snoek R, van Setten J, Keating BJ, Israni AK, Jacobson PA, Oetting WS, et al. NPHP1 (Nephrocystin-1) Gene Deletions Cause Adult-Onset ESRD. J Am Soc Nephrol. 2018;29(6):1772–1779.
Fujimaru T, Kawanishi K, Mori T, Mishima E, Sekine A, Chiga M, et al. Genetic Background and Clinicopathologic Features of Adult-onset Nephronophthisis. Kidney Int Rep. 2021;6(5):1346–1354.
Torres VE, Harris PC. Polycystic kidney disease in 2011: connecting the dots toward a polycystic kidney disease therapy. Nat Rev Nephrol. 2011;8(2):66–68.
Slaats GG, Lilien MR, Giles RH. Nephronophthisis: should we target cysts or fibrosis? Pediatr Nephrol (Berlin, Germany). 2016;31(4):545–554.
Devuyst O, Olinger E, Weber S, Eckardt KU, Kmoch S, Rampoldi L, et al. Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers. 2019;5(1):60.
Bleyer AJ, Wolf MT, Kidd KO, Zivna M, Kmoch S. Autosomal dominant tubulointerstitial kidney disease: more than just HNF1beta. Pediatric nephrology (Berlin, Germany); 37(5):933–946.
Gambaro G, Danza FM, Fabris A. Medullary sponge kidney. Curr Opinion Nephrol Hypertension. 2013;22(4):421–426.
Ria P, Fabris A, Dalla Gassa A, Zaza G, Lupo A, Gambaro G. New nonrenal congenital disorders associated with medullary sponge kidney (MSK) support the pathogenic role of GDNF and point to the diagnosis of MSK in recurrent stone formers. Urolithiasis. 2017;45(4):359–362.
Fabris A, Anglani F, Lupo A, Gambaro G. Medullary sponge kidney: state of the art. Nephrol Dial Transplant. 2013;28(5):1111–1119.
Fabris A, Lupo A, Ferraro PM, Anglani F, Pei Y, Danza FM, et al. Familial clustering of medullary sponge kidney is autosomal dominant with reduced penetrance and variable expressivity. Kidney Internatl. 2013;83(2):272–277.
Fabris A, Lupo A, Bernich P, Abaterusso C, Marchionna N, Nouvenne A, et al. Long-term treatment with potassium citrate and renal stones in medullary sponge kidney. Clinical journal of the American Society of Nephrology. CJASN. 2010;5(9):1663–1668.
Lam HC, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: pathogenesis and therapy. Nat Rev Nephrol. 2018;14(11):704–716.

References

42. Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. Proc Natl Acad Sci U S A. 2006;103(14):5466–5471.
43. Hartman TR, Liu D, Zilfou JT, Robb V, Morrison T, Watnick T, et al. The tuberous sclerosis proteins regulate formation of the primary cilium via a rapamycin-insensitive and polycystin 1-independent pathway. Human Mol Genet. 2009;18(1):151–163.
44. Kingswood JC, Bruzzi P, Curatolo P, de Vries PJ, Fladrowski C, Hertzberg C, et al. TOSCA - first international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. Orphanet J Rare Dis. 2014;9:182.
45. Kingswood JC, Bissler JJ, Budde K, Hulbert J, Guay-Woodford L, Sampson JR, et al. Review of the Tuberous Sclerosis Renal Guidelines from the 2012 Consensus Conference: current Data and Future Study. Nephron. 2016;134(2):51–58.
46. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Belousova E, Frost MD, et al. Everolimus long-term use in patients with tuberous sclerosis complex: four-year update of the EXIST-2 study. PloS One. 2017;12(8):e0180939.
47. Kingswood JC, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Renal Manifestations of Tuberous Sclerosis Complex: key Findings From the Final Analysis of the TOSCA Study Focussing Mainly on Renal Angiomyolipomas. Front Neurol. 2020;11:972.
48. Consugar MB, Wong WC, Lundquist PA, Rossetti S, Kubly VJ, Walker DL, et al. Characterization of large rearrangements in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. Kidney Internatl. 2008;74(11):1468–1479.
49. Sundaram M, Kookana A, Duncan H, Mathew R. PKD1/TSC2 contiguous gene deletion syndrome. Nephrology (Carlton). 2017;22(8):656–657.
50. Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, et al. Renal cell carcinoma in tuberous sclerosis complex. Am J Surg Pathology. 2014;38(7):895–909.
51. Krueger DA, Northrup H, Tuberous I, Krueger DA, Roberds S, Smith K, et al. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatric Neurology. 2013:255–265.
52. Siroky BJ, Yin H, Bissler JJ. Clinical and molecular insights into tuberous sclerosis complex renal disease. Pediatr Nephrol (Berlin, Germany). 2011;26(6):839–852.
53. Sasongko TH, Ismail NF, Zabidi-Hussin Z. Rapamycin and rapalogs for tuberous sclerosis complex. Cochrane Database Syst Rev. 2016;7:CD011272.
54. Schillinger F, Montagnac R. Chronic renal failure and its treatment in tuberous sclerosis. Nephrol Dial Transplant. 1996;11(3):481–485.
55. Vabret E, Couchoud C, Lassalle M, Vigneau C. From tuberous sclerosis complex to end stage renal disease: who are these patients? J Nephrol. 2021;34(2):607–615.
56. Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A Review of Von Hippel-Lindau Syndrome. J Kidney Cancer VHL. 2017;4(3):20–29.
57. Chappell JC, Payne LB, Rathmell WK. Hypoxia, angiogenesis, and metabolism in the hereditary kidney cancers. J Clin Invest. 2019;129(2):442–451.
58. Perazella MA, Dreicer R, Rosner MH. Renal cell carcinoma for the nephrologist. Kidney Internatl. 2018;94(3):471–483.

59. Capitanio U, Rosiello G, Erdem S, Rowe I, Kara O, Roussel E, et al. Clinical, surgical, pathological and follow-up features of kidney cancer patients with Von Hippel-Lindau syndrome: novel insights from a large consortium. World J Urol. 2021.
60. Kaelin WG. Von Hippel-Lindau disease. Annual Rev Pathol. 2007;2:145–

173.
61. Hommos MS, Glassock RJ, Rule AD. Structural and functional changes in human kidneys with healthy aging. J Am Soc Nephrol. 2017;28(10):2838–2844.
62. Ravine D, Gibson RN, Donlan J, Sheffield LJ. An ultrasound renal cyst prevalence survey: specificity data for inherited renal cystic diseases. Am J Kidney Dis. 1993;22(6):803–807.
63. Hong S, Lim JH, Jeong IG, Choe J, Kim CS, Hong JH. What association exists between hypertension and simple renal cyst in a screened population? J Hum Hypertens. 2013;27(9):539–544.
64. Eknoyan G. A clinical view of simple and complex renal cysts. J Am Soc Nephrol. 2009;20(9):1874–1876.
65. Elcioglu OC, Afsar B, Takir M, Toprak AE, Bakan A, Bakan S, et al. Renalase: another puzzle piece between hypertension and simple renal cysts? Internatl Urol Nephrol. 2015;47(7):1181–1186.
66. Bryniarski P, Kaletka Z, Zyczkowski M, Prokopowicz G, Muskala B, Paradysz A. Ten-year treatment outcomes including blood cell count disturbances in patients with simple renal cysts. Med Sci Monit. 2013;19:518–523.
67. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66(3):484–488.
68. Eissa A, El Sherbiny A, Martorana E, Pirola GM, Puliatti S, Scialpi M, et al. Non-conservative management of simple renal cysts in adults: a comprehensive review of literature. Minerva Urol Nefrol. 2018;70(2):179–192.
69. Freire M, Remer EM. Clinical and radiologic features of cystic renal masses. AJR Am J Roentgenol. 2009;192(5):1367–1372.
70. Gumeler E, Onur MR, Karaosmanoglu AD, Ozmen M, Akata D, Karcaaltincaba M. Computed tomography and magnetic resonance imaging of peripelvic and periureteric pathologies. Abdom Radiol (NY). 2018;43(9):2400–2411.
71. Kashgari AA, Ozair N, Al Zahrani A, Al Otibi MO, Al Fakeeh K. Renal lymphangiomatosis, a rare differential diagnosis for autosomal recessive polycystic kidney disease in pediatric patients. Radiol Case Rep. 2017;12(1):70–72.
72. Umapathy S, Alavandar E, Renganathan R, Thambidurai S, Kasi Arunachalam V. Renal Lymphangiectasia: an Unusual Mimicker of Cystic Renal Disease - A Case Series and Literature Review. Cureus. 2020;12(10):e10849.
73. Amano Y, Omori Y, Yanagisawa F, Takagi R. Glomerulocystic kidney identified in older patients by magnetic resonance imaging: relation to renal function and renal corticomedullary differentiation. Medicine. 2019;98(17):e15350.
74. Verhave JC, Bech AP, Wetzels JF, Nijenhuis T. Hepatocyte Nuclear Factor 1beta-Associated Kidney Disease: more than Renal Cysts and Diabetes. J Am Soc Nephrol. 2016;27(2):345–353.
75. Ferre S, Igarashi P. New insights into the role of HNF-1beta in kidney (patho)
physiology. Pediatr Nephrol (Berlin, Germany). 2019;34(8):1325–1335.
76. Kurtz I. Renal Tubular Acidosis: H(+)/Base and Ammonia Transport Abnormalities and Clinical Syndromes. Adva Chronic Kidney Dis. 2018;25(4):334–350.

48

Alport Syndrome and Other Familial Glomerular Syndromes

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ALPORT SYNDROME

Definition

Alport syndrome (AS) is an inherited disorder of basement membranes caused by mutations affecting specific proteins of the type IV (basement membrane) collagen family. The major features of AS are hematuria, progressive nephritis with proteinuria and declining kidney function, sensorineural deafness, and ocular abnormalities. Although AS is a rare disease, affecting approximately 1 in 50,000 people, it is the second most common monogenic kidney disorder, after polycystic kidney disease. AS is seen in patients of all ethnicities and nationalities and accounts for approximately 0.5% of adults and 1.7% of children with end-stage kidney disease (ESKD) in the United States.[1]

Etiology and Pathogenesis

Type IV Collagen

Type IV collagen is a major constituent of basement membranes. The type IV collagen family of proteins involves six isomeric chains, designated α1(IV) to α6(IV). Each of these chains has a major collagenous domain of about 1400 residues containing the repetitive triplet sequence glycine (Gly)–X–Y, in which X and Y represent a variety of other amino acids; a C-terminal noncollagenous (NC1) domain of about 230 residues; and a noncollagenous N-terminal sequence of 15 to 20 residues.

Each type IV collagen molecule is a heterotrimer composed of three α chains. Formation of these heterotrimers is initiated by C-terminal NC1 domain interactions, accompanied by folding of the collagenous domains into triple helices. There are at least three types of type IV collagen heterotrimer: α1(IV)2–α2(IV), α3(IV)–α4(IV)–α5(IV), and α5(IV)2–α6(IV). Type IV collagen triple helices form open, nonfibrillar networks that associate with laminin assemblies through interactions mediated by nidogen to form basement membranes.

The six type IV collagen genes are arranged in pairs on three chromosomes (Fig. 48.1). The 5' ends of each gene pair are adjacent to each other, separated by sequences of varying length that contain motifs involved in transcriptional regulation.

In basement membranes there is a ubiquitous network involving the α1(IV) and α2(IV) chains; and other networks, restricted in distribution, composed of α3(IV), α4(IV), and α5(IV) chains, or α5(IV) and α6(IV) chains. Glomerular basement membrane (GBM) contains separate α1–α2(IV) and α3–α4–α5(IV) networks, whereas epidermal basement membranes (EBMs) contain separate networks of α1–α2(IV) chains and α5–α6(IV) chains. The α3α4α5(IV) network is also expressed in Bowman’s capsule and distal tubule in the kidney, alveolar basement membranes, and basement membranes of the testis, eye, and ear.[2] A network of α1, α2, α5, and α6(IV) chains has been described in smooth muscle basement membranes.[2] These various networks likely have different physical and functional characteristics and interact differently with other matrix components and adjacent cells. α1–α2(IV) chains are also found in mesangial matrix.

Genetics

There are three forms of AS: an X-linked form resulting from mutations at the COL4A5 locus, primarily affecting the α5(IV) chain; an autosomal recessive form arising from mutations at the COL4A3 locus or the COL4A4 locus, affecting the α3(IV) and α4(IV) chains, respectively; and an autosomal dominant form from heterozygous mutations in COL4A3 or COL4A4 (Table 48.1). Approximately 80% of AS was previously thought to be inherited in an X-linked manner, with 15% autosomal recessive and 5% autosomal dominant inheritance patterns observed. With the advent of next-generation sequencing (NGS), it is clear that autosomal dominant AS (ADAS) is more common than previously recognized, accounting for approximately 20% to 30% of affected families.3

X-linked Alport syndrome. X-linked AS (XLAS) is the predominant form of the disease. Hundreds of COL4A5 variants have been described, mostly missense mutations, splice-site mutations, and deletions of fewer than 10 base pairs. A common missense mutation involves replacement of a glycine residue in the collagenous domain of the α5(IV) chain by another amino acid. Such mutations are thought to interfere with the normal folding of the α5(IV) chain into triple helices with other α(IV) chains.

In untreated males with COL4A5 mutations, the risk of progression to ESKD is 50% by age 30 years, 80% by 40 years, and nearly 100% by 60 years, and most experience deafness.4 Genotype has a strong correlation with kidney disease progression in males with XLAS. In males with truncating variants (large deletions, nonsense mutations, truncating splicing variants, or a small mutation changing the mRNA reading frame), the risk for developing ESKD before age 30 years is 90%.

Nontruncating splice-site mutations and missense mutations have a less severe renal phenotype with 70% and 50% reaching ESKD by age 30 years, respectively.4,5 Females with XLAS have a wide variability in disease severity, and there is no genotype-phenotype correlation.6 The severity of disease in a female heterozygous for a COL4A5 mutation probably depends primarily on the relative activities of the mutant and normal X chromosomes in renal, cochlear, and ocular tissues because of random X-inactivation.7

Autosomal recessive Alport syndrome. Autosomal recessive AS (ARAS) arises from mutations affecting both alleles of COL4A3 or COL4A4.8 ARAS should be suspected when an individual with typical clinicopathologic features of the disease lacks a family history, especially when a young female has severe disease, such as deafness, nephrotic syndrome, or impaired kidney function. However, sporadic cases of AS may represent de novo mutations at the COL4A5 locus or a germline COL4A5 mutation in the proband’s mother. Most patients with ARAS develop ESKD and deafness before age 30 years, regardless of sex.8

Genomic Organization of Type IV Collagen Genes
COL4A1

COL4A2
Chromosome 13

COL4A3

COL4A4
Chromosome 2

Genomic
organization

COL4A5

COL4A6
Chromosome X

3´

5´

COO−

Type IV
collagen chain

5´

3´
NH2

NC1

230 residues

1400 residues
(interrupted Gly-X-Y)

Type IV
collagen molecule

Fig. 48.1 Genomic Organization of Type IV Collagen Genes. Each type IV collagen chain is synthesized from one of the pairs of type IV collagen genes. Each type IV collagen molecule is a heterotrimer of three type IV collagen chains (See also Fig. 48.4).

TABLE 48.1

Syndrome

Molecular Genetics of Alport

Inheritance

Affected Locus

Gene Product

X-linked Alport syndrome
(XLAS)
X-linked + leiomyomatosis
Autosomal-recessive
Alport syndrome (ARAS)
Autosomal-dominant
Alport syndrome (ADAS)

COL4A5

α5(IV)

COL4A5 + COL4A6
COL4A3
COL4A4
COL4A3
COL4A4

α5(IV) + α6(IV)
α3(IV)
α4(IV)
α3(IV)
α4(IV)

Autosomal dominant Alport syndrome. Heterozygous mutations in COL4A3 or COL4A4 are associated with a spectrum of phenotypes, including isolated microhematuria, chronic kidney disease (CKD) with proteinuria, and ESKD. We prefer to classify all individuals with heterozygous variants in COL4A3 or COL4A4 as having ADAS, including those with hematuria and attenuated GBMs.[9] Patients with progressive ADAS tend to have a slower course to ESKD than those with XLAS or ARAS.[10,11]

COL4A3 and COL4A4 heterozygous variants may also manifest as focal segmental glomerulosclerosis (FSGS) with or without classic AS GBM findings of thinning or thickening with lamellation. This association has been reported frequently since the initial report in 2007.[12–14]

Type IV collagen mutations are among the most common genetic mutations identified in up to 31% of adults with familial FSGS[14] and up to 10% of a cohort of predominantly sporadic FSGS.[15]

Type IV Collagen in Alport Basement Membranes

The GBMs and tubular basement membranes of males with XLAS usually fail to express the α3(IV), α4(IV), and α5(IV) chains but do express the α1(IV) and α2(IV) chains (Fig. 48.2). Females with XLAS frequently exhibit mosaic expression of the α3(IV), α4(IV), and α5(IV) chains in GBM, whereas expression of the α1(IV) and α2(IV) chains is preserved. Most males with XLAS show no EBM expression of α5(IV), whereas female heterozygotes frequently display mosaicism (Fig. 48.3). Lens capsules of some males with XLAS do not express the α3(IV), α4(IV), or α5(IV) chains, whereas expression of these chains appears normal in other patients.

In most patients with ARAS, GBM shows no expression of the α3(IV), α4(IV), or α5(IV) chains, but α5(IV) and α6(IV) are expressed in Bowman’s capsule, distal thin basement membrane (TBM), and EBM (Fig. 48.4). Therefore, XLAS and ARAS may be differentiated by immunohistochemical analysis. Basement membrane expression of type IV collagen α chains appears to be normal in patients with ADAS. These observations indicate that a mutation affecting one of the chains involved in the α3–α4–α5(IV) network can prevent GBM expression not only of that chain but also of the other two chains as well; evidence suggests that this reflects posttranslational events. Some mutant chains are unable to participate in the formation of trimers; as a result, the normal chains that are prevented from forming trimers undergo degradation. Other mutations may allow formation of abnormal trimers that are degraded before deposition in basement membranes can occur (Fig. 48.5). Ultrastructural studies of human AS cochleae suggest that the hearing deficit may be attributable to a defect in adherence of the organ of Corti to the basilar membrane.16 The lens capsules of AS patients with anterior lenticonus exhibit thinning and dehiscence by electron microscopy (EM) indicative of mechanical failure.17

Clinical Manifestations

Kidney Involvement

Hematuria is the cardinal finding of AS. Affected males have persistent microhematuria. Many also have episodic macrohematuria during upper respiratory tract infections, usually during the first two decades of life. Hematuria has been discovered in the first year of life in affected males, in whom it is probably present from birth. Males who are free of hematuria during the first 10 years of life are unlikely to be affected. More than 90% of females with XLAS have persistent or intermittent microhematuria, but about 5% of obligate heterozygotes never manifest hematuria.6 Hematuria is persistent in both males and females with ARAS. About 50% of individuals with heterozygous variants in COL4A3 or COL4A4 mutations have hematuria.

Proteinuria is usually absent early in life but develops eventually in all males with XLAS and in males and females with ARAS. Proteinuria increases progressively with age and may result in nephrotic syndrome.

α3(IV)

α4(IV)

α5(IV)

Normal

XLAS
male

XLAS
female

Fig. 48.2 Immunohistochemistry of Glomerular Basement Membrane (GBM) in X-Linked Alport Syndrome. In a normal individual (top row), GBM stains strongly for the α3(IV), α4(IV), and α5(IV) chains of type IV collagen. Staining of GBM of an affected male is negative for each of these chains (middle row), whereas an affected female shows mosaic immunoreactivity (bottom row).

Proteinuria develops eventually in at least 75% of heterozygous females6 and in an uncertain percentage of individuals with heterozygous variants in COL4A3 or COL4A4. Hypertension also increases in incidence and severity with age and is more likely in affected males than affected females with XLAS, but there are no sex differences in hypertension frequency in ARAS.

ESKD develops in all affected males with XLAS at a rate determined primarily by the nature of the underlying COL4A5 mutation.4 Thus, the rate of progression is fairly constant among affected males within a particular family, but there is significant interkindred variability. Significant intrakindred variability in the rate of progression to ESKD has been reported in some families with missense COL4A5 mutations.

Progression to ESKD in females with XLAS was considered an unusual event until a 2003 European study of several hundred females with XLAS found that 12% developed ESKD before age 40 years (vs. 90% of males with XLAS), increasing to 30% by 60 years and 40% by 80 years.6 A confirmatory European registry study showed a 15% prevalence of ESKD in heterozygous females.18 The risk for ESKD is significantly increased in heterozygotes with proteinuria. The outcome of XLAS in females is presumed to depend on the relative activities of the normal and mutant X chromosomes, but other unknown factors also likely influence outcome.7 Macrohematuria in childhood, nephrotic syndrome, and the finding of diffuse GBM thickening by EM are risk factors for CKD in affected females.19 Sensorineural deafness and anterior lenticonus also suggest an unfavorable outcome in affected females. Both males and females with ARAS appear likely to progress to ESKD during the second or third decade of life.8

Cochlear Defects

Deafness is frequently but not universally associated with the Alport kidney lesion, occurring in about 90% of males and 25% to 30% of females with XLAS.4 6 In some families with Alport nephropathy and apparently normal hearing, deafness may occur late and may be very slowly progressive.

Hearing loss in AS is never congenital and usually becomes apparent by late childhood to early adolescence in males with XLAS and in both males and females with ARAS. Hearing loss is present in 50% of males with XLAS by approximately age 15 years, 75% by 25 years, and

90% by 40 years.4 Hearing loss is less common in females with XLAS, with 10% of XLAS affected by age 40 years and about 20% by 60 years.6 Hearing loss is also common in ARAS with approximately 40% to 66% of individuals affected8 but less common in ADAS with only 2% to 13% affected.10 11 Hearing impairment in members of families with AS is always accompanied by evidence of kidney involvement. In its early stages, the hearing deficit is detectable only by audiometry, typically

Another common ocular manifestation of AS is a maculopathy, with whitish or yellowish flecks or granulations in a perimacular distribution. This is present in 50% to 60% of males with XLAS, in males and females with ARAS, and in approximately 15% of females with XLAS20 (see Fig. 48.6B). In most individuals the maculopathy does not appear to be associated with any visual abnormalities, although giant macular holes causing visual impairment have been reported in some subjects.20a

Corneal endothelial vesicles (posterior polymorphous dystrophy) have been observed in AS and may indicate defects in the Descemet membrane, the basement membrane underlying the corneal endothelium. Recurrent corneal erosion in AS has been attributed to alterations of the corneal EBM.

E

D

A

Leiomyomatosis

The association of AS with leiomyomatosis of the esophagus and tracheobronchial tree has been reported in about 30 families. Affected females typically also have genital leiomyomas, with clitoral hypertrophy and variable involvement of the labia majora and uterus. Bilateral posterior subcapsular cataracts also occur frequently in affected individuals. Symptoms usually appear in late childhood and include dysphagia, postprandial vomiting, retrosternal or epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor. This syndrome typically arises from a contiguous gene deletion on the X chromosome involving exon 1 of COL4A5, the common promoter region that regulates gene expression of COL4A5 and COL4A6, and the first 2 exons of the adjacent COL4A6 gene.21 The genotype-phenotype relationship in this disorder is uncertain because deletions in this region may occur without associated leiomyomas and, conversely, some families with XLAS and leiomyomas do not have deletions involving the common promoter region and COL4A6.22

E

D

B

E

D

C

Fig. 48.3 Immunohistochemistry of Epidermal Basement Membrane (EBM) in X-Linked Alport Syndrome. (A) In a normal male, EBM shows strong staining for α5(IV) at the dermoepidermal junction (arrows) between dermis (D) and epidermis (E). (B) In an affected female, EBM shows mosaic staining (arrow); the white bracket identifies a length of EBM negative for α5(IV). (C) In affected males, staining of EBM (arrows) for α5(IV) is absent.

Hematologic Defects

An autosomal dominant syndrome of hereditary nephritis, deafness, and megathrombocytopenia called Epstein syndrome has been described in a small number of families. Families with Fechtner syndrome exhibit these features and leukocyte inclusions (May-Hegglin anomaly). Both Epstein and Fechtner syndrome arise from mutations in nonmuscle myosin heavy-chain IIA (MYH9) 23 Although in some patients the ultrastructural changes in GBM resemble those of AS, basement membranes of these patients do not have abnormal expression of type IV collagen α chains. Therefore, Epstein and Fechtner syndromes are best considered distinct forms of hereditary nephritis rather than variants of AS.

Arterial Abnormalities

with bilateral reduction in sensitivity to tones in the range of 2000 to 8000 Hz. In affected males, the deficit extends progressively to other frequencies, including those of conversational speech.

Ocular Defects

Ocular defects occur in 30% to 40% of males with XLAS and in about 15% of XLAS females.4 6 Anterior lenticonus, a cone-shaped distortion of the anterior surface of the lens, is virtually pathognomonic of AS, occurs in about 15% of males with XLAS, and is almost entirely restricted to AS families with progression to ESKD before age 30 years and deafness.4 Anterior lenticonus is absent at birth, usually appearing during the second to third decade of life after the onset of CKD and is bilateral in 75% of patients (Fig. 48.6A). The spectrum and frequencies of ocular lesions appear to be similar in XLAS and ARAS.20 Ocular lesions are almost never observed in ADAS.10 11

Aneurysmal dilation of the thoracic and abdominal aorta and smaller arterial vessels has been described in a small number of males with AS.24

Kidney Pathology

There are no pathognomonic lesions on light microscopy (LM) or immunofluorescence (IF) in AS. In affected males, biopsies obtained before 5 years of age typically show no LM changes. Mesangial hypercellularity and matrix expansion are typically observed in older children and adolescents. Glomeruli of affected males eventually show FSGS, and interstitial fibrosis and tubular atrophy are often found in affected males older than 10 years.25 LM findings in affected females correlate with proteinuria and kidney function; an affected female of any age who has isolated microhematuria is likely to have little or no abnormality by LM. Indirect IF of type IV collagen α-chain expression in renal or skin basement membranes can be diagnostic (see earlier discussion).

α3(IV)

α4(IV)

α5(IV)

A

B

Fig. 48.4 Immunohistochemistry of Kidney in a Patient With Autosomal Recessive Alport Syndrome. (A) Normal glomerular basement membrane (GBM) and Bowman's capsule staining for α3(IV), α4(IV), and α5(IV). (B) Patient shows no GBM staining, but α5(IV) is present in Bowman's capsule (arrow) and distal tubular basement membranes (arrowheads).

EM frequently reveals diagnostic abnormalities. In most patients with AS there is variable thickening, thinning, basket weaving, and lamellation of the GBM (Fig. 48.7). The thick segments measure up to 1200 nm in depth, usually have irregular outer and inner contours, and are found more frequently in males than in females. The lamina densa is transformed into a heterogeneous network of membranous strands, which enclose clear electron-lucent areas that may contain round granules of variable density measuring 20 to 90 nm in diameter. There are variable degrees of epithelial foot process fusion.

Not all Alport kindreds demonstrate these characteristic ultrastructural features. Thick, thin, normal, and nonspecifically altered GBMs have all been described. Affected young males, heterozygous females at any age, and, on occasion, affected adult males may have diffusely attenuated GBM measuring as little as 100 nm or less in thickness rather than the pathognomonic lesion. There are a number of families reported with features of hereditary FSGS with or without the classic AS basement membrane lesion associated with mutations in COL4A3 or COL4A4.[13] These findings highlight the utility of detailed genetic evaluation to avoid misdiagnosis.

Diagnosis and Differential Diagnosis

Fig. 48.8 summarizes the evaluation of patients with hematuria and a positive family history. AS should be included in the initial differential diagnosis of patients with persistent microhematuria after excluding structural abnormalities of the kidneys or urinary tract (see Chapter 63). The presence on EM of diffuse thickening and multilamellation of the GBM predicts a progressive nephropathy, regardless of family history. However, in a patient with a negative family history, EM cannot differentiate de novo XLAS from ARAS. In some patients, the biopsy findings may be ambiguous, particularly in females and young patients of either sex. Furthermore, families with progressive nephritis and COL4A5 mutations in association with GBM thinning have been described, indicating that the classic Alport GBM lesion is not present in all Alport kindreds.

If an undiagnosed patient has hematuria and multiple relatives with hematuria, who should undergo kidney biopsy? The natural history of the AS kidney lesion suggests that older, male individuals are more likely to exhibit diagnostic ultrastructural GBM abnormalities. In families with a firm diagnosis of AS established, evaluation of individuals with newly recognized hematuria can be limited to ultrasound of the kidneys and urinary tract to exclude coincidental tumor or structural anomalies of the urinary tract.

Absence of the α3, α4, and α5 chains of type IV collagen from GBM and distal TBM is unique to AS (Table 48.2). Expression of α5(IV) in the EBM detected by IF may be informative, but apparently normal expression of type IV collagen α chains in basement membranes does not exclude the diagnosis of AS. Although mosaic expression of α5(IV) is diagnostic of a heterozygous COL4A5 variant, a normal result does not exclude heterozygosity.

A firm histologic diagnosis of AS cannot always be established, or it may not be possible to determine the mode of transmission, despite careful evaluation of the pedigree and application of the full range of histologic methods. In these situations, genetic analysis by NGS or whole exome sequencing (WES) provides information essential for determining prognosis and guiding genetic counseling. Genetic analysis for AS is widely available in commercial and research laboratories and ideally should be pursued in all patients with suspected or biopsyconfirmed AS to establish the genotype and facilitate cascade testing of at-risk family members.

Genetic analysis using conventional Sanger sequencing identifies 80% to 90% of males with COL4A5 mutations. NGS and WES allow for simultaneous evaluation of COL4A3, COL4A4, and COL4A5.[26] Identification of a specific genotype can provide valuable prognostic information about the risks for kidney disease progression and

Assembly of Type IV Collagen Heterotrimers in Health
and in Alport Syndrome
α3-α4-α5
network

RER
α3

α4

tetramer

α5

dimer

monomer
α3-α4-α5 triple helix (monomer)
Normal

Severe Alport
phenotype
No α3-α4-α5
network
α3

No α3-α4-α5
triple helix

α4

Effect of a “severe” COL4A5 mutation: deletion, frameshift, premature stop

Severe Alport
phenotype
α3

α4

α5

Degradation of
triple helix

Mild(er) Alport
phenotype
Abnormal α3-α4-α5
network

Abnormal α3-α4-α5
triple helix
Effects of a COL4A5 missense mutation
Fig. 48.5 Assembly of type IV collagen heterotrimers in health and in Alport syndrome. RER, Rough endoplasmic reticulum.

CL

BS

A
A

CL

M

B
Fig. 48.7 Kidney Biopsy in Alport Syndrome. (A) Normal glomerular capillary wall. (B) Glomerular capillary wall from a patient with Alport syndrome, at the same magnification. Note the thickening of the glomerular basement membrane (GBM), the splitting of the lamina densa into multiple strands, and the marked irregularity of the epithelial aspect of the GBM in the patient with Alport syndrome. BS, Bowman's space; CL, Capillary lumen.

B
Fig. 48.6 Ocular Abnormalities in Alport Syndrome. (A) Anterior lenticonus shown by slit-lamp ophthalmoscopy. The anterior surface of the lens is cone shaped (arrow marks apex of the cone), rather than the normal smooth ellipse. (B) Perimacular flecks. Note the white flecks surrounding the macula (M). (From Flinter FA. Disorders of the basement membrane: Hereditary nephritis. In: Morgan SH, Grunfeld JP, eds. Inherited Disorders of the Kidney. Oxford University Press; 1998.)

associated hearing loss and eye findings in an individual patient.4 Once a new diagnosis of AS is made, all potentially affected family members including females should be screened for hematuria to identify those who may be at risk for progressive kidney disease, and targeted mutation analysis can be offered to at-risk individuals.27

Natural History

Microhematuria, the first and invariable kidney manifestation of AS, probably reflects GBM thinning with focal ruptures because of defective expression of the α3–α4–α5(IV) network. Proteinuria likely results from altered podocyte interactions with the abnormal GBM, and declining kidney function is attributable to profibrotic processes in glomeruli and in the tubulointerstitial compartment. What factors initiate and drive the progression of Alport nephropathy to ESKD, and how are these factors influenced by COL4 genotype?

Reduction in the quantity of the α3–α4–α5(IV) network in GBM, as likely occurs in subjects with heterozygous variants in COL4A3 or COL4A4, probably has consequences different from complete loss of this network, as occurs in most males with XLAS and most patients with ARAS. The normal transition from the α1(IV)2 α2(IV)1 network of nascent glomeruli to the α3(IV)– α4(IV)– α5(IV) network of mature glomeruli fails to occur in AS, and α1(IV) and α2(IV) chains accumulate in Alport glomeruli as the disease progresses.28 29 Alport GBM also shows overexpression of other matrix proteins normally absent from GBM or present in scant quantities, including type V collagen, type VI collagen, laminin α2 chain, and fibronectin. These alterations in GBM composition are unique to AS.28 30 Both glomerular endothelial cells and podocytes appear to contribute to the accumulation of these proteins in Alport GBM. Recently mesangial filopodial invasion of the GBM with deposition of ectopic laminin chains was proposed as another mechanism of matrix accumulation.31 Alterations in glomerular extracellular matrix are accompanied by changes in glomerular cell behavior, including expression of transforming growth factor β1, integrins, and matrix metalloproteinases. Activation of fibrogenic pathways in the renal interstitium presumably represents a downstream consequence of glomerular disease.

Treatment

Current recommendations for delaying ESKD in patients with AS focus on the early introduction of renin-angiotensin-aldosterone system (RAAS) blockade to suppress urinary protein excretion.27 32 33 The use of RAAS blockade is based on experimental and clinical evidence as well as practical considerations. Angiotensinconverting enzyme (ACE) inhibition lengthens survival in mice with ARAS, doubling survival when begun before the onset of proteinuria. ACE inhibition begun after the onset of proteinuria also improves survival in Alport mice, to a lesser degree. The effect of

Evaluation of Patient with Hematuria and a Positive Family History

No proteinuria
No family history of ESKD

No proteinuria
Family history of ESKD

Proteinuria
Family history of
hematuria and/or ESKD

Audiogram

Yes – if any clinical
suspicion of deafness

Yes

Yes

Ophthalmic
examination

No

May be helpful

May be helpful

Normal
Supports diagnosis
of TBMN

Skin biopsy
with IHC
for a5[IV] chain

Kidney biopsy
with EM
1IHC for a3, a4, and
a5[IV] chains

Molecular genetics

Abnormal
Diagnostic
of XLAS

Often unnecessary

Often unnecessary

Abnormal
Diagnostic
of XLAS

Normal
Does not rule out
XLAS, ARAS, ADAS

Abnormal
Diagnostic
of XLAS

Normal
Does not rule out
XLAS, ARAS, ADAS

Often diagnostic

Often diagnostic

May not be needed if affected relative has biopsy-proven AS

May not be needed if affected relative has biopsy-proven AS

If patient very young, biopsy of older relative may be more informative

If patient very young, biopsy of older relative may be more informative

May be helpful when full clinical and tissue evaluation fails to provide firm diagnosis or identify genetic type of AS

May be helpful when full clinical and tissue evaluation fails to provide firm diagnosis or identify genetic type of AS

Fig. 48.8 Evaluation of patient with hematuria and positive family history. ADAS, Autosomal-dominant Alport syndrome; ARAS, autosomal recessive Alport syndrome; AS, Alport syndrome; EM, electron microscopy; ESKD, end-stage kidney disease; IHC, immunohistochemistry; TBMN, thin basement membrane nephropathy; XLAS, X-linked Alport syndrome.

ramipril on survival was superior to that of candesartan in a murine comparison study.

Uncontrolled clinical studies in AS have shown that RAAS blockade can reduce proteinuria. In a large multicenter, randomized, doubleblind study comparing losartan with placebo or amlodipine in children with AS and proteinuria, there was a significant reduction in proteinuria with losartan over 12 weeks.[34] A 3-year extension of this study showed comparable efficacy of enalapril and losartan in reducing proteinuria.[35] A retrospective review of treated Chinese children with AS similarly showed a decline in proteinuria with ACE inhibition that was sustained over 5 years of follow-up.[36]

Retrospective data from the European Alport Registry indicates that ACE inhibitor therapy initiated while glomerular filtration rate (GFR) is still normal delays ESKD by years.[37] This also has been shown in pairs of affected brothers discordant for ACE inhibitor therapy with a delay in ESKD of a median of 13 years in the earlier treated brother.[37] The beneficial effect of ACE inhibition is observed in males with XLAS because of truncating and nontruncating variants in COL4A5.[5] ACE inhibitors can be used safely in children with CKD at doses that achieve suppression of urinary protein excretion.[38]

RAAS blockers are relatively inexpensive and widely available, so in theory any individual in the world with AS should be able to receive treatment.

Consensus recommendations for the management of AS children include (1) early screening for hematuria in at-risk children, (2) regular determination of urinary protein excretion on diagnosis, and (3) initiation of RAAS blockade once overt proteinuria develops.33 A recent update of these guidelines recommends consideration of treatment at the time of diagnosis in males with XLAS and males and females with ARAS, even if urine albumin levels are normal. A randomized controlled trial (RCT) examining the effect of RAAS blockade on the transitions from isolated hematuria to microalbuminuria to overt proteinuria showed that RAAS blockade delayed these transitions.39 Prospective trials of add-on therapies such as bardoxolone methyl and anti-microRNA-21 are in progress.

Transplantation

Kidney transplantation is typically successful in patients with AS who reach ESKD with graft survival equivalent to that in patients with other diagnoses.40 However, anti-GBM glomerulonephritis involving the kidney allograft is a rare but dramatic manifestation of AS, occurring in 2% to 3% of male patients with AS who undergo transplantation and typically presents in the first year (see Chapter 25).

Are females who are heterozygous for COL4A5 mutations suitable kidney donors? Clearly, those with proteinuria, hypertension, or reduced GFR should not donate, nor should females with hearing

TABLE 48.2

Immunostaining for Type IV Collagen in Alport Syndrome

Group	Type IV Collagen	Glomerular Basement Membrane	Bowman's Capsule	Distal Tubular Basement Membrane	Epidermal Basement Membrane
Normal (Males and Females)	α3(IV)	Present	Present	Present	Absent
	α4(IV)	Present	Present	Present	Absent
	α5(IV)	Present	Present	Present	Present
X-Linked (Males)a	α3(IV)	Absent	Absent	Absent	Absent
	α4(IV)	Absent	Absent	Absent	Absent
	α5(IV)	Absent	Absent	Absent	Absent
X-Linked (Females)b	α3(IV)				
	α4(IV)				

α5(IV)

Mosaic
Mosaic
Mosaic

Autosomal Recessive (Males and Females)[a]
α3(IV)
Absent
α4(IV)
Absent
α5(IV)
Absent

Absent
Absent
Mosaic
Absent
Absent
Present

Absent
Absent
Present

Absent
Absent
Present

[a] In some Alport kindreds, staining of basement membranes for type IV collagen chains is entirely normal. Therefore, a normal result does not exclude a diagnosis of X-linked Alport syndrome.
[b] Some heterozygous females have normal basement membrane immunoreactivity for type IV collagen chains. Therefore, a normal result does not exclude the carrier state.

loss. A case series of heterozygous donors showed new-onset hypertension, proteinuria, and decline in GFR after kidney donation in most females.41 Given the recent finding that 30% to 40% of heterozygous females may eventually develop ESKD, the risk that a heterozygous donor will ultimately develop significant reductions in GFR must be higher than for the usual kidney donor. However, a common clinical scenario is a mother choosing to donate to her son with AS, and the choices of the whole family should be considered.

HEREDITARY ANGIOPATHY WITH NEPHROPATHY, ANEURYSMS, AND CRAMPS (HANAC SYNDROME)

An autosomal dominant hereditary angiopathy associated with nephropathy, aneurysms, and muscle cramps (HANAC syndrome) is caused by missense mutations in the COL4A1 gene that allow for expression of an abnormal α1(IV) chain.42 Findings in affected individuals include microhematuria and macrohematuria, mild reduction in GFR, and kidney cysts. Retinal arteriolar tortuosity and retinal hemorrhage are common in affected individuals, as are intracranial aneurysms and leukoencephalopathy. Some affected individuals have elevated serum creatine kinase and muscle cramps.
Kidney biopsy in affected individuals with hematuria shows no abnormalities of GBM structure or type IV collagen expression. However, basement membranes of Bowman’s capsules, tubules, and interstitial capillaries may exhibit irregular thickening, splitting into multiple layers and focal interruptions.

FABRY DISEASE (ANDERSON-FABRY DISEASE)

Definition

Fabry disease is caused by hereditary deficiency of the enzyme α galactosidase A (α-Gal A), resulting in the intracellular accumulation of neutral glycosphingolipids with terminal α-linked galactosyl moieties (Fig. 48.9). Clinically, this leads to progressive CKD, pain crises,

sweating abnormalities, vascular cutaneous lesions, and cardiac and eye abnormalities.

Etiology and Pathogenesis

More than 1000 mutations causing Fabry disease have been identified in GLA, the gene for α-Gal A, which is located on the X chromosome. Most of the described mutations are associated with the classic Fabry phenotype, in which there is less than 3% α-Gal A activity with multisystem involvement. Certain missense mutations with greater than 3% α-Gal A activity have been identified in patients with a mild phenotype limited to cardiac abnormalities. Prevalence of the classic form is up to 1 in 22,570 males by newborn screening studies and 1 in 1390 males for the males with milder phenotype.43

Glycosphingolipids are normal constituents of the plasma membrane, the membranes of intracellular organelles, and circulate in association with apolipoproteins. The neutral glycosphingolipids that accumulate in Fabry disease are identical to those found in normal tissue. All tissues except red blood cells accumulate globotriaosylceramide (Gb3), with the highest concentrations found in the diseased kidney.

Clinical Manifestations and Pathology

Fabry disease is a multisystem disorder, with prominent and potentially devastating involvement of the kidneys, heart, and peripheral and central nervous systems. As expected for an X-linked disorder, severe clinical manifestations occur in hemizygous males, whereas heterozygous females have a variable but typically less severe course. In affected males, the initial features of the disease are seen in childhood and early adolescence and consist of paresthesias and pain in the hands and feet with episodic pain crises. The course of the disease is variable but usually leads to ESKD in the third to sixth decade. There is risk of premature death because of myocardial or cerebral infarctions. Severe Fabry disease in a female reflects extensive inactivation of the X chromosome carrying the normal α-Gal A allele.44

Kidney Involvement

Nervous System

Although the earliest manifestation of kidney involvement is a urinary concentrating defect, the nephropathy of Fabry disease typically manifests as mild to moderate proteinuria, sometimes with microhematuria, beginning in the third decade, although proteinuria in childhood is reported. Nephrotic syndrome is unusual. Urinary oval fat bodies, with a Maltese cross configuration when viewed with a polarizing microscope, are a result of the large amounts of glycosphingolipid in the urine (see Chapter 4, Fig. 4.2B). Deterioration of GFR is gradual, with hypertension and ESKD developing by the fourth or fifth decade of life. Heterozygous females typically have mild kidney involvement but up to 10% may develop ESKD.

Glomerular visceral epithelial cells are enlarged and packed with small, clear vacuoles that represent glycosphingolipid material (Fig. 48.10). Vacuoles also may be seen in parietal epithelial cells and the epithelial cells of the distal convoluted tubule and loop of Henle, but only rarely in mesangial cells, glomerular endothelial cells, or proximal tubular epithelial cells. There is progressive segmental and global glomerulosclerosis. Vacuoles are also observed in endothelial cells and smooth muscle cells of arterioles and arteries.

On EM, there are abundant inclusions within lysosomes, particularly within visceral epithelial cells (Fig. 48.11). The inclusions (myelin figures) are typically round, involving concentric layers of dense material separated by clear spaces. The layers may be arranged in parallel (zebra bodies). Detachment of visceral epithelial cells from the underlying basement membrane may be observed. Inclusions are also observed in heterozygous females, although usually in smaller numbers than in affected males. Typical inclusions may be noted in excreted renal tubular cells.

The progression of Fabry nephropathy to ESKD probably reflects two parallel processes. Visceral epithelial cell dysfunction, which results in proteinuria, is followed by visceral epithelial cell detachment and necrosis, leading to capillary loop collapse and segmental sclerosis. Simultaneously, progressive impairment of arteriolar flow may develop as enlarging endothelial cells impinge on vascular lumina, resulting in ischemic glomerular damage.

Autonomic dysfunction is a prominent feature of Fabry disease, typically manifested by hypohidrosis, acral paresthesias and pain, and altered intestinal motility. Cerebrovascular symptoms (secondary to narrowing of the vascular lumen from accumulation of glycosphingolipid in vascular endothelial cells) tend to appear during the fourth decade and include hemiparesis, vertigo, diplopia, dysarthria, nystagmus, nausea and vomiting, headache, ataxia, and memory loss. The vertebrobasilar circulation is preferentially involved.

Symptoms are often recurrent. Life-threatening intracerebral hemorrhage and infarction are not unusual. Dementia arising from glycosphingolipid accumulation in small cerebral blood vessels also has been described.

Skin

Angiokeratomas usually appear during the second decade of life and can be the earliest presentation of Fabry disease, presenting as dark-red macules or papules of variable size (Fig. 48.12), originally known as angiokeratoma corporis diffusum. Typical locations include the lower trunk, buttocks, hips, genitalia, and upper thighs. The number of lesions varies from none up to 40 and increase in size and number.45 On histologic examination, angiokeratomas consist of dilated small veins in the upper dermis, covered by hyperkeratotic epidermis. Telangiectasias may be noted, especially behind the ears.

Heart Defects

Glycosphingolipid accumulation in coronary artery endothelial cells and in the myocardium results in coronary artery narrowing, which may lead to angina, myocardial infarction, or congestive heart failure. Left ventricular hypertrophy (LVH) may be an early finding. Arrhythmias resulting from infiltration of the conduction system and valvular lesions also may occur. Certain missense mutations affecting α-Gal A may present as isolated LVH.

A

Ceramide Trihexosidase Pathway
in Fabry Disease
Ceramide

Glucose

Galactose

Galactose

accumulates in
Fabry disease

α-galactosidase A
(missing in Fabry
disease)
Ceramide

Glucose

Galactose

Further metabolism

Fig. 48.9 Ceramide Trihexosidase Pathway in Fabry Disease. α Galactosidase A deficiency leads to tissue accumulation of trihexosylceramide.

B

Fig. 48.10 Light Microscopy of a Kidney Biopsy Specimen in Fabry Disease. Glomerular epithelial cell glycosphingolipid deposition demonstrated by vacuolation on hematoxylin-eosin staining (A; magnification ×20; B, oil red O staining ×20). (Courtesy Dr. Paolo Menè and Dr. Antonella Stoppacciaro, University of Rome.)

Fig. 48.12 Angiokeratoma in Fabry Disease. Note the multiple periumbilical angiokeratomas. (Courtesy Dr. S. Waldek.)

Fig. 48.11 Electron Micrograph of a Kidney Biopsy Specimen in Fabry Disease. Glycosphingolipid is deposited in cytoplasmic vacuoles in glomerular visceral epithelial cells. Inset, Cytoplasmic vacuoles contain electron-dense material in parallel arrays (zebra bodies) and in concentric whorls (myelin figures). (Courtesy Dr. J. Carlos Manivel.)

Eyes

Characteristic corneal opacities are common in both males and females with Fabry disease, present in approximately 75% of affected males and females.46 These lesions, termed verticillata, are identified by slit-lamp examination and are whorls of whitish discoloration that radiate from the center of the cornea. Cataracts (23% of males and 10% of females) and dilated conjunctival or retinal vessels may be observed.46

Lungs

Dyspnea and cough are common in males with Fabry disease, often with obstructive features on spirometry. This may be a consequence of fixed narrowing of the airways caused by glycosphingolipid accumulation.

Diagnosis

Diagnosis of affected males usually can be made clinically, with the additional information from slit-lamp eye examination to identify corneal opacities. The diagnosis should be confirmed by demonstrating decreased (<25%) or absent α-Gal A activity in serum, leukocytes, cultured skin fibroblasts, or tissue. Atypical variants may have enzyme activity up to 35% of normal. Heterozygous females may have very low (<25%) α-Gal A activity similar to that in males or may have more normal levels, making measurement of enzyme activity an insensitive way of diagnosing carriers. If enzyme levels are equivocal, alternative approaches to diagnosis include careful slit-lamp eye examination, measurement of urinary ceramide digalactoside and trihexoside, kidney biopsy, and genetic testing. Genetic testing for Fabry disease is widely available. Identification of carriers is particularly relevant when family members are being considered as living kidney donors.

Fabry disease should be considered in patients with unexplained ESKD, especially if LVH is present or there is a history of stroke or nondiabetic paresthesia. Fabry disease accounts for 0.1% to 0.2% of patients on hemodialysis and 0.9% of patients with hypertensive LVH.47

Treatment

The introduction of enzyme replacement therapy with recombinant human α-Gal A (agalsidase) has transformed the treatment of Fabry disease. RCTs showed that agalsidase administration for 5 to 6 months resulted in reduced plasma and urine Gb3; amelioration of neuropathic pain; enhanced quality of life; clearing of Gb3 deposits from kidney, heart, and skin; and improved cerebral blood flow.48 Treatment of classic Fabry disease patients with agalsidase-β with baseline proteinuria of less than 1 g/day had stabilization of GFR over 5 years of follow-up. Addition of RAS blockade to enzyme replacement can result in sustained reductions in proteinuria. In patients with ESKD, agalsidase may be infused during hemodialysis because there is little clearance of the enzyme by hemodialysis. Agalsidase therapy has been recommended for all affected males and symptomatic carrier females, but the drug is prohibitively expensive in many parts of the world.49-51An alternative treatment approach based on chemical “chaperones” is under investigation; however, a recent study did not show a significant treatment effect.

Kidney transplantation is an effective treatment for advanced

Fabry nephropathy but does not ameliorate the extrarenal manifestations. Transplanted kidneys from deceased donors or unaffected living donors may develop glycosphingolipid inclusions, but this usually is not clinically significant. Fabry heterozygotes should not become kidney donors. Coronary artery and cerebrovascular disease are the major causes of mortality in patients with Fabry disease who have undergone kidney transplantation. Kidney allograft recipients with Fabry disease are candidates for agalsidase treatment.

Fabry Disease in Childhood

Often it is not appreciated that the signs and symptoms of Fabry disease typically begin in childhood, particularly pain crises, acroparesthesias, angiokeratomas, and corneal opacities, and thus the diagnosis is frequently delayed until adulthood.50 Accumulation of Gb3 in podocytes has been identified in children before onset of proteinuria; however, current recommendations do not support initiation of enzyme replacement therapy for asymptomatic children unless over age 16 years.49 Symptomatic children with Fabry disease are potential candidates for agalsidase therapy.50

NAIL-PATELLA SYNDROME

Definition

Nail-patella syndrome (NPS) is an uncommon autosomal dominant condition characterized by hypoplasia or absence of the patellae, dystrophic nails, dysplasia of the elbows and iliac horns, and kidney disease.

Etiology and Pathogenesis

NPS is caused by mutations in the LIM homeodomain transcription factor LMX1B, including missense, splicing, insertion or deletion, and nonsense alterations. In vitro studies of the transcriptional effects of mixing wild-type and mutant LMX1B suggest that NPS results from haploinsufficiency of LMX1B, rather than a dominantnegative effect. LMX1B is essential for the maintenance of differentiated podocytes in adult kidneys through effects on actin cytoskeletal organization.

Clinical Manifestations

Kidney Involvement

Clinically apparent kidney disease occurs in fewer than half of NPS patients. The nephropathy is usually benign, with an approximately 3% to 5% risk for progression to ESKD.52 53 The clinical signs of NPS nephropathy appear in adolescence or young adulthood and typically include microhematuria and mild proteinuria, although some patients develop nephrotic syndrome and mild hypertension. The severity of these manifestations may differ substantially in related individuals.

A

Skeletal Defects

The patellae are absent or hypoplastic in more than 90% of patients with NPS, which may be associated with knee joint effusions and osteoarthritis (Fig. 48.13).52 53 In about 80% of patients, osseous processes project posteriorly from the iliac wings (iliac horns), which is pathognomonic (Fig. 48.14). Anomalies of the elbows include aplasia, hypoplasia, and posterior processes at the distal end of the humeri.

Nails

Nail abnormalities occur in about 98% of patients and are typically bilateral and symmetric. Fingernails are affected more often than toenails. The nails may be absent or dystrophic with discoloration, koilonychia, longitudinal ridges, or triangular lunulae.52

Kidney pathology

LM findings in NPS are nonspecific and may demonstrate FSGS, mild mesangial hypercellularity, or no changes, in which case EM is required to make the diagnosis. EM shows multiple irregular lucencies of the GBM, giving it a moth-eaten appearance (Fig. 48.15). Such lucencies also may be observed in the mesangium. These lucent areas sometimes contain cross-banded collagen fibrils, which are more easily observed after staining with phosphotungstic acid (Fig. 48.16). The fibrils, which are type III collagen, tend to be arranged in clusters, and the surrounding GBM is often thickened. This may be observed without clinically evident kidney disease, but fibrils have not been found in extraglomerular basement membranes. Cross-banded fibrils of type III collagen have been seen in GBM of patients with glomerular disease who lack nail or skeletal abnormalities, sometimes as a familial condition with autosomal recessive inheritance (collagen III glomerulopathy; see Chapter 29). It is unclear whether there is a pathogenic relationship between collagen type III glomerulopathy and NPS.

Treatment

No specific therapy is available for the nephropathy of NPS. There has been no reported recurrence in transplanted kidneys. Because NPS is an autosomal dominant disorder, careful evaluation of potential living related kidney donors for features of NPS is essential.

B

US

Fig. 48.13 Nail-patella Syndrome. Clinical (A) and radiologic (B) appearance of absence of the patellae. (Courtesy Dr. R. Vernier.)

GBM

CL

Fig. 48.14 Nail-Patella Syndrome. Arrowheads denote iliac horns. ((Courtesy Dr. R. Vernier.))

Fig. 48.15 Electron Micrograph of Kidney Biopsy Specimen in Nail-Patella Syndrome. The glomerular basement membrane (GBM) appears moth-eaten on routine staining. CL, Capillary lumen; US, urinary space. (Courtesy Dr. R. Vernier.)

Fig. 48.16 Electron Micrograph of Kidney Biopsy Specimen in Nail-Patella Syndrome. Black arrows show margins of irregular glomerular basement membrane. Staining with phosphotungstic acid reveals fibrillar collagen (white arrows). US, Urinary space.

SELF-ASSESSMENT QUESTIONS

1. A 15-year-old boy has AS. What statement about his parents is most likely to be true?
A. His father has AS.
B. His mother has AS.
C. Both parents are carriers of AS.
D. Neither parent has AS.
E. None of the above.

2. Which of the following ocular abnormalities have been described in patients with AS?
A. Anterior lenticonus
B. Recurrent corneal erosions
C. Perimacular flecks
D. Posterior polymorphous dystrophy
E. All of the above

3. Which one of the following statements about hearing loss in AS is true?
A. AS may be picked up by neonatal hearing screening.
B. In males with AS, hearing loss is usually undetectable by audiometry until adulthood.
C. Hearing loss in AS initially targets high frequencies above the range of conversational speech.
D. The hearing loss of AS is conductive.
E. Hearing loss in AS is typically unilateral.

REFERENCES

1. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2016;67(Svii):S1–305.
2. Khoshnoodi J, Pedchenko V, Hudson BG. Mammalian collagen IV. Microsc Res Tech. 2008;71:357–370.
3. Fallerini C, Dosa L, Tita R, et al. Unbiased next generation sequencing analysis confirms the existence of autosomal dominant Alport syndrome in a relevant fraction of cases. Clin Genet. 2014;86:252–257.
4. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history in 195 families and genotype- phenotype correlations in males. J Am Soc Nephrol. 2000;11:649–657.
5. Yamamura T, Horinouchi T, Nagano C, et al. Genotype-phenotype correlation and the influence of the genotype on response to angiotensintargeting drugs in Japanese patients with male X-linked Alport syndrome. Kidney Int. 2020.
6. Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a “European Community Alport Syndrome Concerted Action” study. J Am Soc Nephrol. 2003;14:2603–2610.
7. Rheault MN, Kren SM, Hartich LA, et al. X-inactivation modifies disease severity in female carriers of murine X-linked Alport syndrome. Nephrol Dial Transplant. 2010;25:764–769.
8. Storey H, Savige J, Sivakumar V, Abbs S, Flinter FA. COL4A3/COL4A4 mutations and features in individuals with autosomal recessive alport syndrome. J Am Soc Nephrol. 2013.
9. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV alpha345: a position paper of the Alport Syndrome Classification Working Group. Kidney Int. 2018;93:1045–1051.
10. Kamiyoshi N, Nozu K, Fu XJ, et al. Genetic, clinical, and pathologic backgrounds of patients with autosomal dominant alport syndrome. Clin J Am Soc Nephrol. 2016;11:1441–1449.
11. Marcocci E, Uliana V, Bruttini M, et al. Autosomal dominant Alport syndrome: molecular analysis of the COL4A4 gene and clinical outcome. Nephrol Dial Transplant. 2009;24:1464–1471.
12. Voskarides K, Damianou L, Neocleous V, et al. COL4A3/COL4A4 mutations producing focal segmental glomerulosclerosis and renal failure in thin basement membrane nephropathy. J Am Soc Nephrol. 2007;18:3004–3016.
13. Malone AF, Phelan PJ, Hall G, et al. Rare hereditary COL4A3/COL4A4 variants may be mistaken for familial focal segmental glomerulosclerosis. Kidney Int. 2014;86:1253–1259.
14. Gast C, Pengelly RJ, Lyon M, et al. Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2016;31:961–970.
15. Yao T, Udwan K, John R, et al. Integration of genetic testing and pathology for the diagnosis of adults with FSGS. Clin J Am Soc Nephrol. 2019;14:213–223.
16. Merchant SN, Burgess BJ, Adams JC, et al. Temporal bone histopathology in alport syndrome. Laryngoscope. 2004;114:1609–1618.
17. Streeten BW, Robinson MR, Wallace R, Jones DB. Lens capsule abnormalities in Alport’s syndrome. Arch Ophthalmol. 1987;105:1693–1697.
18. Temme J, Peters F, Lange K, et al. Incidence of renal failure and nephroprotection by RAAS inhibition in heterozygous carriers of Xchromosomal and autosomal recessive Alport mutations. Kidney Int. 2012;81:779–783.
19. Grunfeld JP, Noel LH, Hafez S, Droz D. Renal prognosis in women with hereditary nephritis. Clin Nephrol. 1985;23:267–271.
20. Savige J, Sheth S, Leys A, Nicholson A, Mack HG, Colville D. Ocular features in Alport syndrome: pathogenesis and clinical significance. Clin J Am Soc Nephrol. 2015;10:703–709.
20a. Savige J, Sheth S, Leys A, Nicholson A, Mack HG, Colville D. Ocular

features in Alport syndrome: pathogenesis and significance. Clin J Am Soc Nephrol. 2015;10(4):703–709.

21. Zhou J, Mochizuki T, Smeets H, et al. Deletion of the paired alpha 5(IV) and alpha 6(IV) collagen genes in inherited smooth muscle tumors. Science. 1993;261:1167–1169.
22. Sa MJ, Fieremans N, de Brouwer AP, et al. Deletion of the 5'exons of COL4A6 is not needed for the development of diffuse leiomyomatosis in patients with Alport syndrome. J Med Genet. 2013;50:745–753.
23. Heath KE, Campos-Barros A, Toren A, et al. Nonmuscle myosin heavy chain IIA mutations define a spectrum of autosomal dominant macrothrombocytopenias: May-Hegglin anomaly and Fechtner, Sebastian, Epstein, and Alport-like syndromes. Am J Hum Genet. 2001;69:1033–1045.
24. Kashtan CE, Segal Y, Flinter F, Makanjuola D, Gan JS, Watnick T. Aortic abnormalities in males with Alport syndrome. Nephrol Dial Transplant. 2010;25:3554–3560.
25. Kashtan CE, Gubler MC, Sisson-Ross S, Mauer M. Chronology of renal scarring in males with Alport syndrome. Pediatr Nephrol. 1998;12:269–274.
26. Kovacs G, Kalmar T, Endreffy E, et al. Efficient targeted next generation sequencing-based workflow for differential diagnosis of alport-related disorders. PLoS One. 2016;11:e0149241.
27. Savige J, Gregory M, Gross O, Kashtan C, Ding J, Flinter F. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. J Am Soc Nephrol. 2013;24:364–375.
28. Kashtan CE, Kim Y. Distribution of the alpha 1 and alpha 2 chains of collagen IV and of collagens V and VI in Alport syndrome. Kidney Int. 1992;42:115–126.
29. Kalluri R, Shield CF, Todd P, Hudson BG, Neilson EG. Isoform switching of type IV collagen is developmentally arrested in X-linked Alport syndrome leading to increased susceptibility of renal basement membranes to endoproteolysis. J Clin Invest. 1997;99:2470–2478.
30. Kashtan CE, Kim Y, Lees GE, Thorner PS, Virtanen I, Miner JH. Abnormal glomerular basement membrane laminins in murine, canine, and human Alport syndrome: aberrant laminin alpha2 deposition is species independent. J Am Soc Nephrol. 2001;12:252–260.
31. Dufek B, Meehan DT, Delimont D, et al. Endothelin A receptor activation on mesangial cells initiates Alport glomerular disease. Kidney Int. 2016;90:300–310.
32. Kashtan CE, Gross O. Clinical practice recommendations for the dia gnosis and management of Alport syndrome in children, adolescents, and young adults-an update for 2020. Pediatr Nephrol. 2020;36(3):711–719.
33. Kashtan CE, Ding J, Gregory M, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. Pediatr Nephrol. 2013;28:5–11.
34. Webb NJ, Lam C, Shahinfar S, et al. Efficacy and safety of losartan in children with Alport syndrome-results from a subgroup analysis of a prospective, randomized, placebo- or amlodipine-controlled trial. Nephrol Dial Transplant. 2011;26:2521–2526.
35. Webb NJ, Shahinfar S, Wells TG, et al. Losartan and enalapril are comparable in reducing proteinuria in children with Alport syndrome. Pediatr Nephrol. 2013;28:737–743.
36. Zhang Y, Wang F, Ding J, et al. Long-term treatment by ACE inhibitors and angiotensin receptor blockers in children with Alport syndrome. Pediatr Nephrol. 2016;31:67–72.
37. Gross O, Licht C, Anders HJ, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int. 2012;81:494–501.
38. Wuhl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361:1639–1650.
39. Gross O, Tonshoff B, Weber LT, et al. A multicenter, randomized,

placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport’s syndrome. Kidney Int. 2020.

40. Temme J, Kramer A, Jager KJ, et al. Outcomes of male patients with Alport syndrome undergoing renal replacement therapy. Clin J Am Soc Nephrol. 2012;7:1969–1976.

References

41. Gross O, Weber M, Fries JW, Muller GA. Living donor kidney transplantation from relatives with mild urinary abnormalities in Alport syndrome: long-term risk, benefit and outcome. Nephrol Dial Transplant. 2009;24:1626–1630.
42. Plaisier E, Gribouval O, Alamowitch S, et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med. 2007;357:2687–2695.
43. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S. Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015;39:206–216.
44. Echevarria L, Benistan K, Toussaint A, et al. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89:44–54.
45. Orteu CH, Jansen T, Lidove O, et al. Fabry disease and the skin: data from FOS, the Fabry outcome survey. Br J Dermatol. 2007;157:331–337.
46. Sodi A, Ioannidis AS, Mehta A, Davey C, Beck M, Pitz S. Ocular manifestations of Fabry’s disease: data from the Fabry Outcome Survey. Br J Ophthalmol. 2007;91:210–214.
47. Terryn W, Deschoenmakere G, De Keyser J, et al. Prevalence of Fabry disease in a predominantly hypertensive population with left ventricular hypertrophy. Int J Cardiol. 2013;167:2555–2560.

48. Schiffmann R, Kopp JB, Austin 3rd HA, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285:2743–2749.
49. Biegstraaten M, Arngrimsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015;10:36.
50. Hopkin RJ, Jefferies JL, Laney DA, et al. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016;117:104–113.
51. Schiffmann R, Hughes DA, Linthorst GE, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney Int. 2017;91:284–293.
52. Ghoumid J, Petit F, Holder-Espinasse M, et al. Nail-Patella Syndrome: clinical and molecular data in 55 families raising the hypothesis of a genetic heterogeneity. Eur J Hum Genet. 2016;24:44–50.
53. Sweeney E, Fryer A, Mountford R, Green A, McIntosh I. Nail patella syndrome: a review of the phenotype aided by developmental biology. J Med Genet. 2003;40:153–162.

49

Inherited Disorders of Sodium and Water Handling

Detlef Bockenhauer

INTRODUCTION

Glomerular filtration yields about 150 L of water and 21,000 mmol of sodium (Na) in a healthy individual in 24 hours, yet only minute fractions of these quantities are excreted eventually in the urine. The precise amount excreted is tightly regulated to maintain homeostasis. A large number of different tubular transporters are involved in this homoeostatic process and either directly or indirectly dependent on the electrochemical gradient generated by the Na+,K+-ATPase. In this way, Na reabsorption is central not only for volume but also for acid-base and electrolyte homeostasis. This molecular integration of homeostatic processes is reflected in the clinical picture: whereas disorders of water transport primarily cause a disturbance of serum Na concentration, disorders of Na transport generate clinical signs and symptoms related to blood pressure (BP), electrolytes, and acid-base disturbances, which help establish the diagnosis.

PHYSIOLOGY OF SODIUM AND WATER REABSORPTION

Sodium Transporters and the Corresponding Inherited Disorders

In all tubular epithelial cells, a basolateral energy-requiring Na+,K+ATPase will ensure that intracellular Na is kept at low levels, whereas K is high. Coupled with apical K channels, which use the concentration gradient to establish a lumen-positive electrical potential, an electrochemical gradient for Na is created across the apical cell membrane, which drives Na uptake from the tubular lumen into the cell via dedicated transporters and channels.

Based on anatomic and molecular characteristics, the tubule is typically divided in four functional segments: the proximal tubule (PT), the loop of Henle and for sodium handling specifically the thick ascending limb (TAL), the distal convoluted tubule (DCT), and the collecting duct (CD). Each of these segments has specific apical Na transporters or channels (Fig. 49.1). Transport across the basolateral membrane to complete Na reabsorption is facilitated by the Na+,K+-ATPase in all segments. Na transport in these segments is inhibited by specific diuretics, which can help understand inherited disorders of Na transport by comparing them to the effects of the corresponding diuretic.

In the PT, an apical Na-hydrogen (H) exchange protein (NHE3) facilitates most of the Na reabsorption. Because of this connection with H excretion (and thus acid-base homeostasis), this transport process is indirectly blocked by carbonic anhydrase inhibitors, such as acetazolamide. So far, no inherited disorder of isolated Na in the PT has been reported. Instead, impaired reabsorption in the PT typically occurs with a general proximal dysfunction, which underlies the renal Fanconi syndrome (Chapters 13 and 50).

In the TAL, the Na+-K+-2Cl− cotransporter (NKCC2) can be blocked by loop diuretics, such as furosemide and bumetanide. The corresponding inherited disorder is Bartter syndrome, where the function of this transporter is either directly or indirectly impaired. Thus, Bartter syndrome can be conceptualized as “inherited furosemide use.”

In the DCT Na is reabsorbed by the Na-Cl cotransporter (NCCT), which is inhibited by thiazides. Disorders involving this transporter include Gitelman syndrome, caused by inherited loss-of-function of this transporter. Gitelman syndrome can therefore be conceptualized as “inherited thiazide use.” The mirror image of Gitelman syndrome is pseudohypoaldosteronism type 2 (PHA2) or Gordon syndrome. The underlying genetic causes lead to an overactivity of NCCT.

In the CD, Na reabsorption is facilitated by the epithelial sodium channel (ENaC). Amiloride and triamterene specifically block ENaC. Several inherited disorders affect transport through this channel. Inherited loss-of-function of ENaC is called pseudohypoaldosteronism type 1 and is autosomal recessive, whereas gain-of-function underlies Liddle syndrome. Because ENaC is highly regulated by the mineralocorticoid receptor (MR), several other disorders affect ENaC function through dysregulation of the MR. These and other disorders are discussed in detail later and listed in Table 49.1.

Water Reabsorption

In the PT, water follows sodium chloride (NaCl) passively through aquaporins, the constitutively open water transport proteins in apical and basolateral tubular cell membranes. In this way Na transport is directly linked to unregulated water reabsorption. The TAL and the CD are the 2 segments critical for regulated water reabsorption. The TAL is water impermeable and thus also called the diluting segment, as salt transport via NKCC2 dilutes the tubular fluid. This also helps establish the interstitial concentration gradient, which drives water reabsorption in the arginine-vasopressin (AVP)-sensitive parts of the nephron, the late DCT and CD. In this way, sodium transport is also linked to regulated water reabsorption. Consequently, patients with Bartter syndrome have impaired urinary concentrating ability, which helps explain the polyuria associated with this disorder.

Final control over water reabsorption is exerted in the CD and regulated by AVP. In the absence of this hormone, the apical membrane of the epithelial cells in CD are water impermeable, resulting in water diuresis. Binding of AVP to the AVPR2 receptor in the CD initiates a signaling cascade that results in the insertion of the water channel aquaporin 2 (AQP2) into the apical membrane, allowing water to pass through the epithelial cell layer, following the interstitial concentration gradient, resulting in antidiuresis. Inherited disorders affecting the function of AVPR2 or AQP2 cause either nephrogenic diabetes insipidus (NDI) through loss-of-function or nephrogenic syndrome of inappropriate antidiuresis (NSIAD) through gain-of-function.

Molecular Basis of Salt Handling Along the Nephron
Proximal tubule cell
Lumen

Distal convoluted tubule cell

Blood

Na

+

ATP

3Na +

Na ,K
ATPase
+

Glucose
Phosphate

+

2K+

Na +
H+
NHE3

Na +

Lumen
Renal
Fanconi
syndrome

Na +
Cl

NCCT

Cl

ATP
Na + ,K+
ATPase
CLCNKB
Barttin

Ca2+

K

ATP
Na + ,K+
ATPase

*SPAK/

ClC-Kb

Blood
Na +

K+
Cl

OSR1 P

Bartter
syndrome
NKCC2
ROMK
CICNKB
Barttin

WNK1
WNK4

Ub

ENaC

*

H+

Blood
NKCC2

ATP

Na + ,K+
ATPase
KCNJ1
CLCNKB
Lumen (+) (–)
Barttin
2+
Ca
2+
Mg
K+

3Na +
2K+
Cl

Cl
KCNJ10

K+
H2O

Blood
3Na +
2K+
Cl

ATP
HCO3

ENaC
Na +
Lumen (–)
potential
K+

ATP

ATP

K+

Thick ascending limb cell
Lumen
Na +
K+
2Cl

2K+

Collecting duct intercalated cell

Lumen

H+

CUL3
KLHL3

3Na +

Liddle
syndrome
PHA1

*

*

Blood

NCC

+

NCC
P

Na +

3HCO3

Renal epithelial cell
Lumen

Gitelman
syndrome

Na +

ATP
Na + ,K+
ATPase

KCNJ1
Maxi-K+
Aquaporin

Cl
Collecting duct principal cell

Fig. 49.1 Overview of the Molecular Basis of Salt Handling Along the Nephron in the Four Main Functional Subunits of the Tubule. Note that Na+,K+-ATPase is expressed on the basolateral aspect of the epithelial cells along the entire nephron, establishing the electrochemical gradient for Na reabsorption and providing an exit pathway for Na. In contrast, on the apical side, segment-specific transporters and channels provide the entry pathway for Na into the epithelial cells. Salt transport in the proximal tubule: The majority of filtered salt (roughly 70%–80%) is reabsorbed here through a variety of transporters. The electrochemical gradient for Na is used as driver for a number of transport processes, thereby linking Na reabsorption to acid-base and phosphate homeostasis, as well as glucose and other substrate transport. Salt transport in the thick ascending limb (TAL) of the loop of Henle: Approximately 10% to 20% of filtered Na is reabsorbed in this segment with the furosemide-sensitive Na +-K+-2Cl− (NKCC2, variants of which cause Bartter syndrome type 1) cotransporter providing entry into the epithelial cell. Apical K recycling through the KCNJ1 (ROMK) channel (the cause of Bartter syndrome type 2) ensures the efficient functioning of NKCC2 and helps establish a lumen-positive transepithelial voltage that drives paracellular cation reabsorption. Chloride exits the cell through basolateral Cl channels, predominantly CLCNKB (the cause of Bartter syndrome type 3). The β subunit (Barttin, cause of Bartter syndrome type 4) is crucial for normal functioning of CLCNKB. Salt transport in the distal convoluted tubule (DCT): Approximately 5% to 10% of filtered Na is reabsorbed in this segment via the thiazide-sensitive Na-Cl-cotransporter (NCCT, the cause of Gitelman syndrome) on the apical side. Note the presence of the same chloride channel (CLCNKB) on the basolateral side as in TAL. This explains why pathogenic variants in this channel cause Bartter syndrome type 3 (a disorder of TAL) but can phenocopy Gitelman syndrome (a disorder of DCT). Salt transport in a principal cell of the collecting tubule: Approximately 2% to 5% of filtered Na is reabsorbed in this segment via the amiloride-sensitive epithelial sodium Na channel (ENaC). Loss-of-function variants in this channel cause pseudohypoaldosteronism type 1 (PHA1), whereas gain-of-function causes Liddle syndrome. Na uptake is indirectly coupled to K (through ROMK) and proton secretion through the H+-ATPase in the neighboring intercalated cell. Aldosterone activates the mineralocorticoid receptor, which increases the activity of ENaC and Na +,K+-ATPase, which increases Na reabsorption and K and proton secretion, resulting in hypokalemic alkalosis. Cortisol is also a ligand for the mineralocorticoid receptor but is normally removed by oxidation by 11β-hydroxysteroid dehydrogenase to cortisone. ATP, Adenosine triphosphate; WNK, with-no-lysine kinase. (From Hoenig MP, Zeidel ML. Homeostasis, the milieu interieur, and the wisdom of the nephron. Clin J Am Soc Nephrol. 2014;[9]:1272–1281.)

3Na +
2K+

TABLE 49.1

Inherited Disorders of Tubular Sodium and Water Handling

	Inheritance	Gene	Protein	OMIM
Thick Ascending Limb				
Bartter type 1	AR	SLC12A1	NKCC2	#600839
Bartter type 2	AR	KCNJ1	ROMK	#600359
Bartter type 3	AR	CLCNKB	CLC-Kb	#602023
Bartter type 4a	AR	BSND	Barttin	#606412
Bartter type 4b	Digenic	CLCNKA+CLCNKB	CLC-Ka+CLC-Kb	#602024
Bartter type 5	XR	MAGED2	MAGED2	#601199
Autosomal dominant hypocalcemia	AD	CaSR	Calcium-sensing receptor	#601198

Distal Convoluted Tubule
Gitelman syndrome
EAST/SeSAME syndrome
PHA type 2b
PHA type 2c
PHA type 2d
PHA type 2e

AR
AR
AD
AD
AD/AR
AD

SLC12A3
KCNJ10
WNK4
WNK1
KLHL3
CUL3

NCCT
Kir4.1
WNK4
WNK1
KLHL3
CUL3

#600968
#602028
#601844
#605232
#614495
#614496

Collecting Duct
PHA type 1
PHA type 1
PHA type 1
PHA type 1A
Liddle syndrome
Liddle syndrome
AME
GRA
NDI
NDI
NSIAD
NSIAD

AR
AR
AR
AD
AD
AD
AR
AD
XLR
AR/AD
XLR
AD

SCNN1A
SCNN1B
SCNN1G
NR3C2
SCNN1B
SCNN1G
HSD11B2
CYP11B1/CYP11B2
AVPR2

AQP2
AVPR2
GNAS

ENaC α subunit
ENaC β subunit
ENaC γ subunit
MR
ENaC β subunit
ENaC γ subunit
11-β-HSD2
11-β-hydroxylase
AVPR2
AQP-2
V2R
G-α s

#600228
#600760
#600761
#600983
#600760
#600761
#614232
#610613
#300538
#107777
#300538

AD, Autosomal dominant; AME, apparent mineralocorticoid excess; AR, autosomal recessive; AVP, arginine vasopressin; GRA, glucocorticoid remediable aldosteronism; NDI, nephrogenic diabetes insipidus; NSIAD, nephrogenic syndrome of inappropriate antidiuresis; PHA, pseudohypoaldosteronism.

DISORDERS OF SODIUM HANDLING

Based on the clinical and biochemical phenotype, five main categories can be distinguished. Algorithms to help establish the individual diagnoses are shown in Figs. 49.2 and 49.3:

1. Hypokalemic acidosis with low-normal BP (renal Fanconi syndrome and distal renal tubular acidosis, discussed in Chapters 13 and 50)
2. Hypokalemic alkalosis and low-normal BP (Bartter syndrome, Gitelman syndrome, EAST syndrome)
3. Hypokalemic alkalosis and high BP (Liddle syndrome, apparent mineralocorticoid excess [AME], glucocorticoid-remediable hyperaldosteronism [GRA], adrenal 17α-hydroxylase deficiency, adrenal 11β-hydroxylase deficiency, Cushing disease)
4. Hyperkalemic acidosis and low-normal BP (pseudohypoaldosteronism type 1, adrenal 21-hydroxylase deficiency, adrenal aldosterone synthase deficiency)
5. Hyperkalemic acidosis and high BP (Gordon syndrome)

Some of the disorders are caused by mutated renal transport proteins (e.g., Gitelman syndrome) or associated regulatory proteins (e.g., Gordon syndrome). In others, the genetic defect resides in the adrenals, and the changes in adrenal mineralocorticoids and glucocorticoids create the renal phenotype. All the inherited disorders discussed here are rare, with estimated incidences typically around 1:100,000.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND LOW-NORMAL BP

Bartter Syndrome

Bartter syndrome is a genetically heterogeneous disorder of salt reabsorption in the TAL.1

Pathogenesis

Currently, four causative genes have been associated with Bartter syndrome: SLC12A1 (encoding NKCC2) for Bartter syndrome type 1; KCNJ1 (encoding KCNJ1, also called ROMK) for type 2; CLCKNB (encoding CLCK-B), type 3; and BSND (encoding Barttin), type 4 (Table 49.1; see also Fig. 49.1). In addition, another disorder called familial hypocalcemic hypercalciuria, caused by activating mutations in CaSR, encoding the calcium-sensing receptor, can cause Bartter-like electrolyte abnormalities and is thus sometimes referred to as Bartter type 5.[2] Although all the genetic defects directly or indirectly impair salt reabsorption through NKCC2, there are differences between the various forms of Bartter syndrome that typically allow correct classification on clinical grounds (see Fig. 49.2). An important first discriminator is the urine calcium excretion. The TAL is an important segment for calcium reabsorption, which occurs passively through paracellular pathways, lined by claudins, which provide transport specificity.[3] The driving force for this is generated by the combined action of NKCC2

Hypokalemic Alkalosis
Clinical examination:
Volume status, BP
Biochemistry
Serum: Na, K, Cl, HCO3, Ca,
Mg, PO4, albumin, urea,
creatinine, osmolality,
renin, aldosterone
Blood: DNA for genetic tests
Urine: Na, K, Cl, Mg, Ca,
creatinine, osmolality

Hypertension,
hypervolemia,
evidence of salt
retention

Renin, aldosterone
suppressed
Liddle syndrome
Cushing syndrome
AME, GRA

Renin, aldosterone
elevated
Conn syndrome

Amiloride
Cortisol (for GRA)

Amiloride
Evaluation for
surgery

Low normal BP
Eu- or hypovolemia
Evidence of salt
wasting

FECl <0.5%
Likely extrarenal
salt losses: Assess
enteric and or
sweat losses

FECl ≥0.5%
Renal salt losses

Hypercalciuria
Bartter syndrome

Hypocalciuria and
hypomagnesemia
Gitelman syndrome

Salt
supplementation
Consider COX
inhibitor

Salt
supplementation

Fig. 49.2 Diagnostic and management algorithm for inherited conditions causing hypokalemic alkalosis. AME, Apparent mineralocorticoid excess; BP, blood pressure; COX, cyclooxygenase; FECl, fractional excretion of chloride; GRA, glucocorticoid-remediable aldosteronism.

and KCNJ1; transport via NKCC2 is electroneutral, whereas K is recycled back into the tubular lumen via KCNJ1, establishing a lumen positive transepithelial potential. Consequently, calcium reabsorption in the TAL is impaired in Bartter types 1 and 2, leading to hypercalciuria and nephrocalcinosis, whereas it is typically unaffected in types 3 and 4. CLCKNB is also expressed in the DCT, so symptoms of Bartter type 3 can overlap with Gitelman syndrome. Hypomagnesemia is thus a common feature. Finally, Barttin is critical also for inner ear function, so affected patients not only have Bartter syndrome but also sensorineural deafness.

The macula densa is part of the TAL, and it is in the macula densa that the first initial step of tubuloglomerular feedback (TGF) is localized: reduced Cl absorption in the macula densa initiates a signaling cascade that includes enhanced prostaglandin E2 (PGE2) production with consequent activation of renin and aldosterone.[4] Because Cl absorption is impaired in Bartter syndrome, these patients have impaired TGF with elevated levels of PGE2, renin, and aldosterone, and the latter mediates the characteristic hypokalemic metabolic alkalosis.[5] The dramatic upregulation of TGF is reflected in hypertrophy of the juxtaglomerular apparatus.[6]

Clinical Manifestations

Bartter syndrome from pathogenic variants in SLC12A1, KCNJ1, or BSND usually has earlier onset than that caused by variants in CLCKNB. Most manifest already during pregnancy, leading to the term antenatal Bartter syndrome.[7,8] In contrast, the later onset form is often called classic Bartter syndrome, as this is the phenotype originally described by Bartter and colleagues.[6]

The clinical features of antenatal Bartter syndrome include polyuria, hypokalemic metabolic alkalosis, and high urinary chloride excretion in a newborn with vomiting, failure to thrive, and a history of polyhydramnios and premature delivery. In pregnancies affected by polyhydramnios, a prenatal diagnosis of Bartter syndrome may be suggested by elevated protein concentrations in amniotic fluid, if genetic testing is not informative.[9] Bartter syndrome type 2 (BS2) can have a different phenotype in the first days of life, as KCNJ1 is not only involved in salt reabsorption in the TAL but also mediates K secretion in CD. Consequently, patients with BS2 often present initially with hyperkalemia and hyponatremia, leading to an erroneous diagnosis of pseudohypoaldosteronism type 1 (PHA1).[10] Over the first few days to weeks, serum K levels decrease, presumably due

Hyperkalemic Acidosis

Clinical examination:
Volume status, BP
Serum: Na, K, Cl, HCO3,
Ca, urea, creatinine,
osmolality, renin,
aldosterone
Blood: DNA for genetic tests
Urine: Na, K, Cl, Ca,
creatinine, osmolality
Hypertension, hypervolemia,
evidence of salt retention

PHA2

Renin elevated, aldosterone
low: Aldosterone deficiency,
evaluate for aldosterone
biosynthetic defects

Thiazide

Mineralocorticoid
supplementation

Renin suppressed,
aldosterone variable

Low normal BP
Eu- or hypovolemia,
evidence of salt
wasting

Renin, aldosterone
elevated
PHA 1

Salt
supplementation,
consider Naexchange resin

Fig. 49.3 Diagnostic and management algorithm for inherited conditions causing hyperkalemic acidosis. BP, Blood pressure; PHA1, pseudohypoaldosteronism type 1; PHA2, pseudohypoaldosteronism type 2.

to the expression of other K channels in CD that can compensate for the loss of KCNJ1 function.

Hypercalciuria and nephrocalcinosis are typical for BS1 and BS2, as the coupling of the electroneutral NKCC2 transporter with recycling of potassium into the tubular lumen through KCNJ1 is establishing the transepithelial voltage that drives Ca (and Mg) reabsorption through the paracellular pathway.3

Classic Bartter syndrome is typically associated with pathogenic variants in CLCNKB (Bartter syndrome type 3 or BS3). These patients present mostly in the first decade of life with vomiting, polyuria, recurrent episodes of dehydration, and hypokalemic metabolic alkalosis. Interestingly, electrolyte abnormalities are typically more severe than in antenatal Bartter syndrome.7,8 Moreover, hypomagnesemia with renal Mg^{2+} wasting is common. Presumably, this is due to the expression of CLC-

Kb in both TAL and DCT, thus affecting salt reabsorption in both these nephron segments. This may also explain the phenotypic overlap between Bartter and Gitelman syndrome, as some patients with BS3 can phenotypically mimic Gitelman syndrome.[11]

Bartter syndrome type 4 (BS4) is also characterized by sensorineural deafness. Clinically, it typically manifests as a more severe form of BS3, sometimes with extreme electrolyte abnormalities.[5] Presumably, in BS3, the closely related chloride channel CLC-Ka can compensate for the loss of CLC-Kb function in the inner ear and to some degree also in the kidney. However, both channels require Barttin as subunit, so that loss of function of Barttin is functionally equivalent to loss of both chloride channels.[12] Of note, BS4 patients typically experience progressive chronic kidney disease (CKD), although a milder phenotype has been reported, presumably to mutations with residual Barttin function.[13]

Diagnosis

The key features of Bartter syndrome are hypokalemic, hypochloremic alkalosis with evidence of renal Cl and K wasting and low or normal BP.

Differential Diagnosis

In syndromes of chronic severe hypokalemia with metabolic alkalosis, the differential diagnosis may be facilitated greatly by taking into consideration the associated BP and the urinary chloride concentration (Fig. 49.4).

Hypertension with hypokalemic alkalosis indicates a primary activation of salt reabsorption in the CD, such as from pathologic activation of the MR (e.g., hyperaldosteronism) or the sodium channel ENaC. If Bartter syndrome is associated with a normal or low-normal BP, however, extrarenal or renal Cl and Na losses are the cause. Extrarenal loss of sodium occurs in diarrhea, vomiting, or burns and is characterized by very low Cl concentrations in the urine with a fractional chloride excretion less than 0.5%.[14] Congenital chloride diarrhea can be misdiagnosed as BS, as the biochemical picture in the blood is identical, and the large and often clear-appearing stool volume is misinterpreted as urine, especially in female babies in diapers.[15] It is critical to demonstrate the renal loss of salt that is typical of Bartter and Gitelman syndrome, and diuretic use. Further analysis of Mg and urinary Ca excretion can then help distinguish between the various forms of Bartter and Gitelman syndrome (Table 49.2). Genotyping is recommended to confirm the final diagnosis.

Treatment

Neonates with Bartter syndrome typically have marked fluid and electrolyte disturbances that need to be corrected carefully. Salt

Water Reabsorption in the Collecting Duct
Vasopressin

GNAS

AVPR2

Inactive
protein kinase A
(PKA)

Blood

Adenyl cyclase

ATP

Protein
substrates

cAMP

frequent administration of electrolyte supplements may be better tolerated and safer.

A key component of treatment especially of antenatal BS is prostaglandin synthesis inhibition through cyclooxygenase inhibition by nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin (1–3 mg/kg/24 h). Selective COX2 inhibitors may provide similar efficacy with less potential toxicity.[19] NSAIDs act by interfering with the pathologic tubuloglomerular feedback in BS and enhancing proximal sodium reabsorption.[5] Treatment results in reduction of polyuria and polydipsia, improved growth and activity, and better control of plasma electrolytes. Plasma levels of renin and aldosterone often decrease, sometimes into the normal range.

Outcomes

Active PKA

AQP2

Phosphorylated
proteins
AQP2
Exocytic insertion

Water
Lumen

Fig. 49.4 Activation of the basolateral arginine-vasopressin type 2 receptor (AVPR2) initiates the signaling cascade that ultimately results in insertion of the water channel aquaporin 2 (AQP2) in the apical membrane, making it water permeable and thus allowing water reabsorption and urinary concentration. Genetic variants leading to loss-of-function of AVPR2 cause X-linked nephrogenic diabetes insipidus, whereas those with gain-of-function cause nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Similarly, gain-of-function variants in the stimulatory G-protein alpha subunit also cause NSIAD. Loss-of-function variants in AQP2 are the cause of autosomal nephrogenic diabetes insipidus. ATP, Adenosine triphosphate; cAMP, 3',5'-cyclic adenosine monophosphate; GNAS, genome-wide association studies; PKA, protein kinase A.

supplementation is often helpful; however, antenatal Bartter syndrome can be complicated by a secondary form of NDI, in which case a high solute intake can lead to hypernatremia.16 Potassium chloride supplementation is commonly provided. Addition of spironolactone or amiloride may be useful in improving hypokalemia and alkalosis but worsens the salt wasting and thus increases the risk of hypovolemia and should only be provided with sufficient salt supplementation.5 The same applies for angiotensin-converting enzyme (ACE) inhibitors, which are not recommended.17

A key problem in renal wasting disorders is that supplementation primarily results in increased urinary losses. After supplementation, plasma levels transiently rise, leading to an increased concentration in the glomerular filtrate with consequent loss in the urine and decreasing plasma levels. Monitoring the efficacy of supplementation thus depends strongly on the timing of the blood sample. Although cardiac arrhythmias and other severe complications have been reported with marked hypokalemia,18 the dramatic swings in plasma concentration associated with high-dose supplementation may be more harmful than consistent levels below the normal range. Moreover, high-dose supplementation may cause gastrointestinal symptoms (e.g., ulcers, diarrhea) that can worsen the electrolyte profile. Thus, smaller but more

Dramatic complications such as intracranial hemorrhage and bronchopulmonary dysplasia are typically seen in patients with antenatal BS and are a consequence of extreme prematurity. As with most diseases, there is a spectrum of severity. The electrolyte and acid-base imbalance itself can be severe with complications such as arrhythmias, paralysis, rhabdomyolysis, and apnea, yet others may have few symptoms, and some patients are diagnosed incidentally later in life. Importantly, even patients with more severe electrolyte imbalance usually improve clinically with appropriate therapy. Progressive CKD can be a complication of prematurity but can also be seen in BS3 patients born at term and is common in BS4.

Gitelman Syndrome

Gitelman syndrome is an autosomal recessive condition characterized by hypokalemic hypochloremic metabolic alkalosis with hypocalciuria and hypomagnesemia. The prevalence of Gitelman syndrome is estimated at approximately 1:40,000 in White populations, making it arguably the most frequent inherited tubulopathy.20

Pathogenesis

The similarity between the features of Gitelman syndrome and those caused by thiazide administration originally suggested that the defect might be in the DCT, which was subsequently confirmed by genetic studies that linked the condition to inactivating mutations in SLC12A3, the gene encoding the thiazide-sensitive transporter NCCT (see Fig. 49.1 and Table 49.1).21 Loss of NCCT function results in Na and Cl wasting from this segment, leading to hypovolemia with secondary activation of the renin-aldosterone system. As in Bartter syndrome, the resulting increase in CT Na reabsorption is counterbalanced by K and H excretion, causing hypokalemic alkalosis.

The hypocalciuria may be caused by enhanced proximal tubular calcium reabsorption, secondary to plasma volume contraction.22 The renal magnesium wasting is caused by downregulation of the epithelial magnesium channel TRPM6 in DCTs.

Clinical Manifestations and Diagnosis

The severity of symptoms varies widely. More severely affected patients complain of a decreased quality of life with fatigue and muscle weakness, inability to work for extended periods, salt craving, and polyuria.23 Cardiac disturbances, muscle cramps, and tetany are only exceptionally present. Chondrocalcinosis and sclerochoroidal calcifications can occur later in life.20 Laboratory evaluation shows hypokalemic hypochloremic metabolic alkalosis with hypocalciuria and hypomagnesemia with elevated urinary Cl, K, and Mg excretion. BP will usually be in the lownormal range. The differential diagnosis includes Bartter syndrome, especially BS3, HNF1B-related disease, and EAST syndrome, as well as acquired disorders, such as thiazide abuse and Sjögren syndrome.[20] Genotyping should be performed to confirm the diagnosis.

TABLE 49.2

Distinguishing Features of Individual Bartter and Gitelman Syndromes
BARTTER

Feature/Syndrome

Type 1

Type 2

Type 3a

Type 4

Type 5b

Gitelman

Antenatal manifestations
(polyhydramnios)
Age at presentation
Polyuria, polydipsia
Neonatal hyperkalemia/acidosis
Spontaneous resolution
Urinary calcium excretion
Nephrocalcinosis
Hypomagnesemia
Urine prostaglandins

Common

Common

Variable

Common

Always

Absent

Neonate
Marked
Absent
Absent
Elevated
Common
Rare
Elevated

Neonate
Marked
Common
Absent
Elevated
Common
Rare
Elevated

Variable
Rare
Absent
Absent
Variable
Rare
Common
Variable

Neonate
Common
Absent
Absent
Normal
Rare
Common
Elevated

Neonate
Marked
Absent
Always
Elevated
Rare
Rare
Elevated

Childhood/adolescence
Rare
Absent
Absent
Low
Absent
Common
Normal

[a]Note

the intermediate phenotype of Bartter syndrome type 3, which can present with typical features of Bartter syndrome but also phenocopy Gitelman syndrome and even switch between these two phenotypes in an individual.
[b]As Bartter syndrome type 5 spontaneously resolves typically around the estimated date of delivery, features detailed here only are present during the active disease period.

Treatment

Gitelman syndrome is primarily a salt-wasting disorder, and treatment should therefore include a liberal salt intake, if not pharmacologic supplementation. K and Mg supplements are usually given to improve muscle weakness or cramps. However, dosing may be limited by diarrhea and abdominal discomfort, and values in the normal range are typically not achieved. In exceptional cases of severe symptoms, parenteral Mg has been infused. NSAID are usually not helpful. K-sparing diuretics may improve the biochemistry but compound the salt wasting and should thus be considered carefully.
The long-term prognosis is good for cardiac and renal function, as well as for general health, although some patients do complain about markedly impaired quality of life. There is no clear association between severity of the electrolyte imbalance and symptoms, which complicates adjustment of treatment.

CONDITIONS WITH HYPOKALEMIA, METABOLIC ALKALOSIS, AND HYPERTENSION

Conditions with hypokalemia, metabolic alkalosis, and hypertension are caused by primary activation of the MR or its downstream effector, the epithelial Na-channel ENaC (see Fig. 49.1).

Liddle Syndrome

Liddle syndrome is an autosomal dominant disorder caused by gainof-function of ENaC.24 Consequently, the enhanced Na reabsorption through ENaC is independent of MR activation. Renin and aldosterone levels are suppressed, and there is no response to MR blockers, such as spironolactone or eplerenone. However, triamterene and amiloride, which are blockers of ENaC, correct hypertension, renal K loss, and alkalosis.25

Pathogenesis

Liddle syndrome is caused by variants in genes encoding the β (SCNN1B) or γ (SCNN1G) subunit of ENaC. The majority of patients carry a variant that impairs retrieval of the channel from the membrane, leading to enhanced ENaC activity.26 The variants result in truncations of the cytoplasmic C-terminal tail of the affected subunits. CD Na reabsorption depends on the channel density present in the apical cell membrane. Channel density is regulated by removal of ENaC from the cell membrane by ubiquitination and degradation. In Liddle syndrome, the mutated ENaC protein cannot be recognized by NEDD4, a ubiquitin ligase protein; thus, the channels remain in the cell membrane for prolonged periods. This action results in enhanced sodium reabsorption, hypertension, and hypokalemic alkalosis (see Fig. 49.1).

Clinical Manifestations and Diagnosis

Liddle syndrome is a rare disorder of hypertension that typically first presents in teenage children with hypokalemic metabolic alkalosis and low blood levels of renin and aldosterone. However, clinical manifestation as early as the newborn period has been described.

This condition is easily distinguished from primary hyperaldosteronism or renal artery stenosis by the finding of low renin and aldosterone levels. Other conditions with similar phenotype include AME and GRA (Table 49.3), as well as 11β-hydroxylase (steroid 11βmonooxygenase) or 17α-hydroxylase (steroid 17α-monooxygenase) deficiency and can be separated by urinary steroid profiles and genetic testing. An activating mutation of the MR with exacerbation of hypertension in pregnancy has also been reported and should be differentiated.27

Treatment

Therapy consists of ENaC blockade with triamterene or amiloride, which usually normalizes the BP and K levels. Because the pathogenetic disorder is not correctable with age, lifelong therapy is required.

Patients who have developed end-stage kidney disease from uncontrolled hypertension do not experience recurrence of the disease after transplantation, as the graft does not contain the genetic alteration.

Apparent Mineralocorticoid Excess

Pathogenesis

AME is an autosomal recessive condition resulting from deficiency of the type II (renal and placental) isoform of the enzyme 11βhydroxysteroid dehydrogenase. Clinical features of AME are similar to those of Liddle syndrome, but symptoms typically present earlier (in infancy) and more severely.

Normally, aldosterone is the principal ligand for the MR and in this way increases synthesis of various proteins, chiefly Na^+,K^+-ATPase on the basolateral surface and ENaC on the apical surface. These proteins facilitate the increased Na reabsorption and K secretion in the aldosterone-sensitive distal nephron (see Fig. 49.1). Interestingly, MR

TABLE 49.3 Features of Liddle Syndrome, Apparent Mineralocorticoid Excess (AME), and Glucocorticoid-Remediable Aldosteronism (GRA)

Feature/Syndrome

Liddle

AME

GRA

Inheritance
Age at presentation
Plasma aldosterone
Plasma renin activity
Urinary mineralocorticoid metabolites

AD
Childhood/adolescence
Suppressed
Suppressed
Normal

AR
Neonate/infancy
Suppressed
Suppressed
Elevated ratios of THF + allo-THF to THE; free cortisol to cortisone

AD
Childhood/adolescence
Elevated
Suppressed
Elevated cortisol C-18 oxidation products

Yes[a]
Yes
Yes

Yes
Yes
Yes

Response of the Hypertension to:
Glucocorticoids
No
Amiloride
Yes
Spironolactone
No

These syndromes are all characterized by hypokalemia, metabolic alkalosis, and hypertension.

Response to amiloride is representative for all blockers of the epithelium sodium channel (e.g., triamterene), and response to spironolactone is representative for all blockers of the mineralocorticoid receptor (e.g., eplerenone).

[a] Glucocorticoids are not standard treatment of AME. However, exogenous administration of a glucocorticoid that does not activate the mineralocorticoid

receptor (e.g., cortisone) but that suppresses endogenous cortisol production would ameliorate the hypertension.

AD, Autosomal dominant; AR, autosomal recessive; THE, tetrahydrocortisone; THF, tetrahydrocortisol.

is not specific for aldosterone, but can also bind cortisol, which circulates in blood at roughly 1000-fold higher concentration than aldosterone. To provide specificity for aldosterone, the MR is protected by the activity of the 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), which is highly expressed in the distal nephron and metabolizes cortisol to cortisone, which lacks MR binding ability.

Loss-of-function mutations in HSD11B2 thus cause AME by nonspecific activation of MR by cortisol.28 Interestingly, carbenoxolone and glycyrrhizic acid (found in licorice compounds) are potent inhibitors of this enzyme and so can cause an acquired form of AME.

HSD11B2 is also expressed in the placenta, likely explaining the intrauterine growth retardation typically seen in AME patients.

Clinical Manifestations and Diagnosis

AME is characterized by early onset of severe hypertension in childhood, hypokalemia, metabolic alkalosis with suppressed plasma levels of renin and aldosterone, and increased metabolites of cortisol in the urine. A history of low birth weight and subsequent failure to thrive is typical.29 Untreated, stroke and other complications of severe hypertension are seen even during childhood. Milder clinical manifestations can be seen with mutations that retain some functionality of the enzyme. Polyuria due to a urinary concentrating defect is another typical feature and likely linked to the electrolyte abnormalities in blood and urine, as it improves after treatment of AME.30

Establishing the diagnosis of AME is critical for proper treatment and should be prompted by the electrolyte profile and early-onset hypertension with suppressed renin and aldosterone levels. A urinary steroid profile is diagnostic by showing elevated urinary levels of hydrogenated metabolites of cortisol (tetrahydrocortisol plus allotetrahydrocortisol) compared with cortisone (tetrahydrocortisone). The ratio of urinary-free cortisol to cortisone is also increased. Genetic testing confirms the diagnosis.

Treatment

Treatment with blockers of MR (e.g., spironolactone or eplerenone) or its main effector ENaC (e.g., amiloride or triamterene) provides specific treatment. However, as MR blockers are competitive antagonists and in AME compete against the 1000-fold higher cortisol

concentrations (compared with aldosterone), large doses are needed, and ENaC blockers (or a combination of both) are likely to be more effective.

Glucocorticoid-Remediable Aldosteronism

GRA is an autosomal dominant condition. Patients present with typical features of primary hyperaldosteronism: hypertension, suppressed plasma renin activity, and hypokalemia. Unlike primary hyperaldosteronism (due to aldosterone-producing adrenal adenoma), hypersecretion of aldosterone in GRA can be reversed by the administration of corticosteroids. Affected individuals have early-onset hypertension. There is a high prevalence of hemorrhagic stroke, largely as a result of ruptured intracranial aneurysms.

Pathogenesis

Patients with GRA have adrenocorticotropic hormone (ACTH)sensitive aldosterone production occurring in the zona fasciculata of the adrenal gland, which is usually responsible only for cortisol synthesis. Normally, aldosterone is synthesized in the zona glomerulosa.

The two isoenzymes of 11β-hydroxylase involved in the biosynthesis of aldosterone and cortisol are steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), respectively. The genes for these isoenzymes are located close to each other on the long arm of chromosome 8. Unequal meiotic crossovers may produce hybrid genes by fusion of the promoter end of CYP11B1 with the coding sequence of CYP11B2, so that aldosterone synthase is inappropriately regulated by ACTH.31

Diagnosis

Patients with GRA are often misdiagnosed with primary hypertension. Hypertensive patients with early-onset hypertension, early cerebral hemorrhage (<40 years), hypokalemia before or after diuretic therapy, and refractoriness to standard antihypertensive medication are candidates for GRA testing, especially in the presence of a family history of hypertension or early death. Similar to other genetic forms of hypertension (Liddle syndrome, AME, Gordon syndrome), plasma renin activity is suppressed. Aldosterone levels are normal to high and do not change with posture but are suppressed by dexamethasone.

A urinary steroid profile will show the biochemical hallmark of GRA in the form of increased levels of the so-called hybrid steroids (18-hydroxycortisol and 18-oxocortisol).
Genetic testing confirms the diagnosis.

increased sweat Na concentration and can develop a miliary rash from blockage of the sweat glands. In addition, patients can have cystic fibrosis–like lung disease due to viscous high-salt–containing bronchial secretions.

Treatment

Treatment

Treatment with low-dose corticosteroid is effective in GRA patients, as it suppresses ACTH and thus the aberrant ACTH-mediated aldosterone production in the zona fasciculata. Typically, 0.125 to 0.25 mg of dexamethasone or 2.5 to 5 mg of prednisolone is administered at bedtime. Therapeutic goals are normotension and normalization of biochemical markers (urinary 18-oxosteroid, serum aldosterone). MR antagonists (spironolactone, eplerenone) and ENaC antagonists such as amiloride and triamterene are also useful treatments.

The initial emergency treatment focuses on volume resuscitation with 0.9% saline. Without treatment, PHA1, especially arPHA1, can be lethal. Maintenance treatment consists of NaCl and $NaHCO_3$ supplementation adjusted to maintain euvolemia, normonatremia, and acid-base homeostasis. In arPHA1, Na-exchange resins can help stabilize patients by providing a steady source of Na and an alternative means for K excretion. Patients with adPHA1 typically improve spontaneously over the first few months of life and maintain normal plasma electrolytes without supplementation, although they typically maintain increased renin-aldosterone levels.34

Adrenal Enzymatic Disorders

Inherited deficiency of 11β- or 17α-hydroxylase, as well as specific heterozygous variants in the ion channels KCNJ5 and CACNA1H, also cause mineralocorticoid excess with hypertension and hypokalemic metabolic alkalosis. These disorders are covered in endocrinological textbooks and thus will not be discussed here in detail. Hypertension is caused by excessive mineralocorticoid production. Again, a urinary steroid profile helps establish the diagnosis, which can be confirmed by genetic testing.

CONDITIONS WITH HYPONATREMIA, HYPERKALEMIA, METABOLIC ACIDOSIS, AND NORMAL BLOOD PRESSURE

Conditions with hyponatremia, hyperkalemia, metabolic acidosis, and low-normal BP have features of mineralocorticoid deficiency either because of a synthetic defect or because of end organ resistance.

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is a state of renal tubular unresponsiveness to the action of aldosterone.
Type 1 PHA exists in an autosomal dominant (adPHA1) and an autosomal recessive form (arPHA1). The adPHA1 is due to loss-offunction variants in NR3C2 encoding the MR.32 In contrast, arPHA1 is due to loss-of-function variants in the genes encoding the α, β, or γ subunits of ENaC.33

Diagnosis

PHA1 presents typically in the first few days (arPHA1) to weeks (adPHA1) of life with weight loss, hypovolemia, and poor feeding. Biochemistries will reveal the typical electrolyte profile with mild to moderate hyponatremia, often severe (arPHA1) hyperkalemia and metabolic acidosis. Urine biochemistries reveal inappropriately high Na excretion and virtually absent K secretion. Occasionally, patients with BS2 can present similarly (see “Bartter Syndrome” section). PHA1 can be distinguished from aldosterone deficiency states, such as congenital adrenal hyperplasia, by the massively elevated aldosterone levels in blood. The diagnosis can be confirmed by genetic testing. An acquired form of PHA1 can be seen with urinary tract obstruction and/ or pyelonephritis.

Clinical Features

The clinical manifestations are dominated by electrolyte abnormalities and hypovolemia, which untreated can lead to circulatory shock. ENaC is also expressed in the skin and lungs, where it mediates salt reabsorption. Consequently, arPHA1 patients have

Aldosterone Biosynthetic Defects

Patients with defects in aldosterone biosynthesis show salt wasting with hyponatremia, hyperkalemia, hypovolemia, and elevated plasma renin activity yet obviously low or absent aldosterone levels. These conditions are not detailed here.

CONDITIONS WITH HYPERKALEMIA, METABOLIC ACIDOSIS, AND HYPERTENSION

Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

The clinical mirror image of Gitelman syndrome, Gordon syndrome is an autosomal dominant condition characterized by hypertension, hyperkalemia, and mild hyperchloremic metabolic acidosis.

Pathogenesis

Initially, two genes were identified as responsible for PHA2 (Table 49.1).35 These genes encode two members of the with-no-lysine kinase family (WNK1 and WNK4), both expressed in the convoluted tubule and the CDs. WNK4 acts as a negative regulator of thiazide-sensitive NCCT function, reducing cell surface expression of NCCT. WNK4 also downregulates KCNJ1 and epithelial chloride efflux. Pathogenic variants in WNK4 are typically missense and cause loss-of-function, so that WNK4 loses its ability to suppress NCCT and KCNJ1, leading to Na and K retention. WNK1 prevents WNK4 from interacting with NCCT. Pathogenic variants in WNK1 are typically intronic deletions that increase WNK1 expression. Subsequently, two further genes were identified variants in which cause PHA2: CUL3 and KLHL3.36 The encoded proteins form a ubiquitin-ligase complex that regulates WNK1 and WNK4 abundance. Interestingly, in addition to the autosomal dominant inheritance typical for PH2, variants in KLHL3 can also be recessive. Moreover, pathogenic variants in CUL3 are frequently de novo, so that the absence of a family history does not exclude the diagnosis. An acquired form of PHA2 can be seen as a side effect of calcineurin inhibitors, especially tacrolimus, which affect WNK activity.37

Clinical Manifestations and Diagnosis

Hyperkalemia may be present from birth, but as in GRA, hypertension may not manifest until later in life. Patients show hyperchloremic metabolic acidosis; plasma renin and aldosterone are variable, but renin activity is usually suppressed. Patients with CUL3-related disease appear to be phenotypically more seriously affected with higher plasma K levels, more pronounced acidosis and hypertension and consequently younger age at diagnosis.36 In addition, most patients with CUL3 disease have failure to thrive and growth impairment.

Treatment

As specific inhibitors of NCCT, thiazides are able to completely correct the clinical and biochemical features of PHA2, except for the extrarenal manifestations in CUL3-related disease. Establishing the diagnosis is thus critical for targeted and effective treatment.

Congenital Nephrogenic Diabetes Insipidus

Congenital NDI is a rare polyuric disorder characterized by the failure to concentrate urine despite elevated levels of vasopressin. Congenital NDI is caused by mutations in key proteins controlling water reabsorption in the CD. Acquired diabetes insipidus (DI) is much more common, and its diagnosis and management are discussed in Chapter 9.

Pathogenesis

More than 90% of patients have X-linked recessive NDI with pathogenic variants in AVPR2, the gene for the arginine-vasopressin type 2 receptor (AVPR2). Consequently, the majority of patients are male, although female carriers can have a urinary concentrating defect of variable severity, presumably due to nonrandom X inactivation.38 AVPR2 is expressed predominantly in the kidney, where it mediates urinary concentration, but to some degree also in the vasculature, where it mediates vasodilation and release of von Willebrand factor.39 Well over 250 pathogenic variants have been reported so far.38 In fewer than 10% of the families, congenital NDI has an autosomal recessive inheritance with pathogenic variants in AQP2, the gene encoding the water channel AQP2, which constitutes the final effector protein in the vasopressin-initiated signaling cascade. A rare autosomal dominant form of NDI, due to dominant negative variants in AQP2, has also been reported. Some inherited diseases, such as Bartter syndrome and AME, can also be associated with so-called secondary inherited NDI.16 The etiology of the AQP2 deficiency in these disorders is unclear but likely related to the blood and/or urinary electrolyte abnormalities, as both hypokalemia and hypercalciuria have been associated with decreased AQP2 expression.

Clinical Features

Manifestations of congenital NDI typically appear within the first weeks to months of life. NDI does not cause polyhydramnios, as the osmotic load is cleared by the placenta. Clinical features at presentation are typically polyuria and failure to thrive, as well as a history of vigorous sucking followed by vomiting.38 Unrecognized and untreated, the baby can experience hypernatremic dehydration, with delayed development and mental impairment as possible consequences. Cranial computed tomography may occasionally show dystrophic calcification in the basal ganglia and the cerebral cortex in such untreated patients.

Attention-deficit/hyperactivity disorder and impaired school performance are commonly reported and may be secondary to preoccupation with drinking and voiding. An adult patient usually drinks and voids about 10 to 12 L per day. Urinary tract dilation can be seen, especially if there are voiding abnormalities.

Some variants in either AVPR2 or AQP2 may retain partial functionality of the protein, leading to a phenotype of partial NDI, where urinary concentration is possible but subnormal. Clinical symptoms are consequently milder, and the disease may remain undiagnosed throughout life.40

Diagnosis

The initial diagnosis of DI rests on the combination of an inappropriately dilute urine in the context of hypernatremic dehydration. Thus, simple blood and urine chemistries easily establish the diagnosis, yet it is often delayed. When these infants present with a history of vomiting, physicians may be mistakenly reassured by the large urine output, considered as inconsistent with severe dehydration rather than recognizing it as a warning sign in the context of clinical dehydration. Once the diagnosis of DI has been established, the nephrogenic form can then be proven by the absence of a response in urinary concentration after administration of desamino-8-d-arginine vasopressin (DDAVP), a vasopressin analog with high specificity for AVPR2. DDAVP can be administered orally, nasally, or by intramuscular or intravenous injection. The most critical complication of the DDAVP test is the development of acute hyponatremia in those patients who respond to the drug yet keep on drinking. The risk for this is low, as most patients will simply stop drinking with normalization of serum osmolality, but patients with habitual polydipsia and infants hungry for milk are at risk. Careful observation with a limit in the volume of fluid intake equal to the volume of urine produced during the test is key to avoidance of this complication. Intravenous injection has the advantage of the shortest observation period (2 hours) combined with certainty of administration (which is variable via the oral or nasal route) and the ability to distinguish between X-linked and autosomal NDI. As patients with autosomal NDI still express AVPR2, they will show the vascular effects in the form of a small drop in BP, an increase in heart rate, and release of von Willebrand factor, whereas these changes are absent in patients with AVPR2 mutations. Serum levels of DDAVP with other modes of administration are not sufficient to appreciate these changes. A well-established protocol uses 0.3 µg/kg DDAVP intravenously, the same dose as used by hematologists in mild forms of hemophilia or von Willebrand disease.39 A normal renal response to DDAVP is an increase in urine osmolality to greater than 800 mOsm/kg, whereas patients with NDI show no response and urine osmolality remains less than 200 mOsm/kg. An intermediate response may represent partial NDI or simply a washout of the medullary concentration gradient. The latter can be confirmed by achieving a urine osmolality of greater than 800 mOsm/kg after repeated administration of DDAVP. As normal urinary concentrating ability only develops during the first year of life, an intermediate response may be normal in infants.

Differential Diagnosis

Patients with central DI or habitual polydipsia can be distinguished by a normal response to DDAVP. Patients with secondary inherited NDI typically have other electrolyte abnormalities, such as hypokalemia and hypercalciuria, in addition to other features typical for the primary diagnosis, such as polyhydramnios in Bartter syndrome and hypertension in AME. Onset of polyuria later in childhood or adulthood argues for acquired forms of NDI. Patients with partial NDI represent a diagnostic challenge. Further blood tests and a renal ultrasound can help exclude underlying structural or parenchymal renal disease, such as nephronophthisis or tubulointerstitial or cystic kidney disease. Genetic testing can help confirm the diagnosis.

Treatment

Management of NDI concentrates on reduction of polyuria, avoidance of episodes of dehydration, and provision of sufficient calories to allow normal physical growth and development. A key factor in the determination of overall urine output is the osmotic load, which mainly derives from protein and salt intake. The higher the osmotic load, the more water is required to excrete it. Involvement of the dietician thus is key, especially in infancy, to minimize osmotic load, yet ensuring that protein and caloric intake meets the recommended daily intake.

A goal of 15 mOsm/kg is typically achievable; consequently, a patient with an average urine osmolality of 100 mOsm/kg would need 150 mL/kg/day to excrete this load.

Thiazide diuretics, such as hydrochlorothiazide (1–2 mg/kg/12 h), when combined with reduction of salt intake, are effective in reducing urine output. Thiazides inhibit salt reabsorption in DCTs, which leads to mild volume depletion. Hypovolemia stimulates fluid reabsorption in PTs, thereby diminishing water delivery to CDs. Combination therapy with amiloride (0.1–0.2 mg/kg every 8–12 hours) helps control the potential hypokalemia from thiazide treatment and may enhance the antipolyuric effect.

Prostaglandin synthase inhibitors are typically the most effective drugs in reducing urine volume, at least during infancy, probably by enhancing proximal sodium reabsorption. Indomethacin (1–2 mg/kg/day) is used most often but may reduce glomerular filtration rate and cause gastrointestinal side effects. Selective COX2 inhibitors, such as celecoxib, thus may be preferable, but their efficacy in NDI is so far anecdotal.

Nephrogenic Syndrome of Inappropriate Antidiuresis

NSIAD represents the mirror image of NDI and is the inherited equivalent to the syndrome of inappropriate antidiuresis (SIADH).

Pathogenesis

NSIAD is due to gain-of-function variants in AVPR2, leading to constitutive activation of the urinary concentrating mechanism in the CD, irrespective of serum osmolality.41 The inheritance is X-linked dominant, although males are typically more severely affected.42 Specific variants in genome-wide association studies, encoding the stimulatory G-protein alpha subunit, have also been associated with NSIAD and are not always associated with additional endocrine abnormalities.43 44

Clinical Features, Diagnosis, and Treatment

NSIAD is characterized by an inappropriately concentrated urine (>100 mOsm/kg) in the context of hyponatremia and hypoosmolality. In contrast to SIADH, vasopressin levels are adequately suppressed. Genetic testing will confirm the diagnosis. Severely affected patients (typically males) may have recurrent episodes of severe symptomatic hyponatremia, whereas others may have no apparent symptoms. Avoidance of fluid intake, mediated by low serum osmolality, constitutes simple and intuitive treatment and may explain the absence of symptoms in some patients.42 Fluid restriction is difficult in infancy, as fluid and caloric intake is coupled. Increasing the osmotic load (e.g., by urea supplementation) may help symptomatic patients. AVPR2 antagonists (aquaretics) are typically not helpful, as there is no vasopressin excess.

SELF-ASSESSMENT QUESTIONS

1. Which of the following conditions is characteristically associated with hypocalciuria?
A. Bartter syndrome
B. Liddle syndrome
C. Gitelman syndrome
D. Gordon syndrome
2. The treatment of Bartter syndrome may include which of the following?
A. Amiloride
B. Prostaglandin synthesis inhibitors
C. KCl supplementation
D. NaCl supplementation
3. Hypokalemic, hypochloremic metabolic alkalosis is a sign of:

A. aldosterone deficiency.

B. enhanced Na transport through the epithelial sodium channel in the collecting duct.
C. pseudohypoaldosteronism type 1.
D. pseudohypoaldosteronism type 2.

4. Which of the following is the best suited maintenance fluid solution in patients with nephrogenic diabetes insipidus needing intravenous fluids?
A. 0.9% saline
B. Hartman solution
C. 5% dextrose in water
D. 0.45% saline

REFERENCES

1. Kleta R, Bockenhauer D. Bartter syndromes and other salt-losing tubulopathies. Nephron Physiol. 2006;104(2):73–80.
2. Vargas-Poussou R, Huang C, Hulin P, et al. Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a bartter-like syndrome. J Am Soc Nephrol : JASN. 2002;13(9):2259–2266.
3. Haisch L, Almeida JR, Abreu da Silva PR, Schlingmann KP, Konrad M. The role of tight junctions in paracellular ion transport in the renal tubule: lessons learned from a rare inherited tubular disorder. Am J Kidney Dis. 2011;57(2):320–330.
4. Peti-Peterdi J, Komlosi P, Fuson AL, et al. Luminal NaCl delivery regulates basolateral PGE2 release from macula densa cells. J Clin Invest. 2003;112(1):76–82.
5. Plumb LA, Van’t Hoff W, Kleta R, et al. Renal apnoea: extreme disturbance of homoeostasis in a child with bartter syndrome type IV. Lancet. 2016;388(10044):631–632.
6. Bartter FC, Pronove P, Gill Jr JR, Maccardle RC. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. Am J Med. 1962;33:811–828.
7. Peters M, Jeck N, Reinalter S, et al. Clinical presentation of genetically defined patients with hypokalemic salt-losing tubulopathies. Am J Med. 2002;112(3):183–190.
8. Brochard K, Boyer O, Blanchard A, et al. Phenotype-genotype correlation in antenatal and neonatal variants of bartter syndrome. Nephrol Dial Transplant. 2009;24(5):1455–1464.
9. Garnier A, Dreux S, Vargas-Poussou R, et al. Bartter syndrome prenatal diagnosis based on amniotic fluid biochemical analysis. Pediatr Res. 2010;67(3):300–303.
10. Finer G, Shalev H, Birk OS, et al. Transient neonatal hyperkalemia in the antenatal (ROMK defective) bartter syndrome. J Pediatr. 2003;142(3):318–323.
11. Jeck N, Konrad M, Peters M, Weber S, Bonzel KE, Seyberth HW. Mutations in the chloride channel gene, CLCNKB, leading to a mixed bartter-gitelman phenotype. Pediatr Res. 2000;48(6):754–758.
12. Schlingmann KP, Konrad M, Jeck N, et al. Salt wasting and deafness resulting from mutations in two chloride channels. N Eng J Med. 2004;350(13):1314–1319.
13. Brum S, Rueff J, Santos JR, Calado J. Unusual adult-onset manifestation of an attenuated bartter’s syndrome type IV renal phenotype caused by a mutation in BSND. Nephrol Dial Transplant. 2007;22(1):288–289.
14. Walsh PR, Tse Y, Ashton E, et al. Clinical and diagnostic features of bartter and Gitelman syndromes. Clin Kidney J. 2018;11(3):302–309.
15. Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proc Natl Acad Sci U S A. 2009;106(45):19096–19101.
16. Bockenhauer D, Bichet DG. Inherited secondary nephrogenic diabetes insipidus: concentrating on humans. Am J Physiol Renal Physiol. 2013;304(8):F1037–F1042.
17. Ariceta G, Bertholet-Thomas A, Bockenhauer D, et al. Bartter syndrome: consensus/position paper from the ERK-Net expert group for tubular disorders. Kidney Int. 2021. in press.
18. Cortesi C, Lava SA, Bettinelli A, et al. Cardiac arrhythmias and rhabdomyolysis in Bartter-Gitelman patients. Pediatr Nephrol. 2010;25(10):2005–2008.
19. Kleta R, Basoglu C, Kuwertz-Broking E. New treatment options for bartter’s syndrome. N Engl J Med. 2000;343(9):661–662.
20. Blanchard A, Bockenhauer D, Bolignano D, et al. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2016. in press.
21. Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman’s variant of bartter’s syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996;12(1):24–30.

22. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca2+ reabsorption and reduced Mg2+

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channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651–1658.
Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB. Gitelman’s syndrome revisited: an evaluation of symptoms and health-related quality of life. Kidney Int. 2001;59(2):710–717.
Hansson JH, Schild L, Lu Y, et al. A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity. Proc Nat Acad Sci U S A. 1995;92(25):11495–11499.
Botero-Velez M, Curtis JJ, Warnock DG. Brief report: liddle’s syndrome revisited-a disorder of sodium reabsorption in the distal tubule. N Eng J Med. 1994;330(3):178–181.
Schild L, Lu Y, Gautschi I, Schneeberger E, Lifton RP, Rossier BC. Identification of a PY motif in the epithelial Na channel subunits as a target sequence for mutations causing channel activation found in Liddle syndrome. EMBO J. 1996;15(10):2381–2387.
Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science. 2000;289(5476):119–123.
Mune T, Rogerson FM, Nikkila H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 betahydroxysteroid dehydrogenase. Nat Genet. 1995;10(4):394–399.

Palermo M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: an overview. Arq Bras Endocrinol Metabol. 2004;48(5):687–696.
Bockenhauer D, van’t Hoff W, Dattani M, et al. Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases. Nephron Physiol. 2010;116(4):23–29.
Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;355(6357):262–265.
Geller DS, Rodriguez-Soriano J, Vallo Boado A, et al. Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. Nat Genet. 1998;19(3):279–281.
Chang SS, Grunder S, Hanukoglu A, et al. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. Nat Genet. 1996;12(3):248–253.
Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res. 2009;72(1):1–9.
Wilson FH, Disse-Nicodeme S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. Science. 2001;293(5532):1107–1112.
Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature. 2012;482(7383):98–102.
Hoorn EJ, Walsh SB, McCormick JA, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. Nat Med. 2011;17(10):1304–1309.
Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol. 2015;11(10):576–588.
Bichet DG, Razi M, Lonergan M, et al. Hemodynamic and coagulation responses to 1-desamino[8-D-arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus. N Eng J Med. 1988;318(14):881–887.
Bockenhauer D, Carpentier E, Rochdi D, et al. Vasopressin type 2 receptor V88M mutation: molecular basis of partial and complete nephrogenic diabetes insipidus. Nephron Physiol. 2010;114(1):1–10.
Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med. 2005;352(18):1884–1890.
Bockenhauer D, Penney MD, Hampton D, et al. A family with hyponatremia and the nephrogenic syndrome of inappropriate antidiuresis. Am J Kidney Dis. 2012;59(4):566–568.
Linglart A, Maupetit-Mehouas S, Silve C. GNAS -related loss-of-function disorders and the role of Imprinting. Horm Res Paediatr. 2013;79(3):119–129.
Miyado M, Fukami M, Takada S, et al. Germline-derived gain-offunction variants of gsalpha-coding GNAS gene identified in nephrogenic syndrome of inappropriate antidiuresis. J Am Soci Nephrol: JASN. 2019;30(5):877–889.

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Fanconi Syndrome and Other Proximal Tubule Disorders

Annabelle N. Chua, Reeti Kumar, John W. Foreman

The proximal tubule reabsorbs the majority of several key solutes, including glucose, amino acids, bicarbonate, and phosphate. This chapter describes a number of disorders, mainly heritable, that affect proximal tubule reabsorption. Chapters 11 and 13 discuss familial forms of hyperphosphaturia and renal tubular acidosis (RTA), respectively.

Most nonelectrolyte solutes are reabsorbed in the proximal tubule through specific transport proteins that cotransport them in conjunction with sodium (Fig. 50.1). The driving force for this solute transport is the electrochemical gradient for sodium entry maintained by the enzyme Na+,K+-ATPase. Most disorders of isolated solute reabsorption are related to defects in specific transport proteins, whereas disorders affecting multiple solutes, such as Fanconi syndrome, are probably secondary to defects in energy generation, Na+,K+-ATPase activity, or dysfunction of cellular organelles involved with membrane protein recycling.

FANCONI SYNDROME

Definition

In the 1930s, de Toni, Debré, and coworkers and Fanconi independently described several children with the combination of renal rickets, glycosuria, and hypophosphatemia. Fanconi syndrome now refers to global dysfunction of the proximal tubule leading to excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other solutes handled by this nephron segment. These losses lead to the clinical problems of acidosis, dehydration, electrolyte imbalance, rickets, osteomalacia, and growth failure. Numerous inherited or acquired disorders are associated with Fanconi syndrome (Box 50.1).

Etiology and Pathogenesis

The sequence of events leading to Fanconi syndrome is incompletely defined and probably varies with each cause. Possible mechanisms include widespread abnormality of most or all of the proximal tubule carriers, such as a defect in sodium binding to the carrier or insertion of the carrier into the brush border membrane, “leaky” brush border membrane or tight junction, inhibited or abnormal Na+,K+-ATPase pump, or impaired mitochondrial energy generation (see Fig. 50.1).

An abnormality in energy generation has been implicated in multiple disorders, including hereditary fructose intolerance, galactosemia, mitochondrial cytopathies, and heavy metal poisoning, as well as in several experimental models of Fanconi syndrome. Abnormal subcellular organelle function, such as the lysosome in cystinosis or the megalin-cubilin endocytic pathway in Dent disease, is also a cause of Fanconi syndrome (Fig. 50.2).

In adults, the most common causes of persistent Fanconi syndrome are an endogenous or exogenous toxin such as a heavy metal,

a medication, or dysproteinemia. In children, the most common persistent cause is an inborn error of metabolism, such as cystinosis. Specific causes of Fanconi syndrome are discussed after a general description of the clinical manifestations and treatment of the syndrome.

Clinical Manifestations

Fanconi syndrome gives rise to a number of clinical abnormalities (Box 50.2).

Aminoaciduria

Aminoaciduria is a cardinal feature of Fanconi syndrome. Virtually every amino acid is found in excess in the urine, thus the term generalized aminoaciduria. However, there are no clinical consequences because the losses are trivial (0.5–1 g/day) in relation to dietary intake.

Glycosuria

Glycosuria in the absence of hyperglycemia is another of the cardinal features of Fanconi syndrome and results from impaired tubular reabsorption of glucose. It is often one of the first diagnostic clues (Fig. 50.3). As with aminoaciduria, glycosuria rarely causes symptoms such as weight loss or hypoglycemia.

Hypophosphatemia

Hypophosphatemia from impaired phosphate reabsorption is common in Fanconi syndrome. Tubular phosphate handling can be assessed by measuring the tubular reabsorption of phosphate (TRP), which is normally greater than 80%, by the following equation:

$$TRP = 1 - (Up \times Pc / Uc \times Pp) \times 100\ \%$$

where Up, Pp, Uc, and Pc are the urinary and serum phosphate and creatinine concentrations, respectively. Subtle changes in phosphate reabsorption can be assessed by measuring the maximum phosphate reabsorption in relation to the glomerular filtration rate (TmP/GFR) on fasting urine and blood samples, as shown in Fig. 11.15. Elevated parathyroid hormone (PTH) and low vitamin D levels also may play a role in the phosphaturia of Fanconi syndrome, although these hormonal abnormalities are not always present. A few patients have impaired conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D; metabolic acidosis, another feature of Fanconi syndrome, also may impair this conversion. Another mechanism for the hypophosphatemia is impairment of the megalin-dependent reabsorption and degradation of filtered PTH.[1] Unabsorbed PTH then binds to receptors in more distal portions of the proximal tubule, leading to increased endocytosis of apical phosphate transporters and increased phosphaturia. The hypophosphatemia, especially if accompanied by

CHAPTER 50 Fanconi Syndrome and Other Proximal Tubule Disorders

Proximal Tubular Solute Handling
and Potential Defects
Lumen

Cell

Megalin Endocytic Pathway in
Proximal Tubular Cells

Blood

6. Defective
transporter
recycling
1. Defective
solute (S)
influx

3. Decreased
flux into
blood

S

2. Leakage back
into lumen

CIC-5

K+
ATP

S

Na+
Lysosome

5. Increased
backflux across
tight junctions

S
Brush border
membrane

Basolateral
membrane

Fig. 50.1 Defects and Potential Defects in Proximal Tubular Solute Handling. Solute uptake by the brush border membrane from the lumen is coupled to Na+ influx. The favorable electrochemical driving force for luminal Na+ is maintained by the Na+,K+-ATPase pump. Transported solute is then either used by the cell or returned to the blood across the basolateral membrane. Fanconi syndrome could arise because of a defect in one of six areas as shown. ATP, Adenosine triphosphate.

Causes of Fanconi Syndrome

Inherited
- Cystinosis
- Galactosemia
- Hereditary fructose intolerance

- Tyrosinemia
- Wilson disease
- Lowe syndrome
- Dent disease
- Glycogenosis
- Mitochondrial cytopathies
- Idiopathic

Acquired[a]

- Drugs: cisplatin, ifosfamide, tenofovir, cidofovir, adefovir, didanosine, gentamicin, azathioprine, valproic acid (sodium valproate), suramin, streptozocin (streptozotocin), ranitidine
- Dysproteinemias: multiple myeloma, Sjögren syndrome, light-chain proteinuria, amyloidosis
- Heavy metal poisoning: lead, cadmium
- Other poisonings: Chinese herbal medicine, glue sniffing
- Other: nephrotic syndrome, kidney transplantation, acute tubular necrosis

[a] Italics

Proton pump
H
Cl

Endosome

4. Defective
energy generation
or transduction ATP

BOX 50.1

Cell

Lumen

S

Na+

indicate more common causes.

hyperparathyroidism and low 1,25-hydroxyvitamin D levels, often leads to significant bone disease, manifesting with pain, fractures, rickets, or growth failure.

Natriuresis and Kaliuresis

Natriuresis and kaliuresis are common in Fanconi syndrome and can give rise to significant and even life-threatening problems. The decreased proximal reabsorption of sodium leads to increased potassium excretion secondary to increased distal delivery of sodium and

Low-molecular-weight protein
Megalin receptor

Fig. 50.2 Megalin-Cubilin Endocytic Pathway in Proximal Tubular Cells. Low-molecular-weight proteins in the luminal fluid bind to the megalin-cubilin complex and are endocytosed. The recycling of megalin and further catabolism of these proteins depend on acidification of the vesicle by a proton pump. The ClC-5 chloride channel provides an electrical shunt for efficient functioning of the proton pump. This endocytosis pathway plays a role in membrane transporter recycling, and disruption of this pathway interferes with absorption of other luminal solutes.

BOX 50.2

Features of Fanconi Syndrome

Metabolic Abnormalities
- Glycosuria
- Hyperaminoaciduria
- Hypophosphatemia
- Acidosis
- Hypokalemia
- Hypouricemia
- Hypocarnitinemia

Clinical Features
- Rickets, osteomalacia
- Growth retardation
- Polyuria
- Dehydration
- Proteinuria

activation of the renin-aldosterone system from hypovolemia. In some cases, sodium and potassium losses are so great that hypokalemia and metabolic alkalosis result, simulating Bartter syndrome despite the lowered bicarbonate threshold.

Hyperchloremic Metabolic Acidosis

Hyperchloremic metabolic acidosis, another feature of Fanconi syndrome, is a result of impaired bicarbonate reabsorption by the proximal tubule (proximal or type 2 RTA; see Chapter 13). This impaired reabsorption can lead to the loss of more than 30% of the normal filtered load of bicarbonate. As the serum bicarbonate concentration ([HCO3]) falls, the filtered load falls, and excretion drops such that the serum [HCO3] usually remains between 12 and 18 mmol/L. On occasion, there is an associated defect in distal acidification, usually

Proteinuria

Evaluation of Glycosuria
Glycosuria
found on
routine testing

Proteinuria is usually minimal, except when Fanconi syndrome develops in association with the nephrotic syndrome. Typically, only lowmolecular-weight proteins (<30,000 Da) are excreted, such as vitamin D and A binding proteins, enzymes, immunoglobulin light chains, and hormones. Therefore, significant albuminuria is often absent and urine dipstick may be negative for protein.

Treatment of Fanconi Syndrome

Measure serum
glucose

9 mmol/L
(160 mg/dL)

Evaluate for
diabetes mellitus

Normal

Measure serum
potassium,
bicarbonate,
chloride
Measure TRP,
TmP/GFR*

if normal

Renal glycosuria

Low serum potassium, bicarbonate, and TmP/GFR
High serum chloride
Evaluate for
Fanconi syndrome
Fig. 50.3 Evaluation of Glycosuria. GFR, Glomerular filtration rate; TmP, tubular maximum reabsorptive capacity for phosphate; TRP, tubular reabsorption of phosphate.

in association with long-standing hypokalemia or nephrocalcinosis. Ammoniagenesis is usually normal or increased because of the hypokalemia and acidosis unless there is an associated impairment in glomerular filtration rate (GFR).

Polyuria and Polydipsia

Polyuria, polydipsia, and frequent bouts of severe dehydration are common symptoms in young patients with Fanconi syndrome. The polyuria is mainly related to the osmotic diuresis from the excessive urinary solute losses; but some patients have an associated concentrating defect, especially those with prolonged hypokalemia.

Growth Retardation

Growth retardation in children with Fanconi syndrome is multifactorial.

Hypophosphatemia, disordered vitamin D metabolism, and acidosis contribute to growth failure, as do chronic hypokalemia and extracellular volume contraction. Glycosuria and aminoaciduria probably do not play a role. However, even with correction of all these metabolic abnormalities, most patients fail to grow, especially those with cystinosis.

Hypouricemia

Hypouricemia, caused by impairment in the kidney’s handling of uric acid, is often present in Fanconi syndrome, especially in adults. Urolithiasis from the uricosuria only rarely has been reported, probably because the urine flow and pH are increased, inhibiting uric acid crystallization.

Therapy should be directed at the underlying causes of Fanconi syndrome when possible (see later discussion). This includes avoidance of the offending nutrient in galactosemia, hereditary fructose intolerance, or tyrosinemia; penicillamine or other copper chelators for Wilson disease; or chelation therapy for heavy metal intoxication. In these patients, resolution of Fanconi syndrome usually is complete.

In all patients with Fanconi syndrome, therapy is also directed at the biochemical abnormalities secondary to the solute losses and the bone disease often present in these patients. The proximal RTA (type 2 RTA) usually requires large doses of alkali for correction. Some patients benefit from hydrochlorothiazide to minimize the volume expansion associated with these large doses of alkali. Potassium supplementation usually is also needed, especially if there is significant RTA. If given in combination with a metabolizable anion, such as potassium citrate, lactate, or acetate, these supplements will also correct the acidosis. A few patients will require sodium supplementation along with potassium, and even fewer will require sodium chloride supplementation (especially those who have alkalosis as a result of volume contraction from large urinary NaCl losses). Magnesium supplementation may be required to correct the hypokalemia, and adequate fluid intake is essential. Correction of hypokalemia and its effect on the concentrating ability of the distal tubule may lessen the polyuria.

Bone disease is multifactorial, including urinary loss of vitamin D binding protein and vitamin D, decreased synthesis of calcitriol in some patients, hypercalciuria, chronic acidosis, and hypophosphatemia, which is the major factor. Hypophosphatemia should be treated with 1 to 3 g/day of oral phosphate with the goal of normalizing serum phosphate levels. Many patients with Fanconi syndrome will require supplemental vitamin D for adequate treatment of the rickets and osteomalacia. It is unclear whether standard vitamin D (calciferol [ergocalciferol]) or a vitamin D metabolite is better for supplementation, but most clinicians use a vitamin D metabolite, such as 1,25-dihydroxycholecalciferol (calcitriol). These metabolites obviate the concern of inadequate vitamin D hydroxylation by the proximal tubule mitochondria and reduce the risk for prolonged hypercalcemia because of their shorter half-life. Vitamin D therapy will also improve the hypophosphatemia and lessen the risk for hyperparathyroidism. Supplemental calcium is indicated in those with hypocalcemia after supplemental vitamin D is started. Hyperaminoaciduria, glycosuria, proteinuria, and hyperuricosuria usually do not require specific treatment. Carnitine supplementation, to compensate for the urinary losses, may improve muscle function and lipid profiles, but the evidence is inconsistent.

INHERITED CAUSES OF FANCONI SYNDROME

Cystinosis

Definition

Cystinosis, or cystine storage disease, is characterized biochemically by excessive intracellular storage, particularly in lysosomes, of the amino acid cystine.[2] Three different types of cystinosis can be distinguished based on clinical course, age at onset, and intracellular cystine content.

Benign or adult cystinosis is associated with cystine crystals in the cornea and bone marrow only, as well as the mildest elevation in intracellular cystine levels; no kidney disease occurs. Infantile or nephropathic cystinosis is the most common form of cystinosis and is associated with the highest intracellular levels of cystine and the earliest onset of kidney disease. In the intermediate or adolescent form, intracellular cystine levels are between those of the infantile and adult forms, with later onset of kidney disease.

Etiology and Pathogenesis

Nephropathic cystinosis is transmitted as an autosomal recessive trait localized to the short arm of chromosome 17, with an estimated incidence of 1 in 200,000 live births. The CTNS gene codes for a lysosomal membrane protein, cystinosin, that mediates the transport of cystine from the lysosome.3 The benign and intermediate forms of cystinosis are also associated with CTNS mutations but still have some functional transport protein, leading to lower intracellular cystine levels and slower onset of kidney disease in the intermediate form and no kidney disease in the benign form. Cystinosin has been shown to play a role in other cellular processes besides lysosomal cystine transport, which may explain why Fanconi syndrome sometimes persists despite cystine depletion.4

Clinical Manifestations

The first clinical evidence of nephropathic cystinosis relates to Fanconi syndrome and usually appears in the second half of the first year of life. Subtle abnormalities of tubular function can be demonstrated earlier in families with index cases, but there always is a delay between birth and the first symptoms. Rickets is common after the first year of life, along with growth failure. The growth failure occurs before the GFR declines and despite correction of electrolyte and mineral deficiencies. The GFR invariably declines, and end-stage kidney disease (ESKD) occurs by late childhood.

Nephrocalcinosis is relatively common, and a few patients have kidney stones. Photophobia is another common symptom that occurs by 3 years of age and is progressive. Older patients with cystinosis may develop visual impairment and blindness. Children with cystinosis usually have a fair complexion and blond hair, but dark hair has been observed in some. Cystinosis has been observed in other ethnic groups but is less common than in Whites.

The diagnosis is based on the demonstration of elevated intracellular levels of cystine, usually in white blood cells or skin fibroblasts.

Patients with nephropathic and intermediate cystinosis have intracellular cystine levels that exceed 2 nmol half-cystine per milligram of protein (normal <0.2 nmol half-cystine per milligram of protein). Heterozygotes for cystinosis have levels that range from 0.2 to 1 nmol half-cystine per milligram of protein. A slit-lamp demonstration of corneal crystals strongly suggests the diagnosis2 (Fig. 50.4). A prenatal diagnosis can be made with amniocytes or chorionic villi.

Common late complications of cystinosis include hypothyroidism, splenomegaly and hepatomegaly, decreased visual acuity, swallowing difficulties, pulmonary insufficiency, and corneal ulcerations.5 Less frequently, older patients have insulin-dependent diabetes mellitus, myopathy, and progressive neurologic disorders. Decreased brain cortex also has been noted on imaging in some patients. Older patients may develop vascular calcification, especially of the coronary arteries, which can lead to myocardial ischemia.

Kidney Pathology

The morphologic features of the kidney in cystinosis vary with the stage. Early in the disease, cystine crystals are present in tubular epithelial cells, interstitial cells, and rarely glomerular epithelial cells[6,7] (Fig. 50.5A). A swan-neck deformity or thinning of the first part of

Fig. 50.4 Corneal Opacities in Cystinosis. Tinsel-like refractile opacities in the cornea of a patient with cystinosis under slit-lamp examination. (From Foreman JW. Cystinosis and the Fanconi syndrome. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric Nephrology. 5th ed. Lippincott Williams & Wilkins; 2004.)

the proximal tubule is an early finding but is not unique to cystinosis. Later, there is pronounced tubular atrophy, interstitial fibrosis, and abundant crystal deposition with giant cell formation of the glomerular visceral epithelium, segmental sclerosis, and eventual glomerular obsolescence. Electron microscopy (EM) demonstrates intracellular crystalline inclusions consistent with cystine (see Fig. 50.5B). Peculiar “dark cells,” unique to the cystinotic kidney, also have been observed. These are mostly macrophages and some podocytes and are probably dark because of a reaction of cystine with osmium tetroxide.

Treatment

Nonspecific therapy for infantile cystinosis consists of vitamin D therapy and replacement of the urinary electrolyte losses, followed, in due course, by the management of the progressive kidney disease (Table 50.1). Cysteamine therapy can lower tissue cystine levels and slow the decline in GFR, especially in children with normal serum creatinine concentration who are treated before 2 years of age[8] (Fig. 50.6). Cysteamine therapy also improves linear growth but not Fanconi syndrome. The most common problems associated with cysteamine therapy are nausea, vomiting, and a foul odor and taste. Treatment should begin with a low dose of cysteamine soon after the diagnosis is made, increased during 4 to 6 weeks to 60 to 90 mg/kg/day in four divided doses as close to every 6 hours as possible. Slowly increasing the dose minimizes the risk for neutropenia, rash, and arthritis. Leukocyte cystine levels should be checked every 3 to 4 months to monitor effectiveness and compliance, with the goal of achieving and maintaining a cystine level less than 2.0 and preferably 1.0 nmol half-cystine/mg protein. A long-acting formulation of cysteamine is available that allows twice-daily dosing. This formulation is equally effective and may aid compliance, but is significantly more expensive than the standard formulation of cysteamine. Two preparations of topical cysteamine for treatment of the corneal crystals are available: an aqueous solution that is given every hour and a gel formulation that is applied four times a day. Studies are underway to assess the utility of a gene-edited autologous bone marrow transplant in treating cystinosis.

Treatment of ESKD in these children poses no greater problems than in other children. Successful kidney transplantation reverses the kidney failure and Fanconi syndrome but does not appear to improve the extrarenal manifestations of cystinosis. Cysteamine therapy should be continued after transplantation. Cystine does not accumulate in the transplanted kidney, except in infiltrating immunocytes.

TABLE 50.1

A

Treatment of Cystinosis

Problem

Therapy

Removal of lysosomal
cystine

Cysteamine, 0.325 g/m^2 q6h
Delayed-release cysteamine, 0.65 g/m^2 q12h
Goal: Maintain leukocyte cystine level <1 nmol
half-cystine[a]/mg protein

Correction of Tubulopathy
Dehydration
2–6 L/day fluid
Acidosis
2–15 mmol/kg/day K^+ citrate
Hypophosphatemia
1–4 g/day K^+ phosphate
Rickets
0.25–1µg/day calcitriol
Adjunct therapies
NaCl, carnitine, indomethacin,
hydrochlorothiazide
Later Therapies
Growth failure
Hypothyroidism
Kidney failure

Growth hormone
Thyroxine
Renal replacement therapy, ideally kidney
transplantation

[a] By convention, units are half-cystine because the cystine originally was converted to two cysteine molecules, or “broken in half,” before measurement.

Clinical Manifestations
B
Fig. 50.5 Cystine Crystals in the Kidney in Cystinosis. (A) Crystals are seen in photomicrograph of alcohol-fixed nephrectomy specimen, taken through incompletely crossed polarizing filters. Birefringent crystals are evident in tubular epithelial cells and free in the interstitium. (B) Electron micrograph of a renal biopsy specimen shows hexagonal, rectangular, and needle-shaped crystals in macrophages within the interstitium. (Original magnification ×3000.) (A, From Schnaper HW, Cottel J, Merrill S, et al. Early occurrence of end-stage renal disease in a patient with infantile nephropathic cystinosis. J Pediatr. 1992;120:575–578. B, From Van’t Hoff WG, Ledermann SE, Waldron M, Trompter RS. Earlyonset chronic renal failure as a presentation of infantile cystinosis. Pediatr Nephrol. 1995;9:483–484.)

Galactosemia

Etiology and Pathogenesis

Galactosemia is an autosomal recessive disorder of galactose metabolism. It is most often the result of deficient activity of the enzyme galactose-1-phosphate uridyltransferase, the incidence of which is 1 in 62,000 live births.[9] Deficiency of this enzyme leads to the intracellular accumulation of galactose-1-phosphate, with damage to the liver, proximal renal tubule, ovary, brain, and lens. A less frequent cause of galactosemia is a deficiency of galactose kinase, which forms galactose1-phosphate from galactose. Cataracts are the only manifestation of this form of galactosemia.

The pathogenesis of the symptoms of galactosemia is not clear. Accumulation of galactose-1-phosphate subsequent to the ingestion of galactose can inhibit pathways for carbohydrate metabolism, and its level correlates somewhat with clinical symptoms. Defective galactosylation of proteins also has been postulated. Formation of galactitol from galactose by aldose reductase is probably responsible for the cataract formation.

Affected infants ingesting milk containing lactose (the most common source of galactose in the diet) rapidly develop vomiting, diarrhea, and failure to thrive. Jaundice from unconjugated hyperbilirubinemia is common, along with severe hemolysis. Continued intake of galactose leads to hepatomegaly and cirrhosis. Cataracts appear within days after birth, although at first they often are detectable only with a slit lamp. Cognitive dysfunction or developmental delay may develop within a few months. Fulminant Escherichia coli sepsis has been described, possibly a consequence of inhibited leukocyte bactericidal activity.

In addition to these clinical findings, galactose intake leads within days to hyperaminoaciduria and albuminuria. Increased urine sugar excretion is principally due to galactosuria and not glycosuria. There seems to be little or no impairment in glucose handling by the proximal tubule. Galactosemia should be suspected whenever there is a urinary reducing substance that does not react in a glucose oxidase test.

The diagnosis can be confirmed by demonstration of deficient transferase activity in red blood cells, fibroblasts, leukocytes, or hepatocytes.

Most infants with galactosemia are found through newborn metabolic screening.

Treatment

Galactosemia is treated by elimination of galactose from the diet. Acute symptoms and signs resolve in a few days. Cataracts will also regress to some extent. Even with early elimination of galactose, developmental delay, speech impairment, ovarian dysfunction, and growth retardation are common. Profound intellectual deficits are rare even in infants treated late.

Hereditary Fructose Intolerance

Etiology and Pathogenesis

Hereditary fructose intolerance is another disorder of carbohydrate metabolism associated with Fanconi syndrome.[10] Fructose intolerance is inherited as an autosomal recessive trait, with an estimated incidence of 1 in 20,000 live births. It is caused by a deficiency of the B isoform of the enzyme fructose-1-phosphate aldolase, which cleaves

Effect of Cysteamine on Lysosomal Cystine
Normal cell

Cystinosis

Cystinosis plus Cysteamine

Lysosome

Lysosome

Lysosome

Cys-Cys

Cys-Cys

Cys-Cys
plus
Cysteamine
Cys

Cys-Cysteamine

Cystinosin

Fig. 50.6 Effect of Cysteamine on Lysosomal Cystine. In cystinosis, the transporter (cystinosin) for cystine (Cys-Cys) egress from the lysosome is defective, and cysteine accumulates. Cysteamine can easily enter the lysosome and combine with cystine, forming cysteine (Cys) and the mixed disulfide cysteamine-cysteine. Both these compounds can exit the lysosome through a transporter other than the cystine carrier.

fructose-1-phosphate into d-glyceraldehyde and dihydroxyacetone phosphate. Deficient activity of aldolase B leads to tissue accumulation of fructose-1-phosphate and reduced levels of adenosine triphosphate (ATP). Experimentally, mice with aldolase B deficiency can be rescued by blocking fructokinase, which prevents the accumulation of fructose-1-phosphate and maintains ATP.

Proximal Tubule Glucose Reabsorption
Lumen

Proximal tubular cell

Blood

Clinical Manifestations

Symptoms of hereditary fructose intolerance appear at weaning when fruit, vegetables, and sweetened cereals that contain fructose, sucrose, or sorbitol (the latter is converted to fructose in the body) are introduced. Affected children experience nausea, vomiting, and symptoms of hypoglycemia shortly after ingestion of fructose, sucrose, or sorbitol. These symptoms may progress to seizures, coma, and even death, depending on the amount consumed. When they are exposed to fructose, infants may have a catastrophic illness, with severe dehydration, shock, acute liver impairment, bleeding, and acute kidney injury (AKI).

Concomitant serum biochemical findings after fructose ingestion are decreased glucose, phosphate, and bicarbonate and increased uric acid and lactic acid. Chronic exposure to fructose leads to failure to thrive, hepatomegaly and fatty liver, jaundice, hepatic cirrhosis, Fanconi syndrome, and nephrocalcinosis. Children with hereditary fructose intolerance quickly develop an aversion to sweets.

Diagnosis

The diagnosis should be suspected when symptoms develop after the ingestion of fructose. This can be confirmed by assaying the activity of fructose-1-phosphate aldolase in a liver biopsy specimen or through genetic testing of the aldolase B gene.

Treatment

Treatment of hereditary fructose intolerance involves strict avoidance of foods containing fructose and sucrose, but because most patients develop a strong aversion to such foods, this is usually easy. The greatest risk occurs during infancy, before those affected learn to avoid fructose.

Glycogenosis

Most patients with glycogen storage disease and Fanconi syndrome have an autosomal recessive disorder characterized by heavy glycosuria and increased glycogen storage in the liver and kidney, known as the Fanconi-Bickel syndrome, or glucose-losing syndrome, because the glucose losses can be massive.11 These children have massive hepatomegaly, fasting hypoglycemia, and severe growth retardation in addition to Fanconi syndrome. The defect is deficient activity of the glucose transporter GLUT2 (Fig. 50.7). GLUT2 facilitates glucose exit from the basolateral side of the proximal tubule and intestinal cell and sugar entry and exit from the hepatocyte and pancreatic β cell. A few patients with type I glycogen storage disease have mild Fanconi syndrome but not Fanconi-Bickel syndrome. Treatment of this disorder is directed at the renal solute losses, treatment of rickets (which can be severe), and frequent feeding to prevent ketosis. Uncooked cornstarch has been shown to lessen the hypoglycemia and to improve growth.

Na+

Glucose

SGLT 1
Na+
Glucose
SGLT 2

GLUT 1
Glucose
GLUT 2

Fig. 50.7 Proximal Tubule Glucose Reabsorption. Glucose enters the proximal tubule cell coupled to Na+ reabsorption from the lumen through a high-capacity, low-affinity transporter (SGLT2) in the early proximal tubule and a low-capacity, high-affinity transporter (SGLT1) in the late proximal tubule. Glucose exits the cell through the transporters (GLUT1 and GLUT2) located in the late and early proximal tubule, respectively. GLUT1, -2, Glucose transporter protein types 1, 2; SGLT1, sodium-glucose linked cotransporter type 1.

Tyrosinemia

Definition

Hereditary tyrosinemia type I, also known as hepatorenal tyrosinemia, is a defect of tyrosine metabolism affecting the liver, kidneys, and peripheral nerves.12

Etiology and Pathogenesis

The cause of hereditary tyrosinemia type I is a deficiency of fumarylacetoacetate hydrolase (FAH) activity; it is an autosomal recessive disorder. Decreased or absent FAH activity leads to accumulation of maleylacetoacetate (MAA) and fumarylacetoacetate (FAA) in affected tissues. These compounds can react with free sulfhydryl groups, reduce intracellular levels of glutathione, and act as alkylating agents. Maleylacetoacetate and fumarylacetoacetate are not detectable in plasma or urine but are converted to succinylacetoacetate and succinylacetone. Succinylacetone is structurally similar to maleic acid, a compound that causes Fanconi syndrome experimentally in rats and may be the cause of Fanconi syndrome in humans affected with tyrosinemia.

Clinical Manifestations

The liver is the major organ affected, evident as early as the first month of life. Such infants usually have severe disease and die in the first year. All children with tyrosinemia will eventually develop macronodular cirrhosis, and many develop hepatocellular carcinoma. Acute, painful peripheral neuropathy and autonomic dysfunction also can occur.

Proximal renal tubular dysfunction is evident in all patients with tyrosinemia, especially those presenting after infancy. Nephromegaly is very common, and nephrocalcinosis may be seen. Glomerulosclerosis and impaired GFR may be seen with time.

Diagnosis

The diagnosis should be suspected with elevated plasma tyrosine and methionine levels together with their p-hydroxy metabolites. The presence of succinylacetone in blood or urine is diagnostic of hereditary tyrosinemia type I.

Treatment

The institution of a diet low in phenylalanine and tyrosine dramatically improves the renal tubular dysfunction. Nitisinone, which inhibits the formation of MAA and FAA, dramatically improves the renal and hepatic dysfunction.12 Liver transplantation has been successfully used to treat patients with severe liver failure and prevent the development of hepatocellular carcinoma. Liver transplantation leads to rapid correction of Fanconi syndrome.

Wilson Disease

Definition

Wilson disease is an inherited disorder of copper metabolism that affects numerous organ systems.13,14 It has an overall incidence of 1 in 30,000 live births. About 40% of patients present with liver disease, 40% with extrapyramidal symptoms, and 20% with psychiatric or behavioral abnormalities.

Etiology and Pathogenesis

Wilson disease is caused by a defect in the P-type copper–transporting adenosine triphosphatase ATP7B, which is highly expressed in the liver, kidney, and placenta. It impairs biliary copper excretion and the incorporation of copper into ceruloplasmin. These abnormalities cause excessive intracellular accumulation of copper in the liver, with subsequent overflow into other tissues, such as the brain, cornea, and renal proximal tubule.

Clinical Manifestations

Patients typically present with chronic liver disease, often with relatively high serum bilirubin relative to alkaline phosphatase (bilirubin [mg/dL]/alkaline phosphatase >4). Excessive storage of copper in the kidney leads to renal tubular dysfunction in most patients and fullblown Fanconi syndrome in some. Hematuria also has been noted. Renal plasma flow and GFR decrease as the disease progresses, but death from extrarenal causes occurs before the onset of kidney failure. Fanconi syndrome usually appears before the onset of hepatic failure. Hypercalciuria with development of kidney stones and nephrocalcinosis also have been reported. Besides proximal tubular dysfunction, abnormalities in distal tubular function, decreased concentrating ability, and distal RTA (type 1 RTA) also have been observed. Neurologic abnormalities, such as dysarthria and gait disturbances, may be the presenting symptom in young adults with Wilson disease. KayserFleischer rings, dense brown copper deposits around the iris, may be visible but typically can be seen only with a slit lamp.

Kidney Pathology

Histologic examination of the kidney in untreated Wilson disease shows either no alteration on light microscopy or only some flattened proximal tubular cells without recognizable brush borders. Electron microscopy shows loss of the brush border, disruption of the apical tubular network, electron-dense bodies probably representing metalloproteins in the subapical region of tubule cell cytoplasm, and cavitation of the mitochondria with disruption of the normal cristae pattern. Rubeanic acid staining shows intracytoplasmic copper granules. The copper content of kidney tissue is greatly elevated.

Diagnosis

The diagnosis of Wilson disease should be suspected in children and young adults with unexplained neurologic disease, chronic active hepatitis, acute hemolytic crisis, behavioral or psychiatric disturbances, or the appearance of Fanconi syndrome. In such patients, the presence of Kayser-Fleischer rings is an important clue in making the diagnosis. Serum ceruloplasmin levels are decreased in 96% of patients with Wilson disease. A greatly increased urinary copper level is also useful in making the diagnosis, especially if it increases significantly with dpenicillamine. Liver copper levels are increased in untreated patients. Mutational analysis is also available.

Treatment

Treatment with penicillamine 1 to 1.5 g/day reverses the kidney dysfunction and potentially the hepatic and neurologic disease, depending on the degree of damage before the onset of therapy. Recovery, however, is quite slow. Trientine also can chelate copper and is indicated in patients who cannot tolerate penicillamine. Tetrathiomolybdate is a potent agent in removing copper from the body and has been used in some patients with neurologic disease to prevent the immediate worsening of symptoms that can occur with penicillamine. Zinc salts, which induce intestinal metallothionein and blockade of intestinal absorption of copper, are useful in maintenance therapy. Liver transplantation has been successful in some patients but should be reserved for those with liver failure.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome) is characterized by congenital cataracts and glaucoma, severe developmental delay, hypotonia with diminished to absent reflexes, and renal abnormalities.[15,16]

Fanconi syndrome is followed by progressive kidney impairment. Endstage kidney disease usually does not occur until the third to fourth decade of life.

Lowe syndrome is transmitted as an X-linked recessive trait. Despite this inheritance pattern, Lowe syndrome has occurred in a few females. The defective gene codes for phosphatidyl inositol 4,5-bisphosphate 5-phosphatase, OCRL1, involved with cell trafficking and signaling. Light microscopy of the kidney is normal early in the disorder, with endothelial cell swelling and thickening and splitting of the glomerular basement membrane seen by EM. In the proximal tubule cells, there is shortening of the brush border and enlargement of the mitochondria, with distortion and loss of the cristae. Only symptomatic treatment is available.

Dent Disease

Definition

Dent disease is an X-linked recessive disorder characterized by lowmolecular-weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis, and rickets.17 18 Affected males often have aminoaciduria, phosphaturia, and glycosuria. Kidney failure is common and may occur by late childhood. Hemizygous females usually have only proteinuria and mild hypercalciuria. X-linked recessive nephrolithiasis and X-linked recessive hypophosphatemic rickets have similar features, and most have a defect in the renal ClC-5 chloride channel. Dent disease type 2 is a clinically similar disease affecting males, but there is a mutation in the same gene that causes Lowe syndrome, although patients with Dent type 2 do not have the brain or eye involvement seen in Lowe syndrome.17

Etiology and Pathogenesis

Most of these disorders are caused by a mutation in the CLCN5 gene leading to inactive ClC-5 chloride channel function (see Fig. 50.2). The ClC-5 chloride channel spans the membrane of preendocytic vesicles just below the brush border of the proximal tubule. This channel plays a role in the acidification of these vesicles by a proton pump. Lack of this Cl channel interferes with protein reabsorption from the tubule through the megalin-cubilin receptor system and cell surface receptor recycling, which may explain the phosphaturia, glycosuria, and aminoaciduria.

The defective OCRL1 in patients with Dent disease type 2 interferes with normal cell protein trafficking. The kidney disease is similar to that seen in Dent disease type 1. Although patients do not have the eye and brain disease seen in patients with Lowe, a few patients with Dent type 2 have a mild intellectual deficit, hypotonia, and subclinical cataracts.

Filtered PTH is also reabsorbed by the megalin-cubilin system for degradation in the lysosome. Decreased PTH reabsorption allows increased binding to luminal PTH receptors and increased endocytosis of luminal phosphate transporters, leading to increased phosphaturia.1

Mitochondrial Cytopathies

Definition

Mitochondrial cytopathies are a diverse group of diseases with abnormalities in mitochondrial DNA that lead to mitochondrial dysfunction in various tissues.19

Clinical Manifestations

Most of the mitochondrial cytopathies manifest with neurologic disorders such as myopathy, myoclonus, ataxia, seizures, external ophthalmoplegia, stroke-like episodes, and optic neuropathy. Other manifestations include retinitis pigmentosa, diabetes mellitus, exocrine pancreatic insufficiency, sideroblastic anemia, sensorineural hearing loss, pseudoobstruction of the colon, hepatic disease, cardiac conduction disorders, and cardiomyopathy.

The most common kidney manifestation associated with mitochondrial cytopathies is Fanconi syndrome, although a number of patients have been described with focal segmental glomerulosclerosis (FSGS) and corticosteroid-resistant nephrotic syndrome. All the patients with kidney abnormalities have had extrarenal disorders, mainly neurologic disease. Most patients present in the first months of life and die soon afterward.

Diagnosis

A clue to mitochondrial cytopathies is elevated serum or cerebrospinal fluid lactate levels, especially in association with an altered lactate-topyruvate ratio, suggesting a defect in mitochondrial respiration. The presence of “ragged red fibers,” a manifestation of abnormal mitochondria, in a muscle biopsy specimen is another clue, especially with large abnormal mitochondria on EM of muscle tissue.

Treatment

There is little to offer these patients in terms of definitive therapy. Low mitochondrial enzyme complex III activity can be treated with menadione or ubidecarenone. Deficient mitochondrial enzyme complex I activity may be treated with riboflavin and ubidecarenone. Ascorbic acid has been used to minimize oxygen free radical injury. Highlipid, low-carbohydrate diet has been tried in cytochrome c oxidase deficiency.

Idiopathic Fanconi Syndrome

A number of patients develop the complete Fanconi syndrome in the absence of any known cause. Traditionally called adult Fanconi syndrome because it was thought that only adults were affected, it is now clear that children may be affected, and a more proper designation is idiopathic Fanconi syndrome. Not all the features of Fanconi syndrome may be present when the patient is first seen but do appear with time. Idiopathic Fanconi syndrome can be inherited in an autosomal dominant, autosomal recessive, or even X-linked pattern. However, most cases occur sporadically, with no evidence of genetic transmission. The prognosis is variable, and some patients develop ESKD 10 to 30 years after onset of symptoms. A few patients have undergone kidney transplantation; in some, Fanconi syndrome has recurred in the allograft without evidence of rejection, suggesting an extrarenal cause of the idiopathic form.

Renal morphologic descriptions of such cases are scanty. In some reports, no abnormalities were found, and, in others, tubular atrophy with interstitial fibrosis was interspersed with areas of tubular dilation. Greatly dilated proximal tubules with swollen epithelium and grossly enlarged mitochondria with displaced cristae also have been noted.

ACQUIRED CAUSES OF FANCONI SYNDROME

Numerous substances can injure the proximal renal tubule. Injury can range from an incomplete Fanconi syndrome to acute tubular necrosis (ATN) or ESKD. The extent of the tubular damage varies depending on the type of toxin, amount ingested, and host characteristics. A careful history of possible toxin exposure and recent medications is important in patients with tubular dysfunction. Box 50.1 lists the more common causes of acquired Fanconi syndrome.

Heavy Metal Intoxication

A major cause of proximal tubular dysfunction is acute heavy metal intoxication, principally lead and cadmium (see Chapter 65). In lead poisoning, renal tubular dysfunction, mainly aminoaciduria and mild glycosuria and phosphaturia, is usually overshadowed by the development of chronic kidney disease (CKD) and involvement of other organs, especially the central nervous system.[20] Fanconi syndrome associated with cadmium poisoning is associated with severe bone pain, giving rise to the name itai-itai (“ouch-ouch”) disease for its occurrence in Japanese patients affected by industrial contamination of the soil.21

Tetracycline

Outdated tetracycline causes reversible Fanconi syndrome even in therapeutic doses. Recovery is rapid when the degraded drug is stopped. The compound responsible for the tubule dysfunction is anhydro-4tetracycline, formed from tetracycline by heat, moisture, and low pH.

Cancer Chemotherapy Agents

A number of cancer chemotherapy agents have been associated with Fanconi syndrome and renal tubular dysfunction, especially cisplatin and ifosfamide. Carboplatin has been associated with reduced GFR and magnesium wasting but not Fanconi syndrome. The nephrotoxicity of both cisplatin and ifosfamide is dose dependent and often irreversible. Besides the usual manifestations of Fanconi syndrome, cisplatin toxicity is characterized by hypomagnesemia, caused by hypermagnesuria, which can be extremely severe, persistent, and difficult to treat.22 23 Ifosfamide is more often associated with hypophosphatemic rickets.22 Chloroacetaldehyde, a metabolite of ifosfamide, appears experimentally to cause Fanconi syndrome. Both ifosfamide and cisplatin can also cause an irreversible reduction in GFR.

Other Drugs and Toxins

Exposure to a wide range of toxins may give rise to Fanconi syndrome, often in association with a reduced GFR, including 6-mercaptopurine, toluene (glue sniffing), and Chinese herbal medicines containing Aristolochia spp (see Chapter 79).24 In addition, anecdotal reports have associated Fanconi syndrome with valproic acid (valproate), suramin, gentamicin, and ranitidine. Antiviral medications, especially antiretroviral agents such as tenofovir, are an increasingly common cause of Fanconi syndrome.25

Dysproteinemias

Dysproteinemia26 from multiple myeloma, light-chain proteinuria,27 Sjögren syndrome, and amyloidosis is sometimes associated with Fanconi syndrome, which appears to be correlated with urinary free light chains that can cause proximal tubule dysfunction through intracellular crystallization or lysosomal dysfunction.28

Glomerular Disease

Nephrotic syndrome is rarely associated with Fanconi syndrome. Most of these patients have FSGS, and the occurrence of Fanconi syndrome heralds a poor prognosis.

After Acute Kidney Injury

Tubular dysfunction can occur transiently during recovery from AKI from any cause, regardless of whether a known tubular toxin was originally implicated.

After Kidney Transplantation

Fanconi syndrome has appeared rarely after kidney transplantation. The pathogenesis probably is multifactorial, including sequelae of ATN, rejection, nephrotoxic drugs, ischemia from renal artery stenosis, and residual hyperparathyroidism.

(see Fig. 50.3). When the serum glucose concentration is in a physiologic range, virtually all the filtered glucose is reabsorbed in the proximal tubule.29 Filtered glucose enters the proximal tubule through two specific carriers (SGLT1 and SGLT2) coupled to sodium and exits the cell through the sugar transporters GLUT1 and GLUT2 (see Fig. 50.7). However, when the serum level exceeds the physiologic range, the filtered load exceeds the capacity of these carriers, and glucose begins to appear in the urine; this is termed the renal threshold.

Etiology and Pathogenesis

Familial glucose-galactose malabsorption is a rare autosomal disorder caused by mutations in the gene coding for the brush border sodiumglucose cotransporter SGLT1, which is found in the intestinal cell and the S3 segment of the proximal renal tubule cell. The disorder is characterized by the neonatal onset of life-threatening diarrhea from the intestinal malabsorption of glucose and galactose, which resolves rapidly with the removal of glucose and galactose and its dipeptide, lactose, from the diet. These patients frequently also have mild renal glycosuria.

Familial renal glycosuria occurs with an incidence of 1 in 20,000 live births and can be inherited as a heterozygous, homozygous, or mixed heterozygous trait.[29] This disorder is caused by mutations in the SLC5A2 gene that codes for the SGLT2 glucose transporter found in the early portion of the proximal tubule. Inhibitors of SGLT2, which mimic this genetic defect, have been used recently in type 2 diabetes to lower hyperglycemia without causing weight gain or aggravating hyperinsulinism (see Chapter 32).

In the past, renal glycosuria was divided into three types based on the reabsorption patterns observed during glucose infusion studies, but this typing system has been questioned because clearance data suggest patients with renal glycosuria have rates of glucose reabsorption that vary from virtually no reabsorption to near-normal rates, rather than three distinct types, reflecting different mutations in the SLC5A2 gene and differing amounts of functional protein.

Natural History

Patients with familial glucose-galactose malabsorption appear to grow and develop normally with removal of the offending sugars from the diet. The clinical course of hereditary renal glycosuria is benign, except for a few patients with polyuria and salt wasting, and it is not a precursor to diabetes mellitus. Patients need to be aware of the condition in order not to receive unnecessary diagnostic investigations or even treatment for presumed diabetes mellitus.

AMINOACIDURIAS

As with glucose, amino acids are almost completely reabsorbed in the proximal tubule by a series of specific carriers. Studies have described a number of inherited disorders resulting in the incomplete reabsorption of a specific amino acid or a group of amino acids[30] (Table 50.2). Most do not result in kidney disease.

Cystinuria

Definition

FAMILIAL GLUCOSE-GALACTOSE MALABSORPTION AND HEREDITARY RENAL GLYCOSURIA

Cystinuria is characterized by the excessive urinary excretion of cystine and the dibasic amino acids ornithine, lysine, and arginine and accounts for about 1% to 2% of all kidney stones and 6% to 8% of pediatric kidney stones.[31,32]

Definition

Etiology and Pathogenesis

Renal glycosuria refers to the appearance of readily detectable glucose in the urine when the serum glucose concentration is in a normal range

These four amino acids share a transport system on the brush border membrane of the proximal tubule. Because of the relative insolubility of cystine when its urine concentration exceeds 250 mg/L (1 mmol/L), patients with cystinuria have recurrent kidney stones.

Cystinuria is an autosomal recessive trait with a disease incidence of 1 in 15,000 births.[31,32] Early studies suggested there were three genetic types on the basis of in vitro studies of intestinal transport and amino acid excretion in heterozygotes. More recently, two genes (SLC3A1 coding for the protein rBAT and SLC7A9 for the protein b$^{0,+}$AT) have been identified that are defective in cystinuria. SLC3A1 heterozygotes have normal excretion rates for cystine. SLC7A9 heterozygotes have cystine excretion rates that range from normal to almost that of homozygous patients. Based on these data, a newer classification proposed type A for mutations in both SLC3A1 genes and type B for mutations in SLC7A9.[31,32] Type AB is a compound heterozygote. Type A accounts for 38% of cystinuria patients, type B for 47%, and type AB for 14%.

Clinical Manifestations

increase daily fluid intake to greater than 2 L/1.73 m^2 and restrict sodium intake. However, because most patients with cystinuria excrete 0.5 to 1 g/day of cystine, a urine output of 2 to 4 L/day is needed to achieve this goal. Cystine solubility increases in alkaline urine, but the urine pH must be > 7 to 7.5 to be effective. In patients with recurrent stone disease, thiols such as penicillamine and tiopronin are extremely useful through the formation of a more soluble, mixed disulfide of the thiol and cysteine from cystine. Tiopronin is the most commonly prescribed thiol because it has fewer side effects than penicillamine and is started at a low dose (100 mg bid) and slowly increased (doses >1000 mg/day have little added effect) to achieve a urine cystine concentration below 250 mg/L in conjunction with a high fluid intake. Penicillamine is also effective, and the dose should be slowly increased to minimize side effects. Captopril can be useful (an effect resulting from its thiol structure, not its angiotensin-converting enzyme inhibitor effect), but the dose range (75–150 mg/day) may be limited by its hypotensive effects.

Cystine stones (calculi) are typically yellow-brown (Fig. 50.8A) and radiopaque (see Fig. 50.8B). Cystine crystals appear as microscopic, flat hexagons in the urine (see Fig. 50.8C), and this is a clue to the diagnosis.

HEREDITARY DEFECTS IN URIC ACID HANDLING

Diagnosis

Hereditary Renal Hypouricemia

Patients can be tested for cystinuria with the cyanide-nitroprusside test, but type B heterozygotes also may give a positive result. The definitive test is to quantify cystine and dibasic amino acid excretion in a 24-hour urine specimen. Homozygotes excrete more than 118 mmol cystine per mmol creatinine (250 mg/g creatinine). Genetic testing for mutations in the SLC3A1 and SLC7A9 is also readily available.

Hereditary renal hypouricemia is a rare autosomal recessive disorder characterized by very low serum uric acid levels (<2.5 mg/dL [<150 µmol/L] in adult men and <2.1 mg/dL [<124 µmol/L] in adult women) and increased uric acid clearance, ranging from 30% to 150% of the filtered load.[33] In the normal kidney, uric acid is both reabsorbed and secreted in the proximal tubule by two different uric acid–anion exchange transporters and a voltage-sensitive pathway.

In some patients, the defect is in the gene SLC22A12 that codes for the protein URAT1; other patients have been found to have mutations in SLC2A9 (GLUT9). Most patients do not have symptoms, and hypouricemia is found incidentally when a low serum uric acid concentration is noted during routine serum chemistry evaluation. About one-fourth of patients with renal hypouricemia have had kidney stones, but only one-third of these were uric acid stones. There also may be hypercalciuria, and a few patients have had exerciseinduced AKI, thought to be caused by acute tubular injury by passage of uric acid “gravel” in association with volume depletion and reduced urine pH. Most patients require no treatment, but if forming uric acid stones, they should maintain a high fluid intake. Urine alkalinization and allopurinol can be used for patients with persistent uric acid stones.

Treatment

The aim of therapy in cystinuria is to lower the urine cystine concentration to less than 250 mg/L (1 mmol/L).31 32 The first step is to

TABLE 50.2

Inherited Aminoacidurias

Disease	Clinical Findings	Urine Amino Acids
Cystinuria	Urolithiasis	Cystine, lysine, ornithine, arginine
Hartnup disease	Rash, neurologic disease	Neutral amino acids
Iminoglycinuria	None	Proline, hydroxyproline glycine
Lysinuric protein intolerance	Hyperammonemia, vomiting, diarrhea	Dibasic amino acids

A

B

C

Fig. 50.8 Cystinuria. (A) Rough and smooth cystine calculi. (B) Plain radiograph of a cystine calculus in the right renal pelvis and further multiple parenchymal calculi. (C) Urine microscopy showing characteristic flat hexagonal crystals.

Autosomal Dominant Tubulointerstitial Kidney Disease

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare disorders characterized by progressive loss of kidney function, bland urinary sediment, and autosomal dominant inheritance.34 These diseases were previously classified as familial juvenile hyperuricemic nephropathy (FJHN) or medullary cystic kidney disease type 2 (MCKD2). However, as neither hyperuricemia nor renal cysts are pathognomonic, these disorders have been reclassified as ADTKD. There are four main genes that are known to cause ADTKD: UMOD (uromodulin), MUC1 (mucin-1), REN (renin), and HNF1B (hepatocyte nuclear factor β).

The UMOD gene encodes for the Tamm-Horsfall/uromodulin protein, which is synthesized in the epithelial cells of the thick ascending limb (TAL) of the loop of Henle. Defective protein is retained in the endoplasmic reticulum and probably leads to inflammation, interstitial fibrosis, and functional abnormalities of the TAL. The defective protein also causes decreased salt and water reabsorption because UMOD plays a role in regulating the sodium-potassium-chloride transporter35 and the rat outer medullary potassium channel.36 The decreased salt and water reabsorption leads to increased proximal salt reabsorption and secondarily of uric acid, leading to hyperuricemia.

The MUC1 gene encodes for mucin-1, a transmembrane protein, which is expressed in the loop of Henle, distal tubule, and collecting duct. The pathogenesis of how defective mucin-1 leads to tubulointerstitial fibrosis remains unclear. Patients with ADTKD-MUC1 can develop hyperuricemia as well, but gout tends to be a later manifestation of the disease.

The REN gene encodes for preprorenin, which is then converted to prorenin and subsequently renin. Mutation in this gene leads to retention of preprorenin, prorenin, or renin protein in the endoplasm, depending on the location of the defect. As a result of a low renin state, patients with ADTKD-REN are at risk of mild hypotension, mild hyperkalemia, increased risk of AKI in the setting of volume depletion, and transient childhood anemia. Hyperuricemia and gout may also occur, though the exact mechanism is unclear.

The HNF1B gene encodes hepatocyte nuclear factor β, a transcription factor that regulates multiple genes located in the kidney, pancreas, and liver. Patients with HNF1B mutations have variable presentations and can present with extrarenal manifestations. The disease ADTKD-HNF1B occurs in a small subset of patients with HNF1B mutations and is characterized by kidney cysts, maturity onset diabetes of youth, genital abnormalities, pancreatic atrophy, and hypomagnesemia.

Diagnosis of ADTKD should be suspected in patients with CKD and family history of autosomal dominantly inherited CKD. In patients with ADTKD-UMOD, the diagnosis is suggested by a fractional excretion of uric acid of less than 5% (normal, 10%–15%). Definitive diagnosis can be made by genetic testing of the UMOD, MUC1, REN (renin), and HNF1B genes. There are no specific treatments for ADTKD, and management is largely based on CKD care (see Chapter 82). Controversy exists as to whether lowering of serum uric acid slows the progression of CKD; the studies reporting benefit have usually involved starting a xanthine oxidase inhibitor early in the disease.

More recently from genome-wide association studies, variants in the UMOD gene have been identified as risk factors for CKD and hypertension.37 The variants are common, are in the noncoding regions of the UMOD gene, and lead to an increase in functional UMOD protein in contrast to the mutation in ADTKD.

SELF-ASSESSMENT QUESTIONS

A 3-year-old boy presents with failure to thrive and photophobia. His urine contains glucose and +1 protein with a pH of 5.5. Serum chemistries are as follows:

Na+ 135 mmol/L
K+ 2.5 mmol/L
Cl 111 mmol/L
HCO3 15 mmol/L
Glucose 91 mg/dL (5 mmol/L)
Phosphorus 2.5 mg/dL (0.8 mmol/L) (normal for age, 4.5–5.5 mg/dL)
Creatinine 0.4 mg/dL (35 µmol/L)

1. Slit-lamp examination of his eyes shows tinsel-like refractile opacities in his cornea. What is the most likely diagnosis?
A. Lowe syndrome
B. Cystinosis
C. Tyrosinemia
D. Hereditary fructose intolerance
E. Galactosemia

2. Cystinuria is associated with which amino acids in the urine besides cystine?
A. Arginine, lysine, ornithine
B. Arginine, lysine, histidine
C. Lysine, ornithine, histidine
D. Ornithine, glycine, alanine
E. Ornithine, glycine, serine

3. What is the most common cause of Fanconi syndrome in adults?
A. Multiple myeloma
B. Medications
C. Nephrotic syndrome
D. Cystinosis
E. Cadmium

4. The defect in familial glycosuria is an abnormality in which transporter?
A. GLUT1
B. ClC-5
C. Na+-K+-2Cl
D. Na+/H+
E. SLGT2

5. Most patients with Dent disease have a mutation in which transporter?
A. Na+-K+-2Cl
B. GLUT2
C. Na+/H+
D. ClC-5
E. Na+-Cl

REFERENCES

1. Saito A, Sato H, Lino N, Takeda T. Molecular mechanisms of receptormediated endocytosis in the renal proximal tubule epithelium. J Biomed Biotechnol. 2010;403:272.
2. Emma F, Nesterova G, Langman C, et al. Nephropathic cystinosis: an international consensus document. Nephrol Dial Transplant. 2014;(suppl 4):87–94.
3. Town M, Jean G, Cherqui S, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nat Genet. 1998;18:319–324.
4. Andrzejewska Z, Nevo N, Thomas L, et al. Cystinosin is a component of the vacuolar H+-ATPase-Ragulator-Rag complex signaling controlling mammalian target of rapamycin complex 1. J Am Soc Nephrol. 2016;27:1678–1688.
5. Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. Ann Intern Med. 2007;147:241–250.
6. Schnaper HW, Cottel J, Merrill S, et al. Early occurrence of end-stage renal disease in a patient with infantile nephropathic cystinosis. J Pediatr. 1992;120:575–578.
7. Van't Hoff WG, Ledermann SE, Waldron M, Trompter RS. Early-onset chronic renal failure as a presentation of infantile cystinosis. Pediatr Nephrol. 1995;9:483–484.
8. Kleta R, Gahl WA. Pharmacological treatment of nephropathic cystinosis with cysteamine. Expert Opin Pharmacother. 2004;5:2255–2262.
9. Berry GT. Galactosemia: when is it a newborn screening emergency? Mol Genet Metab. 2012;106:7–11.
10. Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. J Inherit Metab Dis. 2010;33:105–112.
11. Santer S, Steinmenn B, Schaub J. Fanconi-Bickel syndrome: a congenital defect of facilitative glucose transport. Curr Mol Med. 2002;2:213–227.
12. de Laet C, Dionisi-Vici C, Leonard JV, et al. Recommendations for the management of tyrosinaemia type I. Orphanet J Rare Diseases. 2013;8:8.
13. Weiss KH, Stemmel W. Evolving perspectives in Wilson disease: diagnosis, treatment and monitoring. Curr Gastroenterol Rep. 2012;14:1–7.
14. Wu F, Wang J, Pu C, et al. Wilson's disease: a comprehensive review of the molecular mechanisms. Int J Mol Sci. 2015;16:6419–6431.
15. Shurman SJ, Scheinman SJ. Inherited cerebrorenal syndromes. Nat Rev Nephrol. 2009;5:529–538.
16. Bökenkamp A, Ludwig M. The oculocerebrorenal syndrome of Lowe: an update. Pediatr Nephrol. 2016;31:2201–2212.
17. Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28:1923–1942.
18. Schaeffer C, Creatore A, Rampoldi L. Protein trafficking defects in inherited kidney diseases. Nephrol Dial Transplant. 2014;29:iv33–iv44.

19. Emma F, Montini G, Parikh SM, Salviati L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. Nat Rev Nephrol. 2016;12:267–280.
20. Barbier O, Jacquillet G, Tauc M, et al. Effect of heavy metals on and the handling by, the kidney. Nephron Physiol. 2005;99:105–110.
21. Prozialeck WC, Edwards JR. Mechanisms of cadmium-induced proximal tubule injury: new insights with implications for biomonitoring and therapeutic interventions. J Pharmacol Exp Ther. 2012;343:2–12.
22. Skinner R. Nephrotoxicity–what do we know and what don't we know? J Pediatr Hematol Oncol. 2011;33:128–134.
23. Karasawa T, Steyger PS. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett. 2015;237:219–227.
24. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008;74:158–169.
25. Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. Nephrol Dial Transplant. 2016;32(3):434–439.
26. Merlini G, Pozzi C. Mechanisms of renal damage in plasma cell dyscrasias: an overview. Contrib Nephrol. 2007;153:66–86.

27. Rikitake O, Sakemi T, Yoshikawa Y, et al. Adult Fanconi syndrome in primary amyloidosis with lambda light-chain proteinuria. Jpn J Med. 1989;28:523–526.
28. Luciani A, Sirac C, Terryn S, et al. Impaired lysosomal function underlies monoclonal light chain-associated renal Fanconi syndrome. J Am Soc Nephrol. 2016;27:2049–2061.
29. Prie D. Familial renal glycosuria and modifications of glucose renal excretion. Diabetes Metab. 2014;40:S12–S16.
30. Camargo SM, Bockenhauer D, Kleta R. Aminoaciduria: clinical and molecular aspects. Kidney Int. 2008;73:918–925.
31. Claes DJ, Jackson E. Cystinuria: mechanisms and management. Pediatr Nephrol. 2012;27:2031–2038.
32. Servais A, Thomas K, Dello Strologo L, et al. Cystinuria:clinical practice recommendations. Kid Internrl. 2021;99:48–58.
33. Sperling O. Hereditary renal hypouricemia. Mol Genet Metab. 2006;89:14–18.
34. Eckhardt K-U, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease; diagnosis, classification and management. A Kdigo Consensus Report. 2015;88:676–683.
35. Mutig K, Kahl T, Saritas T, et al. Activation of the bumetanide-sensitive Na+,K+,2CL- cotransporter (NKCC) is facilitated by Tamm-Horsfall protein in a chloride-sensitive manner. J Biol Chem. 2011;286:30200–30210.
36. Renigunta A, Renigunta V, Saritas T, et al. Tamm-Horsfall glycoprotein interacts with renal outer medullary potassium channel ROMK2 and regulates its function. J Biol Chem. 2011;286:2224–2235.
37. Kottgen A, Glazer NL, Dehghan A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. Nat Genet. 2009;41:712–717.

51

Sickle Cell Diseases and the Kidney

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SICKLE CELL DISEASE

The sickle hemoglobin (Hb) mutation (hemoglobin S, or HbS) results in the replacement of the normal glutamine by valine in the sixth position of the β-globin subunit, thereby changing the configuration of the Hb tetramer molecule in the homozygous person from α2β2 to α2βS2.

Sickle cell disease occurs in those homozygous for HbS (commonly referred to as sickle cell anemia) or in heterozygotes when HbS coexists with another abnormal or missing β-chain (e.g., HbC [α2βSβC] or HbSβ thalassemia [α2βS]). Sickle cell trait occurs in those heterozygous for HbS when the other Hb molecule is normal (HbAS [α2βAβS]).

Several HbS haplotypes—mutations of the HbS molecule—have been identified that have probably arisen independently of each other. There are four major types in Africa—the Benin, Senegal, Cameroon, and Bantu (or Central African Republic) haplotypes—and one Asian haplotype. Variations in these haplotypes determine disease severity; for example, the Senegalese haplotype is associated with a higher fetal Hb (HbF) concentration (a key driver of disease severity) and has a better prognosis than others. In a sample population of Nigerians, Benin haplotype was detected in 92%. Sex also influences disease severity; female HbSS patients with Benin haplotype have a higher HbF level than male patients.4,5

polymerization cycles, sickle RBCs exhibit abnormally high adhesion to activated endothelium, owing to acquired membrane changes and retained adhesion receptors on reticulocytes, especially the stress reticulocytes. This increases microvascular transit time, thereby stimulating further sickling. This results in premature destruction (hemolysis) of the RBCs and frequent, widespread vaso-occlusive episodes with subsequent acute and chronic organ damage.

The tendency of HbS to polymerize is influenced by the presence or absence of HbF, which contains γ-Hb chains in place of β-Hb (α2γ2). In RBCs that contain HbF (known as F cells), the presence of HbF dilutes the concentration of HbS, thus increasing the threshold at which polymerization occurs. In addition, both HbF and its mixed hybrid tetramer (α2βSγ) cannot enter the deoxy sickle Hb polymer phase, further limiting the degree of polymerization that can occur within a cell.6 Therefore, the main determinant of disease severity is the rate and extent of HbS polymerization, which drives the two major pathophysiologic processes: vaso-occlusion with ischemia-reperfusion injury and hemolytic anemia (Fig. 51.2).7

Vaso-occlusion occurs in all patients, often triggered by inflammation, and is typically found in clinical states of infection, hypoxia, hypovolemia, hypothermia, acidosis, and hyperosmolality. Vasoocclusion is probably caused by dynamic endothelial-leukocyte-RBC adhesive interactions in the postcapillary venules and precapillary obstruction by rigid, deformed RBCs. Episodic microvascular occlusion and ischemia can be interrupted by restoration of blood flow and reperfusion, which further promote inflammatory stress and tissue injury. In addition, hemolysis contributes to the development of progressive vasculopathy, characterized by endothelial dysfunction and proliferative changes in the intima and smooth muscle of blood vessels. An important role is ascribed to free Hb, which inactivates nitric oxide and generates reactive oxygen species. These separate pathologic processes have been used to explain the distinct subphenotypes of clinical complications of SCD whereby some patients present with frequent vaso-occlusive crises (VOCs), acute chest syndrome (ACS), and osteonecrosis, whereas others have more severe anemia, recurrent leg ulceration, pulmonary hypertension, priapism, and chronic kidney disease (CKD).8

Pathophysiology

Natural History and Clinical Manifestations

The driving pathophysiologic factor is HbS polymerization. During cellular or tissue hypoxia, dehydration, or oxidative stress, the mutated β-globin chains of the HbS molecule tend to crystallize to a polymer nucleus. Polymerization disrupts the architecture and changes the shape of the red blood cell (RBC) to a characteristic crescent or sickle, which increases its rigidity (Fig. 51.1). Polymerization is dynamic and depends on local oxygen tension. It is also promoted by acidosis (which decreases the affinity of HbS for oxygen) and hyperosmolarity (which increases RBC Hb concentration). As a consequence of repeated

Sickle cell disease is a highly variable condition, though life expectancy is reduced in all subjects, especially in those with symptomatic disease. Median survival in some parts of sub-Saharan Africa may be as low as 5 years, whereas it is 45 to 55 years in the United States and Jamaica.5,9 The clinical manifestations of SCD are individualized and age dependent (Fig. 51.3).10 Newborn babies are asymptomatic for the first couple of months of life because fetal Hb predominates at this age. However, as γ-chains are rapidly replaced through βchain synthesis, symptoms (often potentially life-threatening) begin

Epidemiology

Sickle cell disease (SCD) is an autosomal recessive inherited disorder that predominantly affects persons of African, Mediterranean, Indian, and Middle Eastern descent but was first recognized in West Africa. The high prevalence of SCD in this region probably represents a survival benefit, as the presence of the sickle cell gene protects against malaria. SCD is now a worldwide health problem because the carrier state has spread throughout Africa, around the Mediterranean, and to the Middle East and India, as well as to the Caribbean, North America, and northern Europe. The prevalence of the sickle cell gene is about 8% in African Americans and about 25% in adult Nigerians. Of babies born with SCD, 25% worldwide are born outside of sub-Saharan Africa.1-3

Genetics

A

B

Fig. 51.1 Sickle Cells. (A) Characteristic sickle cell erythrocytes in peripheral blood film of a patient with homozygous sickle cell anemia. (B) Electron micrograph showing two normal and two sickle-shaped erythrocytes. (Courtesy Professor Sally C. Davies.)

Pathophysiology of Sickle Cell Disease

Oxygenated erythrocyte containing HbS
Acute pain
Acute chest syndrome
Hyposplenism
Osteonecrosis
Nephropathy
Deoxygenated erythrocyte with polymerization of HbS

Dehydrated, sickled erythrocyte
Infarction

Occlusion of postcapillary venules
(vaso-occlusion)

Reperfusion

Hemolysis

Free plasma hemoglobin,
inactivating NO and
generating reactive oxygen
species

Free radicals, causing
tissue damage

Inflammation
Increased expression of
VCAM-1 and other
adhesion molecules
Hypercoagulability

Pulmonary hypertension
Priapism
Leg ulcers
Cerebrovascular disease

NO
Functional NO deficiency
Vasculopathy and endothelial dysfunction

Fig. 51.2 Pathophysiology of sickle cell disease. HbS, Hemoglobin S (sickle Hb); NO, nitric oxide; VCAM-1, vascular cell adhesion molecule 1. (Modified from Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018–2031.)

to occur, including dactylitis, ACS, overwhelming sepsis, and acute splenic sequestration. Stroke is also a feature of early childhood, with an incidence of 8% by age 14 years, rising to 11% by age 20 years. However, this has been largely mitigated in wealthy countries by screening at-risk children with transcranial Doppler (looking for increased blood flow velocity, which is suggestive of arterial stenosis)

and the use of chronic transfusion for both primary and secondary prevention.[11] Human parvovirus B19 infection can lead to a severe and sudden fall in Hb in children and adolescents with SCD because the virus destroys RBC precursors for 8 to 10 days, which results in severe anemia. After the age of 5 years, when active bone marrow is withdrawn from the small bones, dactylitis is replaced by the

Genetic Modifiers of Risk for Developing Sickle Cell Nephropathy

Age Distribution of Clinical Problems
in Sickle Cell Disease
Symptom

0

5

Age (years)
10 15 20

25

30

Pain
Digits
Long bones
Trunk
Sequestration
Splenic
Hepatic
Chest syndrome
Mesenteric syndrome
Infection
Pneumococcus
Parvovirus
Salmonella
Priapism
Upper airway obstruction
Stroke
Subarachnoid hemorrhage
Retinopathy
Gallstones
Avascular necrosis
Delayed growth and development
Leg ulcers
Hyposthenuria
Chronic kidney disease
Chronic sickle lung

Fig. 51.3 Age distribution of clinical problems in sickle cell disease. (Modified from Davies SC, Oni L. Management of patients with sickle cell disease. BMJ. 1997;315:656–660.)

classic painful vaso-occlusive crises, which increases in frequency with increasing age. In addition, adolescence is associated with nocturnal enuresis, avascular necrosis of the hip, leg ulcerations, delayed puberty, and priapism. Over the age of 25 to 30 years, the frequency of VOC tends to reduce and is replaced with signs and symptoms of chronic organ damage, including heart failure, pulmonary hypertension, sickle hepatopathy, and sickle cell nephropathy.5 In younger patients, the primary cause of death is usually infection, whereas in older patients the primary cause of death is commonly irreversible organ damage (Fig. 51.4).12

SICKLE CELL NEPHROPATHY

Sickle cell nephropathy (SCN) develops slowly, starting in the very young with glomerular hyperfiltration and leading to albuminuria in late childhood or early adulthood. Although many patients do not progress further, a number develop progressive CKD. These patients are at increased risk for acute kidney injury (AKI) complicating VOC or other interim illnesses, events that often precipitate a further decline in glomerular filtration rate (GFR). The prevalence of albuminuria is approximately 60% in those over 45 years, but only 4% to 12% of patients with SCD develop end-stage kidney disease (ESKD), though this figure may increase as the patient cohort ages.12 13 In keeping with this, in 2008 advanced CKD was reported in 24% of patients with SCD who had survived to 60 years of age or more and was the cause of death in 45%.14

In general, SCN is more prevalent and more severe in those with HbSS-thalassemia and HbSβ0-thalassemia than in those with milder forms of SCD such as HbSC.9 15

Other genetic modifiers are also associated with disease severity and risk for developing SCN, often through their influence on HbF levels. A polymorphism in the BCL11A gene (a fetal Hb silencing factor) leads to higher HbF levels, reduced hemolysis, and amelioration of SCD-related complications. Coinheritance of α-thalassemia and SCD is found in approximately one-third of patients and is associated with reduced hemolysis and protection from albuminuria. Over the past decade, genetic risk factors for CKD have been identified in the African American population, the most important of which are haplotypes of the APOL1 gene. These are associated with increased risk for hemolysis and, when combined with genotypes for α-thalassemia and BCL11A, can be used to stratify risk for progressive CKD in SCD patients.16 Using estimated GFR as a marker of kidney function, the transforming growth factor-β/bone morphogenic protein (TGF-β/BMP) pathway17 has been implicated as a cause of progressive kidney function loss in SCN.

Pathophysiology of Sickle Cell Nephropathy

The pathogenesis of SCN is directly related to the blood supply of the kidney and its circulation. In health the kidneys receive approximately 25% of the cardiac output to achieve effective filtration of the plasma at a rate of approximately 100 mL/min/1.73 m2, despite representing less than 1% of total body weight. As a consequence, the cortex of the kidney is at risk for receiving excess oxygen, which is mitigated by shunting of oxygen from the afferent arteriole to the efferent arteriole. The vessels (vasa recta) that supply the medulla of the kidney branch off early from the efferent arteriole, taking only a fraction of the total renal blood flow (RBF) with them. Much of the blood that enters the kidney cortex is therefore delivered back to the venous circulation without entering the medulla at all. The maintenance of the relatively sluggish but intricate medullary blood flow is critical to maintaining the corticomedullary interstitial solute gradient generated by the countercurrent multiplier system of the loop of Henle, which drives water and solute reabsorption and allows for effective urinary concentration.18 The resulting hypoxia (partial pressure of oxygen 10–35 mm Hg), acidosis, and hyperosmolarity of the inner medulla make it an ideal environment for the polymerization of deoxygenated HbS and subsequent sickling of erythrocytes.

Over time, repeated cycles of sickling and sludging cause microinfarcts and ischemic injury leading to the chronic microvascular disease that is apparent in established SCN (Fig. 51.5).19 Local activation of hypoxia inducible factor 1α (HIF1α) upregulates the expression of endothelin-1 which, in the presence of reduced nitric oxide, leads to an increase in reactive oxygen species and vasoconstriction, thus feeding into a cycle of chronic medullary hypoxia (Fig. 51.6).20

Despite reduced circulation in the kidney medulla, total RBF and GFR are paradoxically increased. The subsequent hyperfiltration eventually results in proteinuria and glomerulosclerosis, which together with tubulointerstitial fibrosis marks the onset of progressive CKD.21

Although partially due to the increased cardiac output seen in patients with SCD, this increase in RBF cannot be completely explained by anemia or increased plasma volume, as it is not reversed by correction of the anemia with transfusion. One explanation involves the hemoxygenase–carbon monoxide system. Heme oxygenase-1 (HO-1) is upregulated in injured kidneys (and other tissues) in response to ongoing hemolysis in SCD, and is responsible for the conversion of heme to biliverdin with the subsequent release of carbon monoxide. Both biliverdin and carbon monoxide at these levels are potent antioxidants, and the carbon monoxide acts locally as a vasorelaxant, thus increasing both RBF and GFR.22 This provides a possible link between the degree of hemolysis experienced by a patient and the likelihood of developing proteinuria.

Mortality in Sickle Cell Disease
Other
(2%)

Irreversible organ
damage (13%)
(lung, kidney,
and/or liver)

Unknown
(9%)

Hypersplenism (13%)

Other
(13%)

Central nervous
system (11%)

Irreversible organ
damage (42%)

Acute
pulmonary
disorders (7%)

Unknown (8%)

(lung, kidney,
and/or liver)

Trauma (9%)
Trauma (9%)
Infection
(5%)

Infection (36%)

Acute
pulmonary
disorders (11%)

Central nervous
system (13%)

< 20 years of age, n ◦ 46
> 20 years of age, n ◦ 186

Fig. 51.4 Mortality in Sickle Cell Disease. Causes of death among 232 HbSS patients, comparing patients <20 years (46 died) with patients >20 years (186 died). Infection category includes both bacterial and viral diseases. (Modified from Powars DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005;84:363–376.)

A

B

Fig. 51.5 Microradioangiography Showing Loss of Vasa Recta in Sickle Cell Nephropathy. (A) Kidney from control, with normal vasa recta. (B) Patient with sickle cell anemia, with the absence of the vasa recta.
(From Statius van Eps LW, Pinedo-Veels C, de Vries GH, et al. Nature of concentrating defect in sickle-cell nephropathy. Microradioangiographic studies. Lancet. 1970;1:450–452.)

Pathobiology of Sickle Cell Disease
↓ pO2
↑ (HbS)

DeoxyHbS

RBC
sickling

HbS
polymer

↑ RBC and WBC adhesion
to endothelium

Vascular
stasis

Hemolysis

Infarction
Systemic endothelial dysfunction

Hemoglobin
and/or heme

↑ Adhesion molecules
↑ Oxidant generation
↓ NO bioavailability
↑ Microparticles
↑ Vascular instability
↑ Growth factors
↑ Permeability
Coagulant activation
Platelet activation
Vasculopathy
Remote organ injury

Vascular
occlusion

Systemic
inflammation
Ischemiareperfusion

Fig. 51.6 Pathobiology of sickle cell disease. deoxyHbS, Deoxygenated HbS; HbS, sickle hemoglobin; NO, nitric oxide; pO2, partial pressure of oxygen; RBC, red blood cell; WBC, white blood cell. (Modified from Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015;11:161–171.)

CLINICAL MANIFESTATIONS OF SICKLE CELL NEPHROPATHY

Glomerular Abnormalities

Hyperfiltration

Glomerular hypertrophy is ubiquitous in SCD and has been reported in children as young as 1 to 3 years of age (Fig. 51.7).[23] Increased kidney growth is observed from infancy in children with SCD and accompanies the early rise in GFR.[24,25] Glomerular filtration rate continues to rise throughout childhood and early adulthood, often exceeding 200 mL/min/1.73 m2. Although this hyperfiltration is not associated with an overt increase in systemic blood pressure (BP), recent studies suggest children with SCD may have a degree of masked hypertension which can be detected with ambulatory monitoring.26 27 Persistent hyperfiltration can eventually lead to damage to the glomerular basement membrane and nephrosclerosis, feeding into a cycle of increasing single-nephron GFR, further nephron loss, and an overall decline in GFR during adulthood.

GFR in Children With Sickle Cell Disease
350
DTPA GFR (mL/min/1.73 m 2)

The endothelial dysfunction and vasculopathic state of SCD described earlier is also pivotal to the development of SCN. Crosstalk between glomerular endothelial cells and podocytes is important to maintain healthy glomerular function; when the endothelium is dysfunctional, this could lead to podocyte injury and the development of glomerular lesions and proteinuria. FMS-like tyrosine kinase 1 is a receptor for vascular endothelial growth factor (VEGF), and increased levels of the soluble form (sFlt-1) have been associated with endothelial dysfunction in preeclampsia. Serum levels of sFlt-1 are raised in SCD and so may play a role in the development of proteinuria.22

(18)
300
(24)

250

(16)

(16)
200

(10)

150
100
50
1-3

4-7

8-11
12-15
16
Age (years)
Fig. 51.7 Diethylenetriaminepentaacetic acid (DTPA) glomerular filtration rate (GFR) in children with sickle cell disease. (From Aygun B, Mortier NA, Smeltzer MP, et al. Glomerular hyperfiltration and albuminuria in children with sickle cell anemia. Pediatr Nephrol. 2011;26:1285–1290.)

Albuminuria and Proteinuria

Albuminuria occurs after a period of prolonged hyperfiltration and is apparent in some patients from late childhood.28 Unlike hyperfiltration, the prevalence of albuminuria continues to increase with age, reaching more than 60% of all patients with HbSS SCD over the age of 45 years.13 29 In some patients, albuminuria progresses and occasionally reaches the nephrotic range (proteinuria >3.5 g/24 h), which is associated with increased mortality.15 Nephrotic syndrome, although uncommon (~4% of all those with proteinuria), is associated with a very poor kidney prognosis. One rare cause of sudden onset of nephrotic syndrome in patients with SCD is recent infection with human parvovirus B19 (HPV B19). Although widespread in the community, this usually benign infection becomes significant in patients with SCD because it causes acute but self-limiting red cell aplasia. In combination with severe hemolysis, this leads to life-threatening anemia requiring supportive transfusion. Several reports have described patients in whom infection was followed by acute nephrotic syndrome within 2 to 3 months. In cases in which biopsy has been performed early, the collapsing variant of focal segmental glomerulosclerosis (FSGS) has been found (with or without evidence of direct HPV B19 infection). Although the acute features of the nephrotic syndrome are self-limiting, the sequelae of the condition are worsening glomerulosclerosis, tubulointerstitial fibrosis, and progressive kidney dysfunction.30

Tubular Abnormalities

Hyposthenuria

Hyposthenuria (the excretion of urine of low specific gravity secondary to inability of the kidney to concentrate the urine) is almost universal in people with SCD (who can rarely achieve a urine osmolality above 450 mOsm/kg, even under water-deprived conditions) and also occurs in older people with sickle cell trait. Hyposthenuria often leads to enuresis in children and can cause marked dehydration. It is primarily caused by sickling in the vasa recta, leading to microthrombi, infarction, and collateral formation of blood vessels. As a consequence, there is a defect in the countercurrent exchange mechanism resulting in insufficient trapping of solute in the inner medulla and leading to abnormalities in water conservation.19 In addition, the increased delivery of salt and water in the tubular filtrate secondary to the high GFR and the intermittent hypoxia caused by sickling in the microvasculature lead to local endothelin-1 release. Endothelin-1 (ET-1) is a potent vasoconstrictor and also has marked natriuretic and diuretic properties through stimulation of ET type b receptors in the kidney collecting ducts, leading to increased salt and water loss.31 Although hyposthenuria is reversible by blood transfusion until the age of 10 years, after this age it becomes irreversible and is associated with a permanently damaged microvasculature and increased urine output, leading to a tendency to dehydration.19 32

Increased Proximal Tubular Function

The increase in sodium and water loss from the nephron leads to a reactive increase in sodium and water reabsorption by the proximal tubule secondary to tubuloglomerular feedback. This reabsorption of sodium is the driving force for the reabsorption of other solutes such as phosphate and β2-microglobulin, and hence many patients have hyperphosphatemia. There is also an increase in proximal tubular secretion of other solutes, such as creatinine and uric acid. Despite this, serum levels of uric acid are often raised as a result of severe hemolysis and may result in episodes of acute gout. In contrast, up to 30% of the total creatinine excretion can arise from tubular secretion resulting in low serum creatinine levels and overestimation of GFR when creatinine-based formulas are used.33 Increased sodium reabsorption requires increased oxygen consumption and hypermetabolism of the kidney tubules, a phenomenon that may exacerbate kidney hypoxia in SCD.[22]

Fig. 51.8 Papillary Necrosis in Sickle Cell Disease. Intravenous urography shows abnormal calyces with filling defects (arrows).

Acidification Defect

A retrospective study in 2014 of 411 homozygous SCD patients with eGFR greater than 60 mL/min/1.73 m^2 revealed that 42% had partial metabolic acidosis as assessed by serum levels of carbon dioxide (52% of women, 27% of men), apparently because of a lack of ammonia buffering capacity rather than a defect in the distal tubule. Although serum potassium levels were not linked to acidosis in this study, hyperkalemia is a common phenomenon in patients with SCD and has been attributed by others to hyperchloremic metabolic acidosis linked to type IV kidney tubular acidosis or resistance of the distal tubule to aldosterone.[22]

Hematuria, Papillary Necrosis, and Kidney Medullary Carcinoma

Hematuria is common in patients with SCD and sickle cell trait. It can range from painless microhematuria, through visible and painless, to visible and painful. It is usually self-limiting but occasionally can be severe enough to require transfusion. Microinfarcts, capillary congestion, and rupture are often the cause, but occasionally, complete occlusion of the vasa recta can lead to papillary necrosis with sloughing of the ischemic papilla, severe hemorrhage, and obstruction, which may be complicated by superimposed infection and painful clot colic (Fig. 51.8).[17] The left-sided predominance of hematuria has been attributed to the so-called nutcracker phenomenon, with compression of the left renal vein between the aorta and the superior mesenteric artery, increasing the pressure in the renal vein. This may contribute to the development of hematuria in patients with SCD, because the increased renal vein pressure could worsen anoxia in the kidney medulla, increasing the likelihood of sickling in the left kidney.

Renal medullary carcinoma (RMC) is an aggressive form of renal cell carcinoma that uniquely affects patients with sickle cell hemoglobinopathies, particularly sickle cell trait or HbSC, especially in teenagers and young adults. It is similar to but distinct from renal cell carcinoma with medullary phenotype (RCC-MP), which is found in individuals who do not carry a sickle gene, but both are characterized by loss of protein expression of the tumor suppressor gene SMARCB1. Chronic medullary hypoxia is thought to contribute to its pathogenesis. The tumors are resistant to chemotherapy and tend to be metastatic at diagnosis, with a reported postsurgical mean survival of only 15 weeks. It is not yet clear whether regular evaluation for RMC in young patients with SCD or trait could result in an early diagnosis and a better survival. Gross hematuria, flank pain, and weight loss are ominous signs of malignancy, particularly in young patients with sickle cell trait. The tumor is typically located deep in the parenchyma, unlike Wilms tumor or renal cell carcinoma.[34]

URINARY TRACT INFECTIONS

Patients with SCD have an increased susceptibility to bacterial infections; even low-grade bacteremia with a common organism may be fatal. In addition to the impaired immunity resulting from autosplenectomy, there is opsonic antibody deficiency, which predisposes to bacterial infections. Bacteriuria was found to be present in 26% of children with SCD presenting with fever in Nigeria, and urinary tract infection complicated pregnancy in 12% of mothers with SCD in a large UK cohort.35 36

Pyelonephritis and urosepsis, as with any infection, may precipitate a sickle cell crisis. The most common organisms isolated include Escherichia coli, Klebsiella spp, and other gram-negative Enterobacteriaceae.

CLINICAL SYNDROMES OF KIDNEY IMPAIRMENT

Acute Kidney Injury

Although much is known about CKD, there is less in the literature about AKI in patients with SCD. It is reported as a complicating factor in 2% to 8% of hospital admissions with painful vaso-occlusive crisis or acute chest syndrome. The severity of the AKI appears to be directly related to the severity of the acute sickling crisis. Other causes of AKI are rhabdomyolysis, sepsis, and drug nephrotoxicity. Less common causes of acute kidney dysfunction are kidney vein thrombosis and hepatorenal syndrome (caused by SCD-related hepatic failure). Volume depletion due to inability to concentrate urine makes patients more susceptible to AKI. Although most patients recover, repeated episodes of AKI increase the risk for CKD. After severe episodes, GFR on recovery is often lower than before the acute event.3 In addition, patients with underlying CKD are more prone to AKI, making this a vicious cycle in patients with frequent hospital admissions.37 38

Progressive Chronic Kidney Disease

Progressive loss of kidney function in SCN is an increasingly large problem as life expectancy increases. Similar to diabetic nephropathy, patients with SCN progress through stages of tubular dysfunction and hyperfiltration, through mild to moderate albuminuria to severe albuminuria, and eventually loss of GFR. Over time, single-nephron GFR increases as other nephrons are lost, resulting in worsening damage to the glomeruli (manifested by FSGS), increasing albuminuria, and subsequent interstitial fibrosis and tubular atrophy. Although hypertension is less common in patients with SCD than in an age- and ethnicity-matched cohort, when it is present it has a marked impact on the rate of progression of CKD.39 For this reason, it may be necessary to aim for lower blood pressure targets in these patients than might be advocated in people without SCD.

Predictors of CKD progression are hypertension, proteinuria, nephrotic syndrome, hematuria, increasingly severe anemia, and inheritance of the Bantu, or Central African Republic, β-globin gene cluster haplotype. In addition, younger age at diagnosis and higher duration of SCD were found to strongly predict the development of nephropathy.40

As GFR declines, the ability of the kidney to synthesize erythropoietin (EPO) also declines. Chronic anemia and tissue hypoxia are strong drivers for EPO synthesis, and patients with SCD with normal kidney function often have EPO levels well above the normal range. However, when the GFR falls below approximately 60 mL/min/1.73 m2, their ability to produce sufficient endogenous EPO also begins to decline, resulting in worsening anemia. In patients who develop progressive kidney dysfunction secondary to SCN, the rate of decline can be quite rapid once the GFR falls below 40 mL/min/1.73 m2, and so timely preparation for kidney replacement therapy (KRT) is very important. Many patients who have suffered frequent admissions to hospital often have very poor peripheral veins and so need expert surgical input when planning for dialysis access.

INVESTIGATION AND MANAGEMENT OF SICKLE CELL NEPHROPATHY

Serum cystatin C is promising as a more accurate marker of kidney function than creatinine in adults and children with SCD and may detect decline in GFR earlier.26 However, it has yet to be fully validated against gold standard measures that calculate true GFR in SCD patients, so creatinine and creatinine-based equations continue to be used in the clinic. It is therefore the pattern and rate of change of either serum creatinine or eGFR that should be considered rather than the absolute value, bearing in mind that relatively modest changes in creatinine at higher levels of GFR can represent significant decline in kidney function. Kidney function and albuminuria should be monitored at least annually.41 Creatinine levels are often low in people with SCD secondary to reduced muscle bulk, hyperfiltration, and increased proximal tubular secretion, resulting in a high eGFR. Increased rate of change of creatinine may therefore indicate declining GFR before the value moves out of the normal range. Anyone with an eGFR that is declining at more than 5 mL/min/yr or an absolute value less than 60 mL/min should be identified and referred to a nephrologist (Fig. 51.9).

Rigorous BP control is recommended, as for other causes of CKD.39 A BP of 140/90 is currently permissible for patients with a negative dipstick result or those with a urine albumin-to-creatinine ratio (uACR) less than 3.5 mg/mmol, but a target of 130/80 should be used for those with a uACR greater than 3.5 mg/mmol.42 Urinary tract infections should be promptly treated with appropriate antibiotics. Glucose-6phosphate dehydrogenase deficiency (G6PD deficiency), which may precipitate intravascular hemolysis, should be excluded because some antibiotics, including sulfonamides and nitrofurantoin, precipitate hemolysis by antagonizing folate synthesis. Long-term use of nonsteroidal antiinflammatory drugs should be avoided in patients with eGFR less than 60 mL/min/1.73 m2; if unavoidable, regular monitoring of kidney function is recommended.

The population at risk for developing SCN is also at risk for other diseases that affect the kidneys, including lupus nephritis, various forms of glomerulonephritis, blood-borne viruses, renal carcinoma, myeloma, and kidney stones. This differential should be considered when investigating a patient with SCD and new-onset proteinuria or hematuria. Although it is common practice not to investigate patients with albuminuria (uACR >3.5 mg/mmol), patients with urinary protein-to-creatinine ratio (uPCR) greater than 50 mg/mmol should be evaluated for other causes of CKD (Fig. 51.9); if any of these investigations are abnormal, or the patient’s signs and symptoms do not conform to those expected within the natural history of SCN as described previously, they should be referred for further evaluation.

In particular, patients with sudden onset of heavy proteinuria, with or without nephrotic syndrome, warrant kidney biopsy to look for causes other than SCN. There is no pathognomonic lesion that defines SCN. Glomerular hypertrophy with distended capillaries is universally found but is not confined to those who have developed albuminuria or proteinuria. FSGS is the most common lesion associated with proteinuria, but it is not specific to SCN (Fig. 51.10). Other lesions that have been reported on kidney biopsy in SCD include thrombotic microangiopathy and membranoproliferative glomerulonephritis; neither is exclusive to SCN. The only characteristic interstitial lesion is abundant

Investigation and Management of
Hematuria and Proteinuria in Sickle Cell Disease
Proteinuria

Patient presents with
proteinuria/hematuria

Hematuria

Associated with
persistent proteinuria?

Associated with
persistent hematuria?
Yes

Yes

No

eGFR 60
mL/min/1.73 m 2 or declining
at 5 mL/min/yr?
No

Yes
Protein/creatinine
ratio 100 mg/mmol?

No

No

Yes

Refer to a
nephrologist

Perform renal imaging
and refer to a urologist
for further investigation

Yes
- Renal ultrasound scan
- Autoantibodies and complement levels
- Serum electrophoresis
- HIV, hepatitis B, hepatitis C
- Serum albumin

Abnormal results or patient has
nephrotic syndrome?
No

Continue 6–12
monthly monitoring

Commence ACE inhibitor/ARB
and continue 6 monthly
monitoring
Target PCR 100 mg/mmol

Continue 6–12
monthly monitoring

Fig. 51.9 Investigation and management of hematuria/proteinuria in patients with sickle cell disease. ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; PCR, protein-to-creatinine ratio.

hemosiderin granules in proximal tubular epithelial cells.43 Kidney iron deposition also has been noted on magnetic resonance scans in patients with SCD but appears not to be related to liver iron concentration, a marker of total body iron load. Kidney iron does appear to be correlated with markers of hemolysis but has not been shown to be associated with kidney dysfunction or degree of albuminuria.44

Inhibition of the Renin-Angiotensin System

Fig. 51.10 Focal segmental glomerulosclerosis in sickle cell nephropathy. There is segmental sclerosis in the upper half of the glomerulus. (Courtesy Professor J. Weening.)

Only one small randomized, controlled trial evaluated angiotensinconverting enzyme (ACE) inhibition in patients with SCD and proteinuria; a more recent systematic review concluded that available evidence was insufficient to offer recommendations on treatment.45 However, based on the evidence available for other causes of proteinuric kidney disease, ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended for the treatment of adults and children with SCD and albuminuria.41 These drugs must be introduced cautiously because many patients have a low or normal BP, and so moderate doses can cause postural hypotension, which can be partially circumvented by taking the medication at bedtime. Patients have reported that this has the benefit of reducing nocturnal urinary frequency, presumably as a direct result of a functional drop in GFR. Patients with SCN are prone to hyperkalemia, which can be exacerbated by ACE inhibitor and ARB treatment and is often the dose-limiting factor. It is also important to inform patients and other caregivers that ACE inhibitors and ARB should be temporarily stopped during acute illnesses associated with dehydration to mitigate the risk for AKI.

Sickle Cell Disease Therapies and Blood Transfusion

Oral hydroxycarbamide (HC; also known as hydroxyurea) was the first licensed drug for the management of SCD. Although HC has pleotropic effects, it primarily acts to increase levels of fetal Hb that serve to dilute the levels of HbS and reduce risk for polymerization. However, there are no RCTs of HC use in the management or progression of SCN in adults and only one in infants, which showed no effect on hyperfiltration, though urinary concentrating ability was improved.46 A number of observational trials of HC in older children and adults have shown a reduction in hyperfiltration and albuminuria.3 HC therefore should be considered for patients with microalbuminuria/proteinuria or abnormal GFR together with an ACE inhibitor or ARB (or in those intolerant of this treatment). Over the past 5 years there have been a number of new treatments for SCD, some of which are now licensed for use in preventing VOC. Although none has yet to be proven to affect the progression of CKD, trials in this area are planned.47

There is little evidence for the benefits of long-term RBC transfusions on prevention of kidney complications of SCD. A retrospective analysis of 120 children with sickle hemoglobinopathies concluded that chronic transfusion protected against the onset of albuminuria when started before the age of 9 years. Two studies, however, found that chronic transfusion made no difference to onset of albuminuria and that prolonged courses of transfusion therapy can lead to iron overload, which is particularly difficult to treat in patients with CKD.3

Erythropoiesis-Stimulating Agents

Erythropoiesis-stimulating agents (ESAs) can be useful, particularly in combination with hydroxycarbamide in patients who are intolerant of hydroxycarbamide alone because of reticulocytopenia. They should be commenced when the Hb has fallen by approximately 10% to 15% from the normal baseline at steady state, though patients with CKD stages 3 to 4 often require very high doses of ESAs to have an impact on Hb levels. Although Hb targets should be lower than in the general population with CKD (80–100 g/dL) because of the increased risk for triggering VOC, they are rarely achieved, and most patients become transfusion dependent by the time they reach ESKD. However, it is often still beneficial to continue ESA therapy after the commencement of KRT because this can prolong the interval between RBC transfusion and minimize the risks for iron overload.3 It is important to ensure that adequate iron stores are maintained to achieve maximum erythropoiesis. Intestinal losses of iron resulting from subclinical bleeding are significant in advanced CKD, and absorption of oral iron is reduced. Intravenous iron supplementation may be necessary therefore in patients deficient in iron, on ESAs, and not receiving iron through regular transfusions.

Hemopoietic Stem Cell Transplantation

Hemopoietic stem cell transplantation (HSCT) is potentially curative and may reduce hyperfiltration in the young48 but has largely been limited to children with severe cerebrovascular complications, acute

chest syndrome, or frequent VOC not responding to hydroxycarbamide therapy. The few reports of HSCT in adults with SCN have mixed kidney outcomes.3

KIDNEY REPLACEMENT THERAPY

Dialysis

Outcome data for patients with SCD on dialysis are few, but an early report from the United States showed that the average age of those reaching ESKD was very young (23.1 years in patients with HbSS), and the mean time to death after was only 4 years despite regular hemodialysis.49 More recent data from France and the United States report that the 5-year mortality rate for patients with SCD with ESKD remains significantly higher than for patients without SCD. They have more complications, are admitted to hospital more frequently and are less likely to be offered a kidney transplant.50,51 Infections and thrombosis of dialysis access were commonly encountered complications in the group with SCD.

Transplantation

Although there may be many obstacles in the path to kidney transplantation, it is probably the preferred modality for patients with SCD requiring KRT. Although long-term graft and patient survival are not quite as good as for patients with other causes of ESKD, the prognosis for individuals with SCN is far better after transplantation with a projected 7-year survival of 67% (vs. 83% for other African Americans) compared with a 10-year survival of only 14% for those who remain on dialysis.21 Although outcomes after transplantation in SCD have improved over the last 20 years, it is not without complications. Delayed graft function and graft loss are more common than in other patient groups, and the recurrence of frequent VOC after transplantation as the Hb rises is problematic.52 Treatment with regular exchange transfusion aimed at keeping the HbS level below 30% may help reduce the risk for these complications and does not appear to be associated with increased rejection rates but is associated with improved patient survival.53

SICKLE CELL TRAIT AND CHRONIC KIDNEY DISEASE

In patients with heterozygous sickle cell trait, approximately 40% of RBC Hb is HbS, and the rest is normal HbA. In general, these patients have normal Hb levels and do not have symptoms of hemolysis or vaso-occlusion. However, there have been reports of catastrophic VOC and sudden death in young people with sickle cell trait under extreme adverse conditions such as excessive exercise or exposure to severe hypoxia. In addition, renal medullary carcinoma is more common in patients with SCT than SCD, though the reasons for this are unclear. Nonmalignant microhematuria and macrohematuria are reported more frequently in patients with sickle cell trait than in the general population, and older patients exhibit a loss of urinary concentrating ability. Patients who coinherit sickle cell trait and adult polycystic kidney disease (APKD) have a more rapid decline to ESKD than family members with APKD who do not carry an HbS gene. Whether having sickle cell trait alone is a risk factor for progressive CKD has been debated, but a recent population-based study in the United States has shown that SCT is associated with both CKD and progression to ESKD (hazard ration 2.03), independent of APOL1 status.54

SELF-ASSESSMENT QUESTIONS

1. Patients with SCD:
A. often develop albuminuria before they are 5 years old.
B. have reduced urinary concentrating capacity.
C. have reduced total kidney blood flow in childhood.
D. are often hypokalemic.

2. Patients with SCD and ESKD:
A. have a lower mortality rate when on dialysis than patients with adult polycystic kidney disease.
B. who have a kidney transplant should avoid blood transfusion, as it is associated with increased rejection rates.
C. who are on dialysis should be prescribed erythropoietin, as this usually avoids the need for blood transfusion.
D. have a higher rate of delayed graft function after kidney transplantation than patients with ESKD of other causes.

3. Hydroxycarbamide:
A. should be avoided in patients with chronic kidney disease.
B. has been shown to reduce hyperfiltration in children with SCD in a randomized controlled trial.
C. works by increasing fetal hemoglobin production.
D. should not be given in combination with inhibitors of the reninangiotensin system.

REFERENCES

1. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381:142–151.
2. Piel FB, Tatem AJ, Huang Z, et al. Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000. Lancet Glob Health. 2014;2:e80–e89.
3. Sharpe CC, Thein SL. How I treat renal complications in sickle cell disease. Blood. 2014;123:3720–3726.
4. Hockham C, Piel FB, Gupta S, et al. Understanding the contrasting spatial haplotype patterns of malaria-protective beta-globin polymorphisms. Infect Genet Evol. 2015;36:174–183.
5. Serjeant GR. The natural history of sickle cell disease. Cold Spring Harb Perspect Med. 2013;3:a011783.
6. Akinsheye I, Solovieff N, Ngo D, et al. Fetal hemoglobin in sickle cell anemia: molecular characterization of the unusually high fetal hemoglobin phenotype in African Americans. Am J Hematol. 2012;87:217–219.
7. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018–2031.
8. Potoka KP, Gladwin MT. Vasculopathy and pulmonary hypertension in sickle cell disease. Am J Physiol Lung Cell Mol Physiol. 2015;308:L314–L324.
9. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330:1639–1644.
10. Davies SC, Oni L. Management of patients with sickle cell disease. BMJ. 1997;315:656–660.
11. Mack AK, Thompson AA. Primary and secondary stroke prevention in children with sickle cell disease. J Pediatr Health Care. 2016.
12. Powars DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltim). 2005;84:363–376.
13. Guasch A, Navarrete J, Nass K, et al. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006;17:2228–2235.
14. Serjeant GR, Serjeant BE, Mason KP, et al. The changing face of homozygous sickle cell disease: 102 patients over 60 years. Int J Lab Hematol. 2009;31:585–596.
15. Drawz P, Ayyappan S, Nouraie M, et al. Kidney disease among patients with sickle cell disease, hemoglobin SS and SC. Clin J Am Soc Nephrol. 2016;11:207–215.
16. Saraf SL, Shah BN, Zhang X, et al. APOL1, alpha-thalassemia, and BCL11A variants as a genetic risk profile for progression of chronic kidney disease in sickle cell anemia. Haematologica. 2017;102:e1–e6.
17. Sharpe CC, Thein SL. Sickle cell nephropathy - a practical approach. Br J Haematol. 2011;155:287–297.
18. Evans RG, Gardiner BS, Smith DW, et al. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol. 2008;295:F1259–F1270.
19. Statius van Eps LW, Pinedo-Veels C, de Vries GH, et al. Nature of concentrating defect in sickle-cell nephropathy. Microradioangiographic studies. Lancet. 1970;1:450–452.
20. Gurbanov K, Rubinstein I, Hoffman A, et al. Differential regulation of renal regional blood flow by endothelin-1. Am J Physiol. 1996;271:F1166–F1172.
21. Scheinman JI. Sickle cell disease and the kidney. Nat Clin Pract Nephrol. 2009;5:78–88.
22. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015;11:161–171.
23. Aygun B, Mortier NA, Smeltzer MP, et al. Glomerular hyperfiltration and albuminuria in children with sickle cell anemia. Pediatr Nephrol. 2011;26:1285–1290.
24. McCarville MB, Luo Z, Huang X, et al. Abdominal ultrasound with scintigraphic and clinical correlates in infants with sickle cell anemia:

baseline data from the BABY HUG trial. AJR Am J Roentgenol. 2011;196:1399–1404.

25. Ware RE, Rees RC, Sarnaik SA, et al. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. J Pediatr. 2010;156:66–70.e61.
26. Lebensburger JD, Cutter GR, Howard TH, et al. Evaluating risk factors for chronic kidney disease in pediatric patients with sickle cell anemia. Pediatr Nephrol. 2017;32:1565–1573.
27. Moodalbail DG, Falkner B, Keith SW, et al. Ambulatory hypertension in a pediatric cohort of sickle cell disease. J Am Soc Hypertens. 2018;12:542–550.
28. Lebensburger JD, Aban I, Pernell B, et al. Hyperfiltration during early childhood precedes albuminuria in pediatric sickle cell nephropathy. Am J Hematol. 2019;94:417–423.
29. Day TG, Drasar ER, Fulford T, et al. Association between hemolysis and albuminuria in adults with sickle cell anemia. Haematologica. 2012;97:201–205.
30. Quek L, Sharpe C, Dutt N, et al. Acute human parvovirus B19 infection and nephrotic syndrome in patients with sickle cell disease. Br J Haematol. 2010;149:289–291.
31. Nakano D, Pollock D. New concepts in endothelin control of sodium balance. Clin Exp Pharmacol Physiol. 2011.
32. Statius van Eps LW, Schouten H, La Porte-Wijsman LW, et al. The influence of red blood cell transfusions on the hyposthenuria and renal hemodynamics of sickle cell anemia. Clin Chim Acta. 1967;17:449–461.
33. Thompson J, Reid M, Hambleton I, et al. Albuminuria and renal function in homozygous sickle cell disease: observations from a cohort study. Arch Intern Med. 2007;167:701–708.
34. Msaouel P, Hong AL, Mullen EA, et al. Updated recommendations on the diagnosis, management, and clinical trial eligibility criteria for patients with renal medullary carcinoma. Clin Genitourin Cancer. 2019;17:1–6.
35. Mava Y, Ambe JP, Bello M, et al. Urinary tract infection in febrile children with sickle cell anaemia. West Afr J Med. 2011;30:268–272.
36. Oteng-Ntim E, Ayensah B, Knight M, et al. Pregnancy outcome in patients with sickle cell disease in the UK-a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease. Br J Haematol. 2015;169:129–137.
37. Lebensburger JD, Palabindela P, Howard TH, et al. Prevalence of acute kidney injury during pediatric admissions for acute chest syndrome. Pediatr Nephrol. 2016;31:1363–1368.
38. McCormick M, Richardson T, Warady BA, et al. Acute kidney injury in paediatric patients with sickle cell disease is associated with increased morbidity and resource utilization. Br J Haematol. 2020;189: 559–565.
39. Gordeuk VR, Sachdev V, Taylor JG, et al. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. Am J Hematol. 2008;83:15–18.
40. Arogundade FA, Sanusi AA, Hassan MO, et al. An appraisal of kidney dysfunction and its risk factors in patients with sickle cell disease. Nephron Clin Pract. 2010;118:c225–c231.
41. Liem RI, Lanzkron S, DC T, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. Blood Adv. 2019;3:3867–3897.
42. Stevens PE, Levin A. Kidney disease: improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158:825–830.
43. Zahr RS, Yee ME, Weaver J, et al. Kidney biopsy findings in children with sickle cell disease: a Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol. 2019;34:1435–1445.
44. Vasavda N, Gutierrez L, House MJ, et al. Renal iron load in sickle cell disease is influenced by severity of haemolysis. Br J Haematol. 2012;157:599–605.

45. Sasongko TH, Nagalla S, Ballas SK. Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease. Cochrane Database Syst Rev. 2013:CD009191.
46. Wang W, Thompson B, investigators BH. Hydroxyurea treatment of infants with sickle cell anaemia: results of the BABY HUG study. Paediatric Blood and Cancer. 2010;54:787.

References

47. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:2040620720955000.
48. Pedersen SJV, Monagel DA, Mammen C, et al. Stable renal function in children and adolescents with sickle cell disease after nonmyeloablative hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2020;67:e28568.
49. Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med. 1991;115:614–620.
50. Olaniran KO, Eneanya ND, Zhao SH, et al. Mortality and hospitalizations among sickle cell disease patients with end-stage kidney disease Initiating dialysis. Am J Nephrol. 2021:1–9.

51. Nielsen L, Canoui-Poitrine F, Jais JP, et al. Morbidity and mortality of sickle cell disease patients starting intermittent haemodialysis: a comparative cohort study with non-Sickle dialysis patients. Br J Haematol. 2016;174:148–152.
52. Gérardin C, Moktefi A, Couchoud C, et al. Survival and specific outcome of sickle cell disease patients after renal transplantation. Br J Haematol. 2019;187:676–680.
53. Willis JC, Awogbade M, Howard J, et al. Outcomes following kidney transplantation in patients with sickle cell disease: the impact of automated exchange blood transfusion. PLoS One. 2020;15:e0236998.
54. Naik RP, Irvin MR, Judd S, et al. Sickle cell trait and the risk of ESRD in blacks. J Am Soc Nephrol. 2017;28:2180–2187.

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Congenital Anomalies of the Kidney and Urinary Tract

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Congenital anomalies of the kidney and urinary tract (CAKUT) are a group of phenotypically diverse structural malformations characterized by defects in kidney and urinary tract development. CAKUT accounts for 20% to 30% of all developmental anomalies identified in the antenatal period and has a prevalence of 3 to 6 per 1000 births.[1] Although usually occurring in isolation, 30% are associated with extrarenal abnormalities, and CAKUT has been associated with more than 200 different syndromes, including Fraser syndrome, Kallman syndrome, and branchio-oto-renal (BOR) syndrome. CAKUT accounts for up to 50% of children with chronic kidney disease (CKD)[2] and is the leading cause of end-stage kidney disease (ESKD) in children, making up 34% to 43% of those requiring kidney replacement therapy (KRT).[2 3] CAKUT also contributes significantly to the burden of kidney disease in young adults, accounting for 26% and 17% of individuals requiring KRT at age 18 to 21 years and 22 to 31 years, respectively,[4] with a median age of KRT initiation of 31 years.[5] Reduced nephron mass secondary to a solitary functioning kidney or posterior urethral valves (PUV) are associated with a worse kidney outcome, with concurrent vesicoureteral reflux (VUR) a poor prognostic sign.[6 7] Even with normal kidney function and blood pressure (BP) in adolescence, individuals with CAKUT have an increased lifetime risk of ESKD.[8]

CLINICAL PRINCIPLES

Congenital kidney and urinary tract anomalies may present in one of the following five settings:

1. Antenatal diagnosis by fetal ultrasound (US) screening
2. Failure to thrive in an infant or young child
3. Investigation of urinary tract infection (UTI)
4. An incidental finding in a child or adult
5. An adult with abnormal urinalysis, stones, hypertension, or reduced glomerular filtration rate (GFR)

The identification of these problems always poses the following questions:

- What is the cause?
- What is the natural history?
- Is surgical intervention required?

If there is a family history of structural malformations, a genetic cause may sometimes be identified, guiding surveillance for extrarenal manifestations, as in the case of HNF1B-related disease, as well as screening of first-degree relatives. Symptomatic UTIs are common in individuals with CAKUT and an increase in frequency of UTIs or deterioration in GFR should prompt investigations to exclude obstruction or bladder dysfunction that may require urologic intervention. Furthermore, as predicted by the Brenner hypothesis,[9] small dysplastic kidneys with reduced GFR develop all the features of glomerular hyperfiltration. The onset of progressive kidney impairment signaled by increasing proteinuria and hypertension should be treated according to standard CKD guidelines with initiation of renin-angiotensin system (RAS) blockade. The details of antenatal and pediatric management of these patients are beyond the scope of this chapter, which focuses on management in adolescence and adult life.

DEVELOPMENT OF THE KIDNEYS AND URINARY TRACT

The kidneys and urinary tract develop simultaneously from the endoderm-derived cloaca and intermediate mesoderm (Fig. 52.1).[10] Kidney development can be divided into three phases: the pronephros, mesonephros, and metanephros. The pronephros develops 22 days after conception and forms a transient, rudimentary, and nonfunctioning system that degrades by day 28. It elongates caudally to meet the cloaca by day 26, becoming the mesonephric (Wolffian) duct, which ultimately contributes to the formation of the urinary bladder and male genital system (epididymis and caudal vas deferens).[11] The mesonephros is derived from the intermediate mesoderm and develops functioning tubules, which start to excrete urine, although most of these subsequently degenerate. By the fifth week of fetal life, the ureteral bud branches from the caudal part of the mesonephric duct into the metanephric mesenchyme to become the metanephros, the precursor to the adult kidney (see Fig. 52.1A). This process is mediated by glial cell line–derived neurotrophic factor (GDNF)/RET signaling, disruptions of which can result in varying phenotypes, including kidney agenesis. Reciprocal induction between the ureteral bud and the metanephric mesenchyme results in branching morphogenesis and elongation of the ureteral bud to form the collecting system and mesenchymal epithelial transformation of the metanephric mesenchyme to generate primitive nephrons (see Fig. 52.1B–D). The metanephros starts to function 6 to 10 weeks after fertilization, with nephrogenesis complete by 36 weeks. Sixty percent of nephrons are formed in the last trimester, which has important clinical implications for preterm and low-birth-weight infants, who have increased long-term risk for CKD.[12] The extent to which reduced nephron number contributes to this increased risk relative to exposure to nephrotoxic insults and acute kidney injury as a neonate is not yet understood.

The lower urinary tract is formed from the endodermal cloaca, which is divided by the urorectal septum into ventral and dorsal parts that develop into the urogenital sinus and rectum, respectively (see Fig. 52.1E). The urogenital sinus gives rise to the early bladder, the urethra and vestibule of the vagina in females, and the posterior urethra in males. Growth of the anterior abdominal wall between the allantois and the urogenital membrane is accompanied by an increase in size and capacity of this bladder precursor. The allantois remains attached to the apex of the fetal bladder and extends into the umbilical root, although it loses its patency and persists as the urachal remnant, the

Development of the Urinary Tract
Mesonephric (wolffian)
duct
Metanephric
mesenchyme

Ductus
deferens

Mesonephric
duct

Allantois

Ureter

Urachus

Primitive
pelvis

A

B

Ureter
Early
bladder
Seminal
vesicle

Urorectal
septum
Urogenital
sinus

C

D

E

Cloacal
membrane

Cloaca

Genital Trigone
tubercle

Rectum

F

Fig. 52.1 Development of the Urinary Tract. Growth and development of the ureter, pelvis, and calyces are shown in parts A to D. (A) The metanephric kidneys first become detectable as small areas in the mesoderm close to the aorta. The primitive epithelial ureter buds off from the mesonephric duct and makes contact with

the metanephric mesenchyme. (B) Under the influence of signals from the ureter, the mesenchyme condenses and proliferates around the ureteral tip, with simultaneous elongation and branching of the ureteral tip. (C–D) A primitive pelvis appears, then branches to form the divisions of the calyces. The branching process continues, with the epithelial system eventually differentiating into the nephrons of the kidney parenchyma. As the fetus grows, the kidney ascends because of the continuous rostral growth. (E) Growth and development of the cloaca during weeks 5 to 6 of gestation. (F) Growth and development of the urogenital sinus into bladder and outflow tract during weeks 8 to 9.

median umbilical ligament, which connects the bladder to the umbilicus (see Fig. 52.1F). By the seventh week, there is a separate opening of the distal mesonephric duct into the bladder at what will become the vesico-ureteral opening and the area known as the trigone. At the same time the paramesonephric (müllerian) ducts start to regress in males and fuse in females to become the uterovaginal cord, which opens into the urogenital sinus and will go on to develop into the vagina.

PATHOGENESIS

Familial clustering, monogenic syndromes associated with urinary tract malformations, and animal models suggest a strong genetic basis for CAKUT. US screening of asymptomatic first-degree relatives reveals structural urinary tract malformations in up to 23%.13

The increasing availability of next-generation sequencing has led to the identification of over 50 monogenic CAKUT-causing genes, but genotype-phenotype heterogeneity and incomplete penetrance mean that a single-gene cause has been identified in less than 20% of individuals.14 In addition, rare copy-number variation (CNV) has been reported in up to 40% of individuals with CAKUT, suggesting that gene dosage may also be an important mechanism.15 Environmental factors, including preexisting and gestational maternal diabetes16 and increases or decreases in maternal vitamin A levels,17 have also been associated with an increased risk of anomalies, and it is likely that CAKUT results from the complex interplay of genetics and maternal and environmental factors.

Kidney and urinary tract development are tightly regulated by a network of transcription factors, growth factors, and adhesion molecules. Pathogenic variants in genes encoding all classes of these molecules, affecting different stages of nephrogenesis, have been identified in patients with CAKUT (Table 52.1). Variants in the transcription factors HNF1B (hepatocyte nuclear factor 1B) and PAX2 (paired box gene 2) are two of the most common causes of CAKUT (both syndromic and isolated) and are associated with cystic kidneys and kidney hypodysplasia (Table 52.2), respectively.

✓•✓ HNF1B mediates the development of the kidneys, liver, pancreas, and urinary tract. Haploinsufficiency resulting from whole-gene deletions (typically a 1.4 Mb 17q12 deletion) or pathogenic heterozygous variants can cause kidney cysts and diabetes syndrome (KCAD). A high frequency of de novo deletions means there may not be a family history. HNF1B-related disease is associated with a wide range of CAKUT phenotypes: kidney hypodysplasia, cystic kidneys, single and horseshoe kidneys, malformations of the collecting system, and autosomal dominant tubulointerstitial kidney disease (ADTKD-HNF1B).18 Extrarenal manifestations include mature-onset diabetes of the young [MODY] type 5, pancreatic hypoplasia, genital malformations, hyperuricemia and early gout, abnormal liver function, and hypomagnesemia, highlighting the utility of a molecular diagnosis in guiding evaluation for possible nonrenal abnormalities.

✓•✓ PAX2 is a key regulator of multiple steps of kidney development, including ureteric bud induction, branching morphogenesis, and nephron differentiation.19 Heterozygous variants in PAX2 were first discovered in patients with renal-coloboma syndrome presenting with kidney hypodysplasia, optic nerve abnormalities, and hearing loss, but variants have now been identified in a wide range of phenotypes, including adult-onset focal segmental glomerulosclerosis (FSGS).20

TABLE 52.1

Monogenic Causes of CAKUT

Inheritance

Gene

Associated Phenotype

Autosomal recessive

CHRM3
FRAS1
FREM1
FREM2
GFRA1
GRIP1
HPSE2

Prune-belly like syndrome
Fraser syndrome, kidney agenesis
Bifid nose, kidney agenesis
Fraser syndrome, kidney agenesis
Bilateral kidney agenesis
Fraser syndrome, kidney agenesis
Urofacial syndrome, neurogenic bladder
Bilateral kidney agenesis
Urofacial syndrome, neurogenic bladder
VACTERL
Congenital lower urinary tract obstruction/PUV
Branchio-oto-renal syndrome
HDR syndrome
Pallister-Hall syndrome
Kidney agenesis
Kidney cysts and diabetes syndrome
Renal-coloboma syndrome, FSGS
Kidney hypodysplasia
Kidney agenesis
Townes-Brocks syndrome, kidney hypodysplasia
Branchio-oto-renal syndrome
PUJO
Syndromic CAKUT
Kallmann syndrome, kidney agenesis

ITGA8
LRIG2

Autosomal dominant

TRAP1
BNC2
EYA1
GATA3
GLI3
GREB1L

HNF1B
PAX2
PBX1
RET
SALL1

X-linked recessive

SIX5
TBX18
ZMYM2
ANOS1

CAKUT, Congenital anomalies of the kidney and urinary tract; FSGS, focal segmental glomerulosclerosis; HDR, hypoparathyroidism, sensorineural deafness, and kidney disease; PUJO, pelvi-ureteral junction obstruction; PUV, posterior urethral valves; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal (kidney) anomalies, and limb anomalies.

KIDNEY PARENCHYMAL MALFORMATIONS

Congenitally abnormal kidneys may be enlarged or small, cystic or dysplastic, and absent or misplaced. These conditions were traditionally discussed based on findings on intravenous urography (IVU) but are now primarily investigated with US, computed tomography (CT), and magnetic resonance imaging (MRI). Functional assessment of obstruction and VUR are carried out using 99mTc-mercaptoacetyltriglycine (MAG3) scintigraphy and voiding cystourethrogram (VCUG), respectively.

Kidney Dysplasia

Table 52.2 presents the range of dysplastic and other malformations of the kidney. Abnormalities of the ureter, bladder, and urethra are often associated with kidney dysplasia, and evidence of concurrent VUR should always be sought. All types of kidney dysplasia can also occur as isolated developmental anomalies and although typically producing small, irregular kidneys, they can also be cystic or multicystic. US features of kidney dysplasia include increased echogenicity, poor corticomedullary differentiation, and parenchymal cysts.

TABLE 52.2

Malformations

Definitions of Kidney

Term

Characteristics

Kidney agenesis

Absence of the kidney or an identifiable metanephric structure.
Severe dysplasia with extremely small kidney, sometimes identifiable only by histologic examination.
Abnormal differentiation of kidney parenchyma with development of abnormal structures, including primitive ducts surrounded by collars of connective tissue, metaplastic cartilage, variety of nonspecific malformations such as preglomeruli of fetal type, and reduced branching of collecting ducts with

cystic dilations and primitive tubules. Dysplastic kidneys often contain cysts.

Significantly reduced kidney mass with either normal or reduced (oligomeganephronia) nephron number without evidence of maldevelopment of parenchyma.

Reduced kidney mass and nephron number with dysplastic features. Previously thought to be secondary to scarring from reflux or reflux nephropathy but now considered to be primary dysplasia with associated reflux.

Severe cystic dysplasia with extremely enlarged kidney full of cystic structures; occurs as an isolated kidney lesion in response to ureteral atresia and urethral obstruction; 10% of patients have a family history.

Kidney aplasia

Kidney dysplasia

Kidney hypoplasia

Kidney hypodysplasia

Kidney multicystic dysplasia

Kidney Hypoplasia

Kidney hypoplasia is defined as a congenitally small kidney (two standard deviations below the expected mean) that lacks evidence of either parenchymal maldifferentiation (kidney dysplasia) or acquired disease sufficient to explain the reduced size. The term is often used loosely and includes small kidneys with a normal number of nephrons as well as oligomeganephronia. This is a type of kidney hypoplasia resulting from a congenital reduction in the number of nephrons. It results from arrested development of the metanephric blastema at 14 to 20 weeks of gestation with subsequent hypertrophy of glomeruli and tubules in the kidney. The hypertrophy and hyperfiltration result in progressive nephron injury and sclerosis later in life. Oligomeganephronia is recognized on kidney biopsy by the large size of the glomeruli and tubules and the small number of glomeruli seen despite a good core of kidney cortex.

Differential Diagnosis of Scarred Kidneys

Kidney hypodysplasia versus reflux. Progressive scarring and kidney failure were once considered to be caused by chronic parenchymal infection (so-called “chronic pyelonephritis”) and were regarded as a consequence of VUR. The 1980s, however, saw a retreat from the paradigm of the primary role of infection, and emphasis was placed on scarring as a result of reflux and the progressive nature of the glomerular lesion associated with glomerular hypertension (or hyperfiltration), so-called “reflux nephropathy” (see Chapter 62). Current thinking is that scarring often follows from kidney dysplasia, and that the reflux is a secondary or incidental feature (Fig. 52.2). Thus, irregular kidneys with normal-caliber ureters are more likely to be caused by primary dysplasia, and no evidence of VUR may be seen.

Kidney scarring in adults. A practical clinical problem is the differential diagnosis of scarred, asymmetric kidneys. Genetic testing

A

Fig. 52.3 Single Pelvic Kidney. Magnetic resonance scan, transverse section, shows single midline pelvic kidney. (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

B

Fig. 52.2 Kidney Dysplasia. (A) Intravenous urogram (IVU) shows gross bilateral scarring in a 20-year-old woman who has been followed since the age of 2 years. Progressive scarring has been observed in the absence of urinary tract infections and obstruction. This probably represents primary kidney dysplasia. (B) Computed tomography IVU shows gross scarring of right kidney. (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

may be useful in younger patients, particularly in those with a family history of kidney disease. With older patients, the differential diagnosis of scarred or “lumpy, bumpy” kidneys widens. Sometimes attributed to other diagnoses, including analgesic nephropathy, this appearance is often designated reflux nephropathy. In older patients, multiple scarring from atheromatous arterial disease and embolization of the kidney is an increasingly important cause of kidney failure. The diagnosis has historically been made by the radiologic features on IVU, but CT and magnetic resonance (MR) urography are now the gold standard, with scarring best demonstrated by technetium 99m–labeled dimercaptosuccinic acid (99mTc-DMSA) scintigraphy.

Absent Kidneys

Unilateral Kidney Agenesis

Complete absence of one kidney occurs in approximately 1 in 3000 live births and may result from involution of a multicystic dysplastic kidney (MCDK) or true kidney agenesis. It can be inherited as an autosomal dominant trait with incomplete penetrance and variable expression, associated with heterozygous variants in RET and GREB1L, or biallelic variants in FRAS1 and FREM2.[1]

Agenesis occurs when the ureteric bud fails to develop and induce formation of the metanephros; typically, there is no ureter, and the ipsilateral half of the bladder trigone is missing. A blind-ending ureter may be seen in cases of MCDK. The remaining kidney is usually hypertrophic, but it may be ectopic, malrotated, or hydronephrotic with a megaureter and associated VUR. The more severe the dysplasia of the remaining kidney is, the earlier the presentation. The ipsilateral testis and seminal tract are usually absent, and in 10% of cases, the adrenal gland is also missing. Females can have an absent fallopian tube or ovary or malformation of the vagina or uterus. Other associations seen in 30% to 50% of those affected include imperforate anus and malformations of the vertebrae and cardiovascular system.

Normality of the single kidney should be confirmed by 99mTcDMSA scintigraphy and isotopic GFR. Compensatory glomerular hyperfiltration means that lifelong follow-up is necessary to monitor for proteinuria, hypertension, and CKD, which can be seen in up to 20% of individuals. Evaluation for urogenital anomalies is recommended in all first-degree relatives of individuals with kidney agenesis.

Bilateral Kidney Agenesis

Bilateral kidney agenesis is lethal. Although usually sporadic, biallelic variants in ITGA8 and GFRA1 have been reported. It is associated with pulmonary hypoplasia and a characteristic facial appearance (Potter facies) caused by intrauterine compression, which is a consequence of oligohydramnios. The prevalence is about 1 in 10,000 births, with risk for occurrence in siblings of about 3%, unless there is a family history of agenesis, in which case risk rises to 15% to 20%.

Misplaced Kidneys

Kidney Ectopia, Malrotation, and Crossed Fused Kidneys

The starting position of the fetal kidney is deep in the pelvis. Kidneys that fail to ascend properly and therefore remain lower than usual occur in 1 in 1000 births (Fig. 52.3). By the eighth week of gestation, the kidney ascends, and the pelvis comes to face more medially. The most common anomaly is for the pelvis to face forward. Those that do not migrate past the pelvic brim are called pelvic kidneys. The more ectopic the kidney is, the more severe the rotation is and the more abnormal the appearance. In more than 90% of ectopia, there is fusion of both kidneys, which may cross the midline (crossed fused ectopy). This is best visualized on CT or MR urography (Fig. 52.4). Symptoms and complications, if any, are usually caused by associated VUR, but in the absence of additional anomalies or obstruction, no follow-up is required.

Horseshoe Kidney

If both kidneys are low, they may fuse at the lower pole and are usually drained by two ureters (Fig. 52.5). The kidneys lie lower than normal,

A
A

B
Fig. 52.5 Horseshoe Kidney. (A) Intravenous urogram soon after pregnancy in a 25-year-old woman shows the horseshoe kidney joining in the midline as well as dilated ureters as a transient effect of pregnancy. (B) Dimercaptosuccinate scan shows a horseshoe kidney and the urinary bladder.

B
Fig. 52.4 Crossed Fused Ectopia. (A) Magnetic resonance scan shows fused kidneys on right. (B) There are two ureters (arrows). (Courtesy Dr. A. Kirkham, University College Hospitals, London.)

and further ascent is prevented by the root of the inferior mesenteric artery. Horseshoe kidney occurs in 1 in 600 to 1800 births and is more common in males (2:1). VUR and pelvi-ureteral junction (PUJ) obstruction are commonly seen with kidney calculi also occurring in up to 20%. Hydronephrosis in a horseshoe kidney should be investigated with a 99mTc-MAG3 renogram to differentiate obstruction from urinary stasis and urologic opinion sought if necessary. In most cases, individuals remain asymptomatic and do not require nephrologic follow-up.

Calyceal Abnormalities

Hydrocalyx and Hydrocalycosis

Dilated calyces are usually caused by obstruction. Focal dilation also can be caused by congenital infundibular stenosis, extrinsic compression from vessel or tumor, stones, or tuberculosis. If obstruction is excluded, the appearance is likely to be a congenital abnormality and can be an incidental finding. Moreover, if the GFR is normal and the divided function of the kidneys is 50:50, surgery to improve the anatomy should not be attempted.

Megacalycosis

In megacalycosis, there is bizarre dysplasia of the calyceal system with an increase in the number of calyces. There is no obstruction, and the cause is malformation of kidney papillae. Megacalycosis is congenital, usually unilateral, and an incidental finding. It is much more common in males (6:1). Bilateral disease is confined to males and segmental, unilateral disease to females, which suggests an X-linked partially recessive gene with reduced penetrance in females. There may be an associated ipsilateral segmental megaureter, usually affecting the distal third.

Calyceal Diverticulum (Calyceal Cyst)

A calyceal diverticulum is a cavity peripheral to a minor calyx that is not a closed cyst but rather is connected to the calyx by a narrow channel (Fig. 52.6). It is usually an incidental finding and may manifest with symptoms relating to stones or infection within the cavity.

Bardet-Biedl Syndrome

Multiple calyceal clubbing and calyceal diverticula are the characteristic features of the kidney dysplasia seen in Bardet-Biedl syndrome (formerly known as Laurence-Moon-Biedl syndrome). This rare autosomal recessive condition is characterized by retinitis pigmentosa, polydactyly, obesity, hypogonadism, learning difficulties, and kidney anomalies in 80%. Calyceal malformation is associated with parenchymal

Algorithm to Exclude Obstruction
Ultrasound of kidney
indicates pelvic dilation
or a rise in serum creatinine
Concern about
obstruction?
Dynamic isotope scintigram
^{99m}Tc-labeled MAG3

Hold-up of isotope
in pelvis

No hold-up

Give furosemide
No
obstruction

Isotope
washes out
Retention of isotope
after furosemide and
after standing up

No rise in
pressure

Fig. 52.6 Calyceal Cyst. Intravenous urogram shows an upper pole calyceal cyst filled with contrast (arrows). Plain abdominal radiograph showed a group of stones in the floor of the cyst.

Antegrade nephrostogram
(pressure–flow study,
Whitaker test)

Obstruction

dysplasia, fetal lobulation, kidney cysts, horseshoe kidneys, and VUR; kidney failure in early adult life is common. Bardet-Biedl syndrome is caused by a defect of the basal body of ciliated cells,[21] and mutations in 22 genes coding for different proteins located in the basal body and primary cilia of the cell have been reported, making the syndrome an archetypal ciliopathy.

COLLECTING SYSTEM ABNORMALITIES

Pelvi-ureteral Junction Obstruction

PUJ obstruction occurs in 1 in 1500 live births and is one of the most common causes of antenatally detected hydronephrosis. It is seen more frequently in males (2:1), preferentially affecting the left kidney. The condition is usually congenital, caused by intrinsic stenosis or kinking of the proximal ureter at the PUJ, but can have an acquired mechanical basis as a result of external compression from an aberrant or accessory lower pole vessel or adhesions. Associated abnormalities are common, and up to 50% of infants have another urologic abnormality, such as contralateral PUJ obstruction, contralateral dysplastic and multicystic kidney, minor degrees of VUR, and contralateral kidney agenesis.

Older children can present with an abdominal mass or with intermittent flank pain that worsens during a brisk diuresis (e.g., after consumption of caffeine or alcohol), a phenomenon called Dietl’s crisis. Hematuria secondary to mild trauma and UTIs may also occur. Hypertension is unusual but can occur temporarily after surgical correction.

^{99m}Tc-MAG3 diuretic renogram should be used to differentiate between significant obstruction that requires surgical correction and congenital ectasia of the renal pelvis, in which case surgery is not indicated (Fig. 52.7). Kidneys with good function can generally be left alone, and pyeloplasty is indicated only when function is clearly deteriorating (>10% decrease in split kidney function) or for symptomatic relief of pain, infection, or stones.22

Fig. 52.7 Algorithm to Exclude Pelvi-Ureteral Junction (PUJ) Obstruction. Diagnostic path used to differentiate between significant PUJ obstruction and congenital ectasia of renal pelvis. MAG3, Mercaptoacetyltriglycine.

Duplex Collecting System

Partial or complete duplication of the ureter and renal pelvis is a common anomaly, with an incidence of about 1 in 150 births; unilateral duplication is six times more frequent than bilateral. It is more common in females. If duplication has been detected in a patient, the likelihood of another sibling with duplication rises to 1 in 8.

Pathogenesis

If the ureteral bud bifurcates after its origin from the mesonephric duct but arises at a normal site, an incomplete ureteral duplication with a Y ureter will develop. Complete ureteral duplication occurs if there are two ureteral buds, one in the normal location and the other in a low position. The normal bud ends in a correct site on the trigone in the bladder and is nonrefluxing. The lower bud, representing the ureter of the lower pole of the kidney, ends in the bladder as a lateral orifice with a short submucosal tunnel. The lower pole ureter is therefore often associated with VUR.

If there are two ureteral buds, one with a normal location and one with a high position, the upper ureter can be incorporated into the developing bladder, ending more distally and medial to the normal one, or inserted ectopically elsewhere. The ectopic ureter can result in obstruction or VUR, and there is often associated dysplasia of the upper pole moiety.

Clinical Manifestations

In most adult patients, ureteral duplication is asymptomatic and causes no long-term problems. Children with ureteral duplication often have VUR. The spontaneous disappearance of reflux is less common in duplex ureters than in patients with a single ureter. Duplex ureters are

Ectopic ureters are best visualized by CT or MR urography. A voiding cystourethrogram shows reflux into the lower pole of the kidney in 50% of patients.

Ureterocele

A

Ureteroceles are cystic dilations of the terminal segments of the ureter. Ureteroceles affect females more than males (4:1), and 10% are bilateral. Ectopic ureters and ureters with ureteroceles frequently (80%) drain the upper pole of a duplex collecting system and are often associated with dysplastic or nonfunctional kidney tissue. These usually present in childhood with infection; when large, they can obstruct the bladder neck or even the contralateral ureter. In adults, ureteroceles typically manifest with stones in the lower ureter.

First-line management of ureteroceles is endoscopic decompression, although partial nephroureterectomy, ureteral reimplantation, or ureterocele excision and bladder neck reconstruction may be required. There are usually no medical sequelae.

Megaureter

B

Fig. 52.8 Duplex Kidney. (A) Intravenous urogram shows a duplex left kidney. The lower pole is scarred and shows evidence of reflux damage. The two ureters enter the bladder separately, with the lower pole ureter in the abnormal location. The right kidney also shows features of reflux, with clubbing of the calyces and some scarring. (B) Computed tomography scan shows an isolated right-sided megaureter (arrows).

best diagnosed by CT urogram. PUJ obstruction of the ureter draining the lower pole of the kidney can occur. Associated conditions, such as ectopic ureters and ureterocele (see later discussion), usually cause problems in early life and therefore have been addressed by adolescence. Upper pole scarring is associated with an ectopic ureter and lower pole scarring with VUR (Fig. 52.8A).

Ectopic Ureters

Ectopic ureters are almost always associated with ureteral duplication and insert along the developing mesonephric system; 10% are bilateral and there is a female-to-male ratio of 7:1. The ectopic ureter comes from the upper pole and inserts into the bladder more distally and toward the bladder neck or opens into the upper urethra. In females, the ureter may end in the bladder neck or upper urethra, vagina, cervix, or uterus, and patients present with incontinence, UTIs, or a persistent vaginal discharge, particularly if the external sphincter is damaged, as during labor.

Ectopic ureters are rare in males and manifest as UTI. Usually, there is a single ureter associated with a dysplastic kidney, which ends in the posterior urethra, seminal vesicle, or vas deferens. Males are usually continent because the ureter is proximal to the external sphincter.

Primary megaureter occurs in 3 to 4 per 10,000 live births, is seen more frequently in males, and is bilateral in 30% to 40% of cases. Isolated dilation of the ureter does not necessarily imply obstruction. There are three broad groups of conditions with widely dilated ureters, as follows:

1. Obstruction of the ureter itself. This may be intrinsic (e.g., stone)

or extrinsic (e.g., retroperitoneal fibrosis); it is not associated with reflux.

2. Bladder outflow obstruction, with secondary ureteral obstruction. Examples include a neuropathic bladder and posterior urethral valves; this may or may not be associated with reflux.
3. A dilated but nonobstructed ureter. This often occurs without reflux, and there can be normal kidney function; this may be caused by an adynamic segment of the lower ureter (see Fig. 52.8B).

Pathogenesis

In the normal ureter, there is a characteristic helical orientation of muscle fibers. When the megaureter is secondary to bladder outflow obstruction, there is muscle hyperplasia and hypertrophy of the ureteral wall. In primary megaureter, a variety of abnormalities of muscle orientation are described or there may be absence of muscle fibers at the proximal end of the undilated segment. Electron microscopy shows an increase in collagen between the muscle bundles at the level of the obstructing segment. Obstruction appears to be caused by a failure of peristalsis through the distal ureteral segment.

Clinical Manifestations

Most cases of megaureter associated with obstruction present in childhood with severe infections, often complicated by septicemia. These patients have a high incidence of other congenital abnormalities. In less severe cases or with no obstruction, patients can present with abdominal pain, loin pain, hematuria, and UTI. Kidney stones can form easily in the dilated systems. The exclusion of obstruction is often established only by an antegrade pressure-flow study (Whitaker test), in which a nephrostomy is placed in the renal pelvis and contrast material infused at 10 mL/min.[23]

Treatment

It must be definitively determined whether obstruction exists (see Fig. 52.7). The current view is that patients with asymptomatic nonobstructed disease should be managed conservatively, and most do well with this approach, with spontaneous remission rates of up to 85%.

Vesico-ureteral Reflux

VUR describes the retrograde passage of urine from the bladder to the upper tract. Such patients fall into two broad groups. First, there is a group of patients who appear to have normal bladders without outflow obstruction and normal caliber ureters when not micturating, described as having primary VUR resulting from a congenitally shortened intravesical ureter. The remainder have some form of anatomic or functional bladder outflow dysfunction that causes secondary VUR and dilated upper urinary tracts, the most common cause of which is PUV in males. VUR has an incidence of around 1%, is seen more frequently in females, and usually spontaneously regresses with age. Although previously believed to cause “reflux nephropathy” or “chronic pyelonephritis,” where recurrent infection leads to acquired kidney scarring, advances in genetics and developmental biology indicate that kidney impairment is usually the result of associated primary kidney dysplasia rather than reflux itself.

Pathogenesis

There is a strong familial association with primary VUR; 27% of siblings and 36% of offspring of affected parents have been found to have VUR.23 Linkage and genome-wide studies have yet to identify any robust genetic associations, highlighting the heterogeneity of this often-undiagnosed condition.

Clinical Manifestations

VUR is usually diagnosed after a febrile UTI by voiding cystourethrogram (VCUG). Severity is graded I to V with grades IV and V (high-grade VUR) defined by gross dilation of the ureter and collecting system, blunting of the calyces, and tortuosity of the ureter (see Chapter 62). The higher the grade, the less likely it is that spontaneous resolution will occur and the higher the prevalence of recurrent symptomatic UTI. US and DMSA imaging should be undertaken to look for associated kidney anomalies, differential function, and cortical defects. Concurrent lower urinary tract symptoms may also occur.

Treatment

Management of VUR aims to prevent recurrent infections and preserve kidney function. In children, antibiotic prophylaxis reduces the risk of recurrent UTI but has not been shown to have an effect on kidney scarring.24 Indications for surgical intervention include grade III to V reflux, which does not spontaneously remit and is associated with breakthrough infections on prophylaxis. Endoscopic injection of a bulking agent around the intravesical ureter (DEFLUX) or open ureteric reimplantation are valid options, although VUR is more likely to recur after endoscopic correction. Current guidelines do not recommend the screening of siblings or offspring because of uncertainty regarding the clinical importance of asymptomatic VUR.

BLADDER AND OUTFLOW DISORDERS

Prune-Belly Syndrome

Prune-belly syndrome (PBS) nearly always affects males and is characterized by the absence of anterior abdominal wall muscles, bizarre malformations of the urinary tract with gross dilation of the bladder and ureters, and bilateral undescended testes.25 When the disorder is diagnosed early, kidney outcome is related to the degree of kidney dysplasia. There are incomplete forms of PBS (pseudoprune). Rarely, a similar megacystis or megaureter may be seen in a male or female patient.

Fig. 52.9 Prune-Belly Syndrome. Note the lax abdominal musculature leading to a pot-bellied appearance. There is also marked thoracic cage deformity. (Courtesy Prof. C.R.J. Woodhouse, University College Hospital, London.)

Pathogenesis

The incidence of PBS varies from 1 in 35,000 to 1 in 50,000 live births. Some familial cases have been reported, implicating genes affecting smooth muscle function. Biallelic loss-of-function mutations in CHRM3, a muscarinic acetylcholine receptor involved with parasympathetic-mediated detrusor contraction, have been identified in one family with prune-belly–like syndrome.26 There is also evidence for a primary, localized arrest of mesenchymal development, supported by the lack of prostatic differentiation; the epithelial element in the prostate is absent or hypoplastic. Ultrastructure studies of the ureter show massive replacement of smooth muscle with fibrous and collagen tissue and the absence of nerve plexuses. An almost identical syndrome can result from fetal urethral obstruction, including urethral atresia.

Clinical Manifestations

The prognosis depends on the degree of kidney dysplasia and injury. Three prune-belly groups can be distinguished.25 In group I (20%), complete urethral obstruction causes stillbirth or neonatal death. In group II (20%), acute, early presentation requires diversion and reconstruction. In group III (60%), good health and kidney function continue despite urologic appearances.

There is complete absence or incomplete formation of the rectus abdominis and other muscles, which leads to the wrinkled abdominal wall of the prune infant (see Fig. 52.10C). This gives way to a fairly smooth “pot belly” in later life (Fig. 52.9). Reconstructive surgery is not normally required. The patients grow up physically active and strong but cannot sit up directly from a supine position. Abnormalities of the thoracic cage, such as pectus excavatum, are common.

Although true outflow obstruction may be present, the gross and irregular dilation of the urinary tract characteristic of PBS is primarily caused by a developmental defect with a variable degree of smooth muscle aplasia leading to aperistaltic ureters (Fig. 52.10A–B).

B

A

C

Fig. 52.10 Prune-Belly Syndrome. (A) Typical intravenous urogram appearance of a patient with prune-belly syndrome and good kidney function. Often, the ureters are extremely dilated and tortuous. (B) Computed tomography urogram showing gross bilateral hydronephrosis. (C) Absence of anterior abdominal wall musculature (arrows).

Urodynamic studies are often difficult to interpret because of gross VUR, but typically there is a low-pressure bladder with significant residual urine volumes. With late manifestation, some patients have detrusor instability. UTIs are common as a result of VUR and urinary stasis with constipation resulting from a defective Valsalva maneuver also increasing susceptibility.

Differential Diagnosis

In severe cases of megacystis or megaureter with gross impairment of kidney function (often with dysplastic kidneys), the differential diagnosis of PBS includes PUV, kidney dysplasia with or without multiple congenital defects, or neuropathic bladder.

Natural History

Once any outflow obstruction is addressed, usually in infancy, the GFR should remain stable despite the frightening radiologic appearances. In PBS patients observed in our unit for up to 40 years, kidney deterioration and hypertension have been rare. In the small number who have progressed, recurrent infection, hypertension, and proteinuria have been warning signs of impending trouble. Kidney scarring should be assessed by isotopic DMSA scintigraphy and kidney function followed by serial isotopic GFR measurements. Lifelong attention to blood pressure, UTIs, and stones is necessary.

Treatment

In all children with PBS, even with good kidney function, a careful search for obstruction should begin with the urethra and work up to the PUJ. Often, however, no obstruction is found, and no surgery is required. In many other patients, the floppy bladder is not anatomically obstructed, but bladder emptying is improved by urethrotomy (“functional obstruction”). In infancy, there is debate about the need for reconstructive surgery. Certain patients born with severely compromised kidney function require reconstruction after stabilization by early diversion.

The current view is that the testes should be brought down to the scrotum (orchiopexy) in infancy in the hope that earlier surgery will produce proper germ cell development and thus preserve fertility. Although men with PBS have azoospermia, and are by definition infertile, there are case reports of successful paternity using intracytoplasmic sperm injection.

Bladder Exstrophy (Ectopia Vesicae)

Classic bladder exstrophy is the failure of the anterior abdominal wall and bladder to close, resulting in an open, inside-out appearance. These anomalies form part of the bladder exstrophy-epispadias complex (BEEC), which range from epispadias of an otherwise normal penis to major cloacal abnormalities (Fig. 52.11). The condition occurs in 1 in 50,000 births. The male-to-female ratio is 2:1.

Pathogenesis

Failure of growth of the lower abdominal wall between the allantois and the urogenital membrane coupled with breakdown of the urogenital membrane leaves a small, open bladder plate, a low-placed umbilical root, and diastasis of the pubic bones (Fig. 52.12B). The genital tubercle is probably placed lower in these patients, and the cloacal membrane ruptures above it, leading to a penis with an open dorsal surface that is continuous with the bladder plate. A midline closure defect causes a failure of fusion of the lower anterior abdominal wall, including the symphysis pubis, lower urinary tract, and external genitalia. Familial clustering suggests a genetic basis for the disorder, and association with the ISL1 locus and 22q11.2 duplications have been reported.27

Fig. 52.11 Bladder Exstrophy. The entire length of the penis is also open (epispadias). (Courtesy Prof. C.R.J. Woodhouse, University College Hospital, London.)

Clinical Manifestations

In severe cases, the bladder mucosa lies exposed on the lower abdominal wall, with the bladder neck and urethra laid open. The prostate and testes are normal. Most patients have normal kidneys at birth, but approximately 18% are reported to have duplex, ectopic, or hypodysplastic kidneys.28 Kidney function may be preserved after urinary diversion, although reflux is common (see Fig. 52.12A). Other congenital abnormalities affecting the heart, abdomen, skeleton, and joints are seen in approximately 50%.28 More severe cloacal abnormalities are associated with imperforate anus and high or low rectal atresia.

A

Natural History

Long-term kidney outcome depends on the bladder. In a study with 12-year follow-up, the kidneys survive much better with a wellfunctioning bladder; 13% of those with a good bladder had significant kidney damage compared with 82% with ileal conduits, 22% with nonrefluxing colonic conduits, and 33% with ureterosigmoidostomy.29

Currently, the bladder is most commonly augmented (enterocystoplasty, ileocystoplasty, caecocystoplasty) or occasionally replaced by bowel (intestinal reservoir). In a study of 53 such patients monitored for more than 10 years, kidney function deteriorated (GFR decrease ≥20%) in only 10 patients.30

Treatment

When the infant is born, the three urologic treatment goals are to close the abdominal wall, establish urinary continence to preserve kidney function, and reconstruct cosmetically acceptable genitalia. Surgery can be performed using either a staged or complete primary repair approach. The aim of initial surgery is to close the bladder, posterior urethra, and abdominal wall and convert the defect to a complete epispadias (Fig. 52.13). Repair of the epispadias is carried out later in infancy followed by reconstruction of the bladder neck and bilateral ureteral implantation at the age of 4. If the bladder is small, intestinal augmentation is required. Patients may be able to void, but many have to use catheters. Incontinence may be a longterm problem.

Neurogenic Bladder

In childhood, the most common cause of a neurogenic bladder is myelomeningocele, although with antenatal diagnosis and termination of affected pregnancies, as well as folate supplementation, it is becoming less common. A neurogenic bladder may also be seen without associated neurologic or other obvious causes (Table 52.3). The principal consequences are incontinence, infection, and reflux with upper tract

B

Fig. 52.12 Cystography in Bladder Exstrophy. (A) A 26-year-old woman with bladder exstrophy who has a continent Mitrofanoff system (see Fig. 52.18) with use of the colon to create a reservoir. There is reflux into the left kidney. Reflux also occurs into the right kidney, but the kidney is obscured by the full reservoir. Glomerular filtration rate is 130 mL/min. (B) Magnetic resonance scan of a patient with bladder exstrophy shows a scarred, small left kidney with several kidney calculi (arrow). Note widely splayed symphysis pubis.

dilation and subsequent kidney failure. Early urodynamic assessment is essential (Fig. 52.14). Three different patterns of bladder behavior are seen: contractile, intermediate, and acontractile.

Contractile Behavior

An overactive detrusor (hyperreflexia) can produce some bladder emptying (incontinence). Unfortunately, 95% of patients have sphincter dyssynergia (inability to relax the urethral sphincter), which results in no relaxation and incomplete emptying of the bladder. Patients with incomplete lesions may have some control of the distal sphincter and normal anal and sacral reflexes. Ironically, although this latter group has the least neurologic deficit, they have the worst bladder situation, generating high pressures and great risk for kidney injury. The bladder becomes progressively hypertrophic, fibrotic, and poorly compliant.

Urodynamics
Normal
Obstructed
Cough

50
cm H_2O
0

Vesical
pressure Pves
Abdominal
pressure Pabd
Detrusor
pressure
Pdet = Pves − Pabd

Flow rate

Fig. 52.13 Epispadias. Result of multiple surgeries to close the epispadias and to lengthen the penis. (Courtesy Prof. C.R.J. Woodhouse, University College Hospital, London.)

TABLE 52.3

Causes of Neurogenic Bladder

Site of Lesion	Causes
Cerebral	Cerebrovascular accident, cerebral palsy, encephalopathy, trauma, Parkinson disease, dementia
Spinal	Isolated (no other neurologic features), trauma, multiple sclerosis, compression, spina bifida, spinal dysraphism, tethered cord, sacral agenesis, sacral teratoma
Peripheral nerve	Pelvic surgery, diabetes

Botulinum toxin A can be injected into the bladder wall to improve compliance and reduce bladder pressure; it is increasingly being used in children with neurogenic bladders to delay or avoid the need for augmentation cystoplasty.

Intermediate Behavior

These patients have some detrusor activity but not sufficient to empty the bladder. These intermediate bladders are poorly compliant, and patients have no voluntary control of their sphincters. Any rise in bladder pressure tends to cause incontinence, or the high intravesical pressures lead to kidney injury.

Acontractile Behavior

About 25% of patients have no detrusor activity, and the bladder overflows when it is sufficiently full. This acontractile bladder is not usually associated with kidney failure.

Myelodysplasia

Myelodysplasia refers to a group of neural tube anomalies that primarily affect the lumbar and sacral segment of the spinal cord and are the most common cause of neurogenic bladder dysfunction in children. Spina bifida reflects defective fusion of the posterior vertebral arches, of which there are several different types. Meningocele implies that the meninges extend beyond the confines of the vertebral canal with no neural elements contained inside. The most severe type of spina bifida is myelomeningocele, which has neural tissue protruding with the meningocele. Closed spinal dysraphism (spina bifida occulta) defines a group of structural anomalies of the caudal end of

Filling

Voiding

50
cm H_2O
0
50
cm H_2O
0
25
ml/s
0
500
ml
0

Filling volume
50s

Fig. 52.14 Urodynamic Assessment by Cystometrography. The vesical pressure is measured simultaneously with the abdominal pressure through the rectum; the detrusor pressure is the difference. A cough is used as a marker to show that the system is working. During filling, the first desire to void is normally at a detrusor pressure of <10 cm H_2O. This point is noted. The voiding pressure should normally be <40 cm H_2O (and is lower in women). Detrusor instability is an unstable (spontaneous) contraction occurring with a detrusor pressure >15 cm H_2O. Higher pressure can cause incontinence. In combination with radiologic imaging (videocystometrography), the following are recorded: bladder neck, closed or open; bladder pressure, end filling; voiding detrusor pressure; bladder stability; compliance; flow rate, maximum; sensation, first; volume, voided and residual. (Courtesy Prof. M. Craggs, University College London.)

the spinal cord that do not result in an open vertebral canal but are associated with incomplete fusion of the posterior vertebral arches and are usually asymptomatic. Sacral agenesis is a rare anomaly in which part or all of two or more vertebral bodies is absent. It occurs early in fetal development when there is failure of ossification of the lowest vertebral segments. and is strongly associated with maternal type 1 diabetes.[31] Partial sacral agenesis can be associated with an anterior meningocele.

Pathogenesis

The neural tube normally forms as the neural folds close over and fuse, starting in the cervical region and progressing caudally. The embryologic defect is likely an incomplete tubularization of the neural tube, with inadequate mesodermal invagination and subsequent arrest of vertebral arch formation.

The incidence of myelodysplasia varies from 1 to 7 in 1000 live births, but there are wide geographic variations. Monozygotic twins are often discordant for spina bifida, but siblings are at increased risk (1:10–1:20), and children of affected parents have a 4% chance of having a similarly affected child. Myelomeningocele accounts for more than 90% of myelodysplastic infants. Folic acid supplements taken during the first trimester reduce the incidence of myelodysplasia by 70%.32

Clinical Manifestations

All causes of tethered cord can produce a variable neurologic deficit. During development, some children experience progressive neurologic disturbance with bladder dysfunction, bowel dysfunction, scoliosis, and a syndrome of pes cavus and limb growth failure. Learning difficulties may also be seen in individuals with myelomeningocele, especially those who have required ventriculoperitoneal shunting for associated hydrocephalus.

Bladder dysfunction. Nearly all individuals with myelomeningocele have a neurogenic bladder, which may result in urinary incontinence and an adverse impact on the upper tracts. It can be an isolated problem with abnormal urodynamic studies but a normal neurologic examination.

Bowel dysfunction. Bowel dysfunction is often present and needs to be treated accordingly. There may be severe constipation and overflow incontinence. First-line management involves the use of laxatives, suppositories, and enemas, followed by transanal irrigation or antegrade continent enterostomy for those who have refractory symptoms. The appendix is brought out to the abdominal surface, and thus the colon can be irrigated antegrade with saline.

Natural History

About 14% of patients have kidney complications at birth and are at high risk in the next few years. Ultimately, 26% will develop CKD and 1.3% ESKD by early adulthood, with continence achieved in 37%.[33] Poor kidney outcome can be predicted by urodynamic findings, with worst outcomes related to increased bladder wall thickness, degree of reflux, urethral pressures above 70 cm H_2O, and reduced bladder capacity (Fig. 52.15). VUR occurs in 3% to 5% of newborns with detrusor hypertonicity or dyssynergia. Without treatment, this increases to 30% to 40% by age 5 years.[34]

A

Treatment

Management of the bladder depends on the urodynamic findings. In the 1970s, clean intermittent self-catheterization was introduced, but before that time, urinary diversion was the usual treatment. Currently, management is early initiation of intermittent self-catheterization, and antimuscarinic drugs (e.g., oxybutynin) are used for high pressure, hyperreflexic bladders with VUR to increase bladder compliance. Intravesical administration of oxybutynin should be considered in individuals with severe side effects (dry mouth, facial flushing, blurred vision, heat intolerance). With persisting symptoms related to bladder storage or detrusor overactivity, bladder wall injection with botulinum toxin type A1 is offered, with effects lasting 15 months on average.[35] In the presence of deteriorating kidney function or intractable symptoms, ileal or colonic bladder augmentation and creation of continent catheterizable channels may be required.[36]

Bladder Outflow Obstruction

Congenital bladder outflow obstruction is rare and is usually caused by a neurogenic bladder, PUV, or an ectopic ureterocele.

Posterior Urethral Valves

PUV are the most common cause of severe subvesical obstruction, occurring in 1 in 4000 male births.[37] As a result, bilateral hydronephrosis and megaureter occur. Obstruction is caused by a diaphragm that extends from the floor to the roof of the urethra at the apex of the prostate. Valves appear as mucosal folds in the posterior urethra below the verumontanum. There is dilation of the proximal urethra and bladder wall hypertrophy and trabeculation. Above the valves, the prostatic urethra dilates, undermining the bladder neck. The valves obstruct flow only in one direction, and therefore a catheter can be passed without difficulty.

Pathogenesis

The urethra develops in two parts: differentiation of the urogenital sinus (posterior urethra) and tubularization of the urethral plate

B

Fig. 52.15 Sacral Spina Bifida With Neuropathic Bladder. (A) Intravenous urogram shows evidence of a previous hydronephrosis and subsequent scarring of the right kidney. The architecture of the left kidney is well preserved. (B) Micturating cystogram. The typical tapering, hypertrophied, trabeculated bladder gives the characteristic “pinecone” appearance. Note the gross reflux on the right side. This is probably helping to protect the left kidney by acting as a “pop-off” mechanism. This is analogous to the protection that can occur in males with posterior urethral valves.

(anterior urethra). Persistence of the urogenital membrane and abnormal integration of the mesonephric (Wolffian) duct into the posterior urethra have been proposed as potential mechanisms underlying PUV. Monogenic defects appear to be rare, although heterozygous variants in BNC2, a zinc finger protein expressed in the embryonic urethra, have been identified in familial PUV.27

Clinical Manifestations

Most cases of PUV are detected antenatally on US as evidenced by bilateral hydronephrosis, dilated bladder, posterior urethra (keyhole sign), and, in severe cases, oligohydramnios. Infants present with a palpable distended bladder and enlarged kidneys, abnormal urine stream, or failure to thrive as a result of kidney failure. Kidney dysplasia is common and around a third of children also have VUR.38 Children with less severe disease present with poor stream, incontinence, UTI, or kidney failure. However, late presentation is also associated with worse outcome.39

Three abnormal features can help protect the kidney, reducing the high pressures generated during voiding: massive unilateral reflux, usually with ipsilateral kidney dysplasia (thereby protecting the other kidney); large bladder diverticulum; and urinary extravasation, often with urinary ascites. These protective mechanisms are referred to as pop-off mechanisms (see Fig. 52.15B).40 US can show the bladder thickening, dilated system, and dilation of the posterior urethra. A specific diagnosis should be documented by videocystometrography (see Urodynamics).

Natural History

In the 1960s, 25% of children with PUV died within the first 12 months, and 25% died later in childhood, including fatalities because of ESKD. By the late 1990s, early mortality was less than 5%,41 and lifetime risk of ESKD is now estimated at 28.5%, reached in the majority before the age of 30.42 The bladder may become stretched, resulting in poor emptying, or unstable, leading to poor compliance, unsuppressed detrusor contractions, and high storage pressure. Both situations are exaggerated by progressive polyuria. Such patients may have a daily urine volume of 5 L. Urodynamic follow-up studies suggest that instability decreases with time; bladder capacity increases, but there are unsustained voiding contractions. Prognosis correlates with the nadir serum creatinine value once obstruction has been relieved and with the degree of bladder dysfunction.43 Despite adequate early treatment, CKD as a result of bladder dysfunction and associated kidney dysplasia develops in many children.42 43

Treatment

All children have endoscopic transurethral resection of their valves in infancy. Bladder diversion should be avoided. Bladder instability and poor bladder compliance must be treated, regardless of whether symptoms result. Males with substantial residual volumes can be managed by clean intermittent self-catheterization, but adherence is often poor because of urethral discomfort or because previous urethral surgery has made the passage of catheters difficult. Adherence is a particular problem with adolescents who are continent and for whom kidney failure is too abstract a concept. Continence often improves spontaneously at puberty but can be helped by imipramine. Deterioration in GFR will require further examination of urine flow rate and exclusion of urethral stricture.

Urethral Diverticulum

Urethral diverticulum usually occurs in males and is rare. It may manifest with UTI, obstruction, or stones. The two types are anterior and posterior. The anterior type can be associated with anterior urethral valves and obstruction.

Other Congenital Causes of Bladder Outflow Obstruction

Urofacial Syndrome

Urofacial syndrome (UFS), or Ochoa syndrome, is a rare autosomal recessive disease characterized by facial grimacing when attempting to smile and failure of the urinary bladder to void completely, despite a lack of anatomic bladder outflow obstruction or overt neurologic

BOX 52.1

General Principles of Management of Congenital Urinary Tract Abnormalities

- Educate to encourage adherence.
- Review urologic status.
- Find cause of urinary tract obstruction and treat.
- Control blood pressure.
- Monitor kidney function and proteinuria.
- Treat acidosis.
- Prevent bone disease.
- Check for stones.
- Institute clean intermittent self-catheterization for chronic urinary retention.
    - Maintain bladder storage pressure <40 cm H_2O.
    - Maintain bladder volume <400 mL.

damage.27 Patients present with enuresis and UTI and all the features of a neurogenic bladder together with dilated upper tracts. They are at risk for kidney failure. Biallelic mutations of HPSE2 and LRIG2 have been reported. The proteins they encode are detected in nerves found in the fetal bladder, implying UFS may be a peripheral neuropathy of the bladder.27 UFS is part of a spectrum of congenital bladder disorders that include nonneurogenic neurogenic bladder or Hinman syndrome.

Gonadal Dysgenesis

Disorders of sex development, gender identity, and micropenis are beyond the scope of this chapter and rarely encountered in adult practice. Patients will be met, however, with ESKD who are phenotypically female but are genotype XY and have mutations of WT1 (Denys-Drash and Frasier syndromes). They have gonadal dysgenesis and must have their streak ovaries removed; otherwise, gonadoblastomas will develop.

GENERAL MANAGEMENT OF CONGENITAL KIDNEY AND URINARY TRACT ABNORMALITIES

The principles of management of congenital urinary tract abnormalities are shown in Box 52.1. The most important part of the management is ensuring that the patient, family, and primary care physician know what can and must be done. First, they must understand the necessity of long-term follow-up at least annually. ESKD often occurs when a patient is lost to follow-up, often manifesting later with accelerated hypertension and rapid loss of GFR.

Clinical Evaluation

By the time the adolescent attends an adult clinic, it is assumed that the urinary tract is not obstructed and that further surgery is not required. Nevertheless, it is the responsibility of the nephrologists and urologists who care for these young people to review this aspect periodically.

Symptomatic UTI is common and must be treated promptly. Increase in frequency or severity of infections must lead to investigations to find the cause.44 The BP must be monitored regularly and kept normal. Finally, kidney function must be monitored, proteinuria assessed, and the cause of any deterioration identified. As in any kidney condition, the residual GFR may decline inexorably, which is associated with increasing proteinuria and hypertension. As with other kidney conditions, kidney function is usually stable when proteinuria is minimal or absent. Deterioration in the absence of proteinuria must alert the physician to the likelihood of obstruction or the adverse effect of a nephrotoxic drug.

TABLE 52.4 Monitoring Patients With Congenital Urinary Tract Abnormalities: Routine Investigations for Assessment of Clinical Status

Baseline Measurements	Reason for Test
Radiology	
CT KUB	Exclude stones
Ultrasound	
Ultrasound of kidneys	Assess kidney size and hydronephrosis
Ultrasound of bladder after micturition	Assess residual volume
Urine flow rate	Ensure adequacy
Scintigraphy	
Glomerular filtration rate: ^{51}Cr-labeled EDTA	Baseline kidney function
Dynamic isotope scan: ^{99m}Tc-labeled MAG3 or DTPA	Assess outflow obstruction
Static isotope scan: ^{99m}Tc-labeled DMSA	Assess scarring and divided function
Biochemistry	
Urine protein-creatinine ratio	Assess proteinuria

^{51}Cr, Chromium-51; CT, computed tomography; DMSA, dimercaptosuccinic acid; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediaminetetraacetic acid; KUB, kidney, ureter, bladder; MAG3, mercaptoacetyltriglycine; ^{99m}Tc, technetium-99m.

The routine investigations performed to document the current situation act as a reference point for the future (Table 52.4). If the bladder empties completely with an adequate flow rate (15 mL/s), no problems should arise. If there is any doubt about the condition of the bladder, urodynamic investigations are necessary. If the clinical situation changes, further investigations are required. An increase in UTIs might suggest a stone or increase in residual urine. With an unexpected decline in kidney function, obstruction again must be excluded.

The patient should keep a 24-hour urine volume diary every 6 to 12 months, recording the time of voiding and volume passed. It is best to ask patients to do this on 2 consecutive days to determine the maximum bladder capacity and the total 24-hour urine volume. This should be done before urodynamic investigations because results can be misleading if the bladder is not filled to capacity.

Exclude Obstruction

Obstruction must always be excluded if there is a decline in GFR. The possibility of obstruction may be raised by a routine US (see Fig. 52.7) and should be pursued with 99mTc- MAG3 scintigraphy to exclude obstruction (Fig. 52.16).

In patients with conduits, obstruction can be excluded by infusion of contrast material into the loop (loopogram) and demonstration of reflux up the ureter.

Rarely, in patients with large bladders or in transplant recipients, the kidney may become obstructed when the bladder reaches a certain volume. This can be investigated by filling the bladder by catheter and performing 99mTc-labeled MAG3 scintigraphy, initially with the bladder full. If there is no excretion, the bladder volume can be reduced in 100-mL increments until there is flow down the ureter (Fig. 52.17).

Urodynamics

Any urodynamic investigation should start with a free urine flow rate. Provided the flow rate is normal and the bladder empties completely

(leaving no residual volume on postmicturition US), it can be assumed that there is no significant bladder outflow obstruction.

Complete investigation of abnormalities of bladder and urethral function requires synchronous recordings of intravesical and intrarectal pressures taken during bladder filling and emptying (see Fig. 52.14). Combined with radiologic imaging, the study is known as videocystometrography (VCMG).

Surgical Correction of the Urinary Tract

A normal bladder acts as a low-pressure, good-volume urine reservoir that is continent, is sterile, and empties freely and completely.

Any other form of urine reservoir aims to recreate such an environment. When this is not achieved in either a natural or a reconstructed bladder, complications such as sepsis and kidney dysfunction can occur.

A variety of conduits and continent reservoirs have been developed to replace unusable bladders. Ileal conduit diversion has been most widely used for native kidneys, although deterioration in kidney function frequently results from long-term complications, including urosepsis, kidney calculi, and, most often, stenosis, leading to obstruction or reflux with ureteral dilation. There is an overall complication rate of 45%, but with a high index of suspicion and an aggressive diagnostic and therapeutic approach, many of these problems can be detected and treated early, with resultant good long-term function of native kidneys. Similar results may be obtained when kidney transplantation is performed in these patients.45 Other forms of urinary diversion that are continent and therefore more socially acceptable to patients are now widely used in general urologic practice and are being encountered in kidney transplantation (see Fig. 52.12A). These forms include augmented bladders draining through the urethra and augmented or intestinal bladders draining through continent stomas.

COMPLICATIONS

Urinary Tract Infections

Symptomatic UTIs are common. Risk factors include stagnation of urine, stones, foreign bodies (stents, catheters), previous infections, and kidney scarring. UTIs must be treated promptly after a urine culture specimen (midstream or catheter specimen) has been taken.

Recurrent UTIs, particularly after a period of stability, must lead to further investigations to exclude stones or obstruction, including CT kidney, ureter, bladder (KUB); kidney US, and postmicturition bladder US.

Asymptomatic UTIs often do not require treatment (except during pregnancy). For patients with urinary diversions, it is important to obtain a catheter specimen of urine because urine taken from a bag is invariably infected. Cloudy, malodorous urine should be treated initially with increased fluid intake and frequency of self-catheterization (every 1–2 hours for 12 hours).

It is sometimes appropriate to give prophylactic antibiotics, such as trimethoprim or nitrofurantoin, in the context of recurrent UTIs (≥3/yr). Nitrofurantoin should be avoided if eGFR is less than 45 mL/min/1.73 m2 because its efficacy relies on excretion into the urinary tract. Quinolones should not be used for prophylaxis, if possible, because of the risk for inducing resistance. Antibiotic prophylaxis in children has been shown to reduce the incidence of repeat symptomatic UTI but has little impact on “kidney scarring.”[46] When foreign bodies such as stones remain, attempts to sterilize the urinary tract are unlikely to be successful. If prophylactic antibiotics are no longer effective at preventing infection, it is advisable to stop all antibiotics and give the patient a supply of antibiotics to treat symptoms arising at home.

Dynamic Renal Scintigram

L

R

100

Label (counts/min) × 103

Left kidney
Right kidney
80

B

60

40
Furosemide 40 mg

20

0.0
0

A

5

10

15

20

C

25

min

Fig. 52.16 Dynamic 99mTc-Labeled Mercaptoacetyltriglycine Kidney Scintigram. (A) Time-activity curve showing accumulation of isotope in right kidney that washes out after furosemide, thus excluding significant obstruction. (B–C) Images from the same study showing holdup of isotope in dilated right (R) renal pelvis (B) that washes out into the bladder after furosemide (C), excluding significant obstruction.

Single Kidney Obstruction by Full Bladder

30
60

25
R Kidney

cpm × 103

20

100 ml
100 ml
100 ml
100 ml

15
10

0
0

min

15

20

25

cpm × 103

40

5

A

R Kidney

50

100 ml
30

100 ml
100 ml

20

B

2-3 min

5-6 min

10-11 min

15-16 min

100 ml
75 ml
Free Drainage
100 ml
Total

10

0
0

C

10

20

30
min

40

Fig. 52.17 Dynamic Isotope Scan (Mercaptoacetyltriglycine) Starting with Bladder Full in a Patient With a Solitary Right Kidney. (A) Rising curve of tracer accumulating in kidney and showing no excretion. (B) Accumulation of isotope in hydronephrotic pelvis without excretion to bladder. (C) The 100-mL increments of fluid removed from bladder result in eventual free drainage of the kidney. cpm, Counts per minute.

50

60

Glomerular Hyperfiltration

Salt Depletion

If kidney function is declining with proteinuria and hypertension, glomerular hyperfiltration is likely, although all other causes of kidney dysfunction must be excluded. Patients should be treated with RAS blockade with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Patients with tubular damage may have a salt-losing tendency. Patients typically have a cool periphery and constricted hand veins with no peripheral edema. Increasing salt intake can relieve cramps, improve kidney function, and reduce hyperuricemia, but at the cost of increasing BP. With patients who are salt depleted, it is important to give sodium chloride because it is the chloride anion that is deficient and responsible for the reduction in circulating volume.

Proteinuria and Progressive Kidney Failure

Can progression to ESKD be predicted, and does treatment with ACE inhibitors delay or prevent this? We investigated this in a retrospective review of patients with scarred irregular kidneys caused by primary kidney dysplasia or abnormal bladder function.[47,48] All patients had at least 5 years of follow-up, and when ACE inhibitors were started, eGFR was less than 60 mL/min/1.73 m^2 (mean, 41 mL/min), with mean proteinuria of 1.7 g/24 h. ESKD developed in 46% of patients but in none with proteinuria less than 0.5 g/24 h and in only 2 of 18 patients with eGFR greater than 50 mL/min/1.73 m^2.[47] The outcome of the two groups was similar whether there was primary kidney dysplasia or abnormal bladder function. ACE inhibitor treatment slowed decline in kidney function at all levels of function.[48] The similar outcome of the two groups indicates that progressive kidney failure in young males born with abnormal bladders is caused by intrinsic kidney pathophysiologic processes, in contrast to the view that it is a result of poor bladder function.

Hypertension

Hypertension is common in the presence of scarred kidneys, but it is usually controlled easily with one or two drugs. Patients in whom CKD is secondary to obstruction tend to have volume contraction and therefore often have normal BP or only mild hypertension. ACE inhibitors or ARBs are preferred for patients with proteinuria and progressive kidney failure. Diuretics should not be used if the patient is volume-contracted.

Stones

Stones that form in the presence of infected urine are typically magnesium ammonium phosphate (struvite) or calcium phosphate (hydroxyl apatite, carbonate apatite, calcium hydrogen phosphate [brushite], tricalcium phosphate [whitlockite]). These salts are poorly soluble in alkaline urine. In 90% of patients, the infecting organism is Proteus spp., but other urea-splitting organisms (including some staphylococci and Pseudomonas spp.) also generate ammonia. Stones, usually calcium phosphate, are common in conduits because of the alkaline environment and occur in 5% to 30% of ileal conduits.[49] Stones must be suspected if UTIs recur or become more frequent, if kidney function suddenly deteriorates, or if there is an unexplained sterile pyuria.

Tubular Dysfunction

Patients whose kidney failure is secondary to obstruction have significant tubular injury. This may cause problems, in particular with urinary concentration, acidification, and sodium reabsorption.

Polyuria

Nocturia is one of the most significant symptoms in the assessment of patients in whom obstruction or tubular dysfunction is suspected. Overfilling of the bladder or reservoir is an important cause of intermittent upper tract obstruction and deteriorating function. The 24hour urine volume diary is a simple way to assess this.

Metabolic Acidosis

There is often a metabolic acidosis disproportionate to the degree of kidney impairment, particularly in individuals with a ureterosigmoidostomy (see later). This is secondary both to a proximal tubular failure of bicarbonate reabsorption and a distal tubular failure to secrete hydrogen ions. It is our practice to give sufficient sodium bicarbonate to correct the serum bicarbonate into the normal range.

Bone Disease

In addition to the typical bone disease of progressive CKD, acidosis contributes significantly to osteomalacia. Growing children are particularly vulnerable to osteomalacia, and great care must be taken to correct acidosis and actively manage bone disease.

Urinary Diversions

Ureterosigmoidostomy

Fortunately, it is now rare to meet a patient who has a ureterosigmoidostomy, which was widely used as a technique for urinary diversion until the 1970s. The ureters were anastomosed directly into the sigmoid colon with no disruption of bowel continuity. This technique was most often used in patients with bladder exstrophy. Although patients start with normal kidney function, there is frequently deterioration in function. In one series of 25 patients, significant kidney damage occurred in 50%. Stones, infection, and ureteral strictures are common, and patients remain at risk for colonic carcinoma, with a 10% incidence of carcinoma at 20-year follow-up.50 However, this diversion is probably best known for the hyperchloremic, hypokalemic acidosis that occurs. Once the urine is in contact with the colonic mucosa, the urinary sodium exchanges for potassium and the chloride for bicarbonate via the SLC26A3 anion exchanger, with large quantities of ammonium ions produced by the action of fecal bacteria on urinary ammonia. Ammonium ions are absorbed both with chloride and in exchange for sodium. The severe acidosis is caused by ammonium ion retention and stool loss of bicarbonate. Patients are managed with large doses of oral sodium bicarbonate, which is titrated to keep plasma bicarbonate in the normal range (>22 mmol/L).

Ileal Conduits

Unlike the sigmoidostomy, in which urine enters a reservoir, the ileal conduit is free flowing, with rapid urinary transit and no reservoir. Therefore, metabolic complications are much less common, although again the bowel can exchange sodium and chloride for potassium and bicarbonate. B12 deficiency and diarrhea secondary to impaired bile acid absorption can occur. A number of other complications of ileal and colonic conduits can lead to progressive loss of kidney function (Box 52.2).

Enterocystoplasty and Intestinal Urinary Reservoirs

In 53 patients with bladder exstrophy and intestinal reservoirs, monitored more than 10 years with serial isotopic GFRs, kidney function deteriorated (GFR decrease ≥20%) in only 10 (~20%).30 Loss of GFR was caused principally by chronic urinary retention with or without infection in poorly compliant patients who did not catheterize regularly. Patients also must be checked regularly to ensure that anastomotic stenoses and high-pressure reservoirs do not occur. Stones are common and occur in up to 52% of patients.51 An increased risk of malignancy is also seen in augmentation cystoplasty, predominantly adenocarcinomas occurring at the entero-urinary anastomosis after a median of 19 years. Macroscopic hematuria should trigger prompt referral for cystoscopy.

Long-Term Complications of Urinary Diversion

BOX 52.2

- Pyelonephritis and recurrent urinary tract infections
- Calculi
- Obstruction
- Strictures
- Bladder mucus causing obstruction
- Cancer at intestinal-ureteral anastomosis
- Hyperchloremic acidosis
- Delayed linear growth in children
- Effects of intestinal loss from gastrointestinal tract (e.g., vitamin B12 deficiency)
- Complications related to abnormal pelvic anatomy (e.g., in pregnancy)
- Psychological and body image problems

END-STAGE KIDNEY DISEASE AND TRANSPLANTATION

This group of patients presents two important problems if they develop ESKD. First, because of multiple abdominal surgeries, continuous ambulatory peritoneal dialysis (CAPD) is often challenging, although if there is any doubt and the patient is interested, CAPD should be attempted. Second, the bladder and urinary reservoir must be suitable for kidney transplantation. If a bladder has just destroyed two good native kidneys, it is likely to do the same to a transplant kidney. Most patients will be maintained on hemodialysis, but it is frequently difficult to establish a good arteriovenous fistula because of chronic hypovolemia and venoconstriction. Patients receiving dialysis often continue to pass 1 L or more of urine per 24 hours, and they also remain at risk for serious UTI and pyelonephritis.

Pretransplantation Assessment

Transplantation into the abnormal lower urinary tract requires careful evaluation and follow-up. Thorough preoperative assessment of bladder function is essential (Fig. 52.18). Patients considered to have normal bladders require at least postmicturition bladder US and urinary flow rate.

All patients with abnormal bladders or reservoir must have a full VCMG to ensure that the bladder reservoir is large and adequately compliant. If the bladder is small or has not been used for some time, bladder cycling, which involves periodically filling and distending the

Pretransplant Assessment
Potential transplant
recipient with CAKUT

Ileal conduit

Loopogram and
endoscopy

Small volume,
noncompliant
bladder

Bladder cycling
± suprapubic
catheterization

Augmented bladder
or urinary diversion

Urodynamics and postmicturition
bladder ultrasound

Videocystometrogram

Large volume,
compliant bladder

Poor urinary flow
15 mL/s with postvoid residual 100 mL

Urinary flow rate
15 mL/s and postvoid residual ≤100 mL

Clean intermittent
self-catheterization
±
Mitrofanoff stoma

Proceed to renal transplantation

Fig. 52.18 Pretransplant assessment of patients with an abnormal lower urinary tract. CAKUT, Congenital anomalies of the kidney and urinary tract.

bladder through a suprapubic catheter, may be required. A urodynamic study before transplantation indicated that poor bladder function, as shown by small bladder volumes, is a predictor of graft loss even in patients with previously normal bladder function.[52] Intermittent selfcatheterization is safe and effective for a patient with a poor flow rate who fails to empty the bladder. This, however, is possible only with a normal urethra and a cooperative patient. When this is not practical, we attempt to establish suprapubic drainage through a continent channel, such as a Mitrofanoff stoma (Fig. 52.19). If a conduit is to be used, a loopogram and endoscopy must ensure it is in good condition. We do not remove native kidneys unless they are causing recurrent UTI.

Transplant Outcome

In an 18-year experience, we performed transplantation in 65 patients with abnormal bladders, with a total of 72 kidney transplants.[53] In 52 cases the ureters were transplanted into unaugmented bladders; in 20 cases, there was some form of augmentation or diversion. Results were compared with 59 transplants in 55 patients who had kidney failure from kidney dysplasia and whose bladder function was considered normal. There was no difference in actuarial graft survival in the two groups at 10 years (abnormal bladders, 66%; normal bladders, 61%), although longer follow-up showed an advantage for normal bladders, with graft survival of 29 to 33 years compared with 15 years for the abnormal bladders. UTIs were relatively common in all patients but produced problems only in patients with abnormal bladders. A recent study also reported comparable 10-year graft survival rates of 70% to 76% for individuals with kidney hypodysplasia and PUV, but an increased risk of graft loss for PUV after this time point.[54] This suggests that although short-term outcomes appear to be equivalent in individuals with normal and abnormal bladders, longer-term graft survival may be limited by bladder dysfunction.

Short-term outcomes after transplantation have been shown to be more favorable in both children and adults with CAKUT compared with individuals with primary glomerular or non-CAKUT diseases at 5 to 10 years, although recipients were more likely to be younger and receive a preemptive transplant.[5,55,56] Young adulthood (15–24 years) is also a particularly challenging time, and the high rates of graft loss and eGFR decline observed during this period may be exacerbated by nonadherence to CISC in adolescents with bladder dysfunction.[57]

Management

A double-J ureteral stent should be placed routinely at the time of transplant surgery. Adequacy of urinary drainage must be assessed frequently, even when graft function seems to be good. Two months after transplantation, when the ureteral stent has been removed, we recommend performing a baseline postmicturition US of the transplant kidney and bladder, in addition to a dynamic 99mTc-MAG3 scintigraphy scan in patients with abnormal bladders.

Fig. 52.19 Mitrofanoff Stoma. This patient was born with bladder exstrophy and has had a successful kidney transplant for 22 years. Her kidney is plumbed into a colonic reservoir, and she catheterizes herself through a continent Mitrofanoff stoma, which is covered by a small bandage in the photograph.

US and 99mTc-MAG3 scintigraphy are then repeated when clinically indicated. The protein-to-creatinine ratio is measured on a random urine sample at every outpatient visit. If there is kidney dysfunction, imaging tests are repeated, and if there is a change from baseline, kidney biopsy is performed to exclude an immunologic cause of graft dysfunction. If there is deterioration in GFR in the absence of rejection or calcineurin inhibitor toxicity, the DMSA scan is repeated (to see whether new scarring has occurred) and the bladder reassessed urodynamically.58

Complications

UTIs must be detected and treated early, and recurrent UTIs may require long courses of antibiotics or even removal of the native tracts. Symptomatic UTIs are common in the first 3 months after transplantation (63%); fever and systemic symptoms occur in 39% of patients with normal bladders and 59% with abnormal bladders. UTI directly contributes to graft loss in patients with abnormal bladders but causes no consequences in those with normal bladders.44 Prophylactic administration of antibiotics for the first 6 months significantly reduces the subsequent incidence of UTI. When UTIs recur, a cause must be sought with ultrasound of the kidneys and bladder. A CT KUB can be done to look for stones in native or transplant kidneys and the bladder or urinary diversion. If there is a residual volume after double micturition, the patient must be instructed to perform clean intermittent self-catheterization. With these measures, good results are obtained.

SELF-ASSESSMENT QUESTIONS

1. Which statement about unilateral kidney agenesis is false?
A. It occurs in 1 in 10,000 births.
B. Typically, there is no ureter.
C. The fallopian tube may be absent in females.
D. Kidney ultrasound is recommended in first-degree relatives.
E. It can be part of a syndrome.
2. Which statement about prune-belly syndrome is false?
A. It usually occurs in males only.
B. The muscles of the anterior abdominal wall are absent.
C. Gross dilation of the bladder occurs, with normal ureters.
D. Males have bilateral undescended testes.
E. Patients are usually infertile.

3. Ureterosigmoidostomy may lead to all of the following except:
A. Hyperchloremia
B. Hyperkalemia
C. Acidosis
D. Ammonium ion retention
E. Colonic carcinoma

4. Which of the following statements about posterior urethral valves is false?
A. They are usually detected antenatally.
B. Patients require urethral surgery.
C. Progressive kidney failure is associated with proteinuria.
D. Posterior urethral valves may be confused with urofacial (Ochoa) syndrome.
E. Posterior urethral valves occur in males and females.

5. Which of the following statements about urinary tract infection (UTI) in an augmented bladder is false?
A. The patient with UTI does not require treatment when asymptomatic.
B. UTI often causes calcium oxalate stones.
C. Recurrent UTIs should be investigated with ultrasound, including assessment of postvoid residual volume.
D. UTI may indicate poor bladder emptying.

REFERENCES

1. Nicolaou N, Renkema KY, Bongers EMHF, Giles RH, Knoers NVAM. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015;11:720–731.
2. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27:363–373.
3. Chesnaye N, et al. Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA-EDTA registry. Pediatr Nephrol. 2014;29:2403–2410.
4. Neild GH. Primary renal disease in young adults with renal failure. Nephrol Dial Transplant. 2010;25:1025–1032.
✓ 5. ✓ Wühl E, et al. Timing and outcome of renal replacement therapy in patients with congenital malformations of the kidney and urinary tract. Clin J Am Soc Nephrol. 2013;8:67–74.
6. Sanna-Cherchi S, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. Kidney Int. 2009;76:528–533.
✓ 7. ✓ Westland R, Kurvers RAJ, van Wijk JAE, Schreuder MF. Risk factors for renal injury in children with a solitary functioning kidney. Pediatrics. 2013;131:e478–e485.
8. Calderon-Margalit R, et al. History of childhood kidney disease and risk of adult end-stage renal disease. N Engl J Med. 2018;378:428–438.
9. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med. 1982;307:652–659.
✓ 10. ✓ Woolf AS, Jenkins D. Development of the kidney. In: Jennette JC, Olson JL, Silva FG, D’Agati VD, eds. Heptinstall’s Pathology of the Kidney. Wolters Kluwer Health; 2014:67–89.
✓ 11. ✓ Winyard P. Human kidney development. In: Turner N, et al., ed. Oxford Textbook of Clinical Nephrology. Oxford University Press; 2015.
12. Starr MC, Hingorani SR. Prematurity and future kidney health: the growing risk of chronic kidney disease. Curr Opin Pediatr. 2018;30:228–235.
13. Bulum B, et al. High frequency of kidney and urinary tract anomalies in asymptomatic first-degree relatives of patients with CAKUT. Pediatr Nephrol. 2013:2143–2147.
14. van der Ven AT, et al. Whole-exome sequencing identifies causative mutations in families with congenital anomalies of the kidney and urinary tract. J Am Soc Nephrol. 2018;29:2348–2361.
15. Verbitsky M, et al. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. Nat Genet. 2019;51:117–127.
16. Parimi M, Nitsch D. A systematic review and meta-analysis of diabetes during pregnancy and congenital genitourinary abnormalities. Kidney Int Rep. 2020;5:678–693.
17. van der Ven AT, Vivante A, Hildebrandt F. Novel Insights into the pathogenesis of monogenic congenital anomalies of the kidney and urinary tract. J Am Soc Nephrol. 2018;29:36–50.
18. Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1Bassociated renal and extra-renal disease—an expanding clinical spectrum. Nat Rev Nephrol. 2015;11:102–112.
19. Sharma R, Sanchez-Ferras O, Bouchard M. Pax genes in renal development, disease and regeneration. Semin Cell Dev Biol. 2015;44:97–106.
✓ 20. ✓ Wang M, et al. Contributions of rare gene variants to familial and sporadic FSGS. J Am Soc Nephrol. 2019;30:1625–1640.
21. Ansley SJ, et al. Basal body dysfunction is a likely cause of pleiotropic Bardet–Biedl syndrome. Nature. 2003;425:628–633.
22. Koff SA, Campbell KD. The nonoperative management of unilateral neonatal hydronephrosis: natural history of poorly functioning kidneys. J Urol. 1994;152:593–595.
23. Skoog SJ, et al. Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. J

Urol. 2010;184:1145–1151.

24. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;370:2367–2376.
2✓ 5.✓ Woodhouse CR, Ransley PG, Innes-Williams D. Prune belly syndromereport of 47 cases. Arch Dis Child. 1982;57:856–859.
2✓ 6.✓ Weber S, et al. Muscarinic acetylcholine receptor M3 mutation causes urinary bladder disease and a prune-belly-like syndrome. Am J Hum Genet. 2011;89:668–674.
2✓ 7.✓ Woolf AS, Lopes FM, Ranjzad P, Roberts NA. Congenital disorders of the human urinary tract: recent insights from genetic and molecular studies. Front Pediatr. 2019;7:136.
28. Ebert A-K., et al. Association between exstrophy-epispadias complex and congenital anomalies: a German multicenter study. Urology. 2019;123:210–220.
29. Husmann DA, McLorie GA, Churchill BM. A comparison of renal function in the exstrophy patient treated with staged reconstruction versus urinary diversion. J Urol. 1988;140:1204–1206.
30. Fontaine E, Leaver R, Woodhouse CR. The effect of intestinal urinary reservoirs on renal function: a 10-year follow-up. BJU Int. 2000;86:195–198.
31. Nalbandyan M, et al. Descriptive and risk factor analysis of nonsyndromic sacral agenesis: national Birth Defects Prevention Study, 1997–2011. Am J Med Genet. 2019. https://doi.org/10.1002/ajmg.a.61290.
32. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev. 2015. https://doi.org/10.1002/14651858.CD007950.pub3.
33. Veenboer PW, Bosch JLHR, van Asbeck FWA, de Kort LMO. Upper and lower urinary tract outcomes in adult myelomeningocele patients: a systematic review. PLoS One. 2012;7:e48399.
34. McLorie GA, Perez-Marero R, Csima A, Churchill BM. Determinants of hydronephrosis and renal injury in patients with myelomeningocele. J Urol. 1988;140:1289–1292.
35. Kask M, Rintala R, Taskinen S. Effect of onabotulinumtoxin A treatment on symptoms and urodynamic findings in pediatric neurogenic bladder. J Pediatr Urol. 2014;10:280–283.
36. Bauer SB. Neurogenic bladder: etiology and assessment. Pediatr Nephrol. 2008;23:541–551.
37. Brownlee E, et al. Current epidemiology and antenatal presentation of posterior urethral valves: outcome of BAPS CASS National Audit. J Pediatr Surg. 2019;54:318–321.
38. Heikkilä J, Rintala R, Taskinen S. Vesicoureteral reflux in conjunction with posterior urethral valves. J Urol. 2009;182:1555–1560.
39. Bomalaski MD, et al. Delayed presentation of posterior urethral valves: a not so benign condition. J Urol. 1999;162:2130–2132.
40. Rittenberg MH, Hulbert WC, Snyder 3rd HM, Duckett JW. Protective factors in posterior urethral valves. J Urol. 1988;140:993–996.
41. Herbst KW, et al. Survival and kidney outcomes of children with an early diagnosis of posterior urethral valves. Clin J Am Soc Nephrol. 2019;14:1572–1580.
42. Heikkilä J, Holmberg C, Kyllönen L, Rintala R, Taskinen S. Long-term risk of end stage renal disease in patients with posterior urethral valves. J Urol. 2011;186:2392–2396.
4✓ 3.✓ DeFoor W, et al. Risk factors for end stage renal disease in children with posterior urethral valves. J Urol. 2008;180:1705–1708. discussion 1708.
44. Lee JBL, Neild GH. Urinary tract infection. Medicine. 2007;35:423–428.
45. Crowe A, et al. Renal transplantation following renal failure due to urological disorders. Nephrol Dial Transplant. 1998;13:2065–2069.
46. Hewitt IK, Pennesi M, Morello W, Ronfani L, Montini G. Antibiotic prophylaxis for urinary tract infection–related renal scarring: a systematic review. Pediatrics. 2017;139.
47. Neild GH, et al. Renal outcome in adults with renal insufficiency and

irregular asymmetric kidneys. BMC Nephrol. 2004;5:12.
48. Neild GH. What do we know about chronic renal failure in young adults? II. Adult outcome of pediatric renal disease. Pediatr Nephrol. 2009;24:1921–1928.

References

49. Dretler SP. The pathogenesis of urinary tract calculi occurring after ileal conduit diversion. I. Clinical study. II. Conduit study. 3. Prevention. J Urol. 1973;109:204–209.
50. Austen M, Kälble T. Secondary malignancies in different forms of urinary diversion using isolated gut. J Urol. 2004;172:831–838.
✓ 51. ✓ Woodhouse CRJ, Robertson WG. Urolithiasis in enterocystoplasties. World J Urol. 2004;22:215–221.
52. Kashi SH, Wynne KS, Sadek SA, Lodge JP. An evaluation of vesical urodynamics before renal transplantation and its effect on renal allograft function and survival. Transplantation. 1994;57:1455–1457.
53. Neild GH, Dakmish A, Wood S, Nauth-Misir R, Woodhouse CRJ. Renal transplantation in adults with abnormal bladders. Transplantation. 2004;77:1123–1127.
54. McKay AM, Kim S, Kennedy SE. Long-term outcome of kidney transplantation in patients with congenital anomalies of the kidney and urinary tract. Pediatr Nephrol. 2019;34:2409–2415.

55. Monteverde ML, et al. Kidney transplantation in children with CAKUT and non-CAKUT causes of chronic kidney disease: do they have the same outcomes? Pediatr Transplant. 2020;24:e13763.
56. Cornwell LB, Ingulli EG, Mason MD, Ewing E, Riddell JV. Renal transplants due to Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) have better graft survival than non-CAKUT controls: analysis of over 10,000 patients. Urology. 2021. https://doi.org/10.1016/j.urology.2021.01.005.
57. Hamilton AJ, Plumb LA, Casula A, Sinha MD. Associations with kidney transplant survival and eGFR decline in children and young adults in the United Kingdom: a retrospective cohort study. BMC Nephrol. 2020;21:492.
58. Cairns HS, Spencer S, Hilson AJ, Rudge CJ, Neild GH. 99mTc-DMSA imaging with tomography in renal transplant recipients with abnormal lower urinary tracts. Nephrol Dial Transplant. 1994;9:1157–1161.

53

Urinary Tract Infections in Adults

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DEFINITION

Most episodes of urinary tract infection (UTI) in adults can be categorized into six common categories: females with acute uncomplicated cystitis, females with recurrent cystitis, females and males with acute uncomplicated pyelonephritis, males with cystitis, complicated UTI, and asymptomatic bacteriuria (Box 53.1).[1] Additionally, UTIs in chronic kidney disease (CKD), those needing urethral catheterization or other indwelling devices, and patients with a spinal cord injury require different approaches to diagnosis and management. Chapter 44 discusses UTI in pregnancy, and Chapter 62 describes vesicoureteral reflux (VUR) in children. UTI in autosomal dominant polycystic kidney disease is discussed in Chapter 46

Complicated UTI is defined as UTI occurring in a patient with a condition that increases the risk for treatment failure or recurrence. Potentially complicating conditions are presented in Box 53.2; not all of these conditions confer a similar risk for treatment failure or recurrence. Complicated UTIs may require different pretreatment and posttreatment evaluation than do uncomplicated UTIs, and type and duration of antimicrobial treatment may also differ. On occasion, complicated UTIs are diagnosed only after a patient has a poor response to treatment and the underlying condition is identified.

EPIDEMIOLOGY

Several million episodes of acute uncomplicated cystitis and at least 250,000 episodes of acute pyelonephritis occur annually in the United States. The incidence of cystitis in sexually active young females is about 0.5 per 1 person-year.[2] Acute uncomplicated cystitis may recur in 27% to 44% of healthy females.[3] The incidence of pyelonephritis in young females is about 3 per 1000 person-years.[4] The self-reported incidence of symptomatic UTI in postmenopausal females is about 10% per year.[5] The incidence of symptomatic UTI in adult males younger than 50 years is lower than in females, ranging from 5 to 8 per 10,000 males annually.

Complicated UTIs occur in a wide range of settings (see Box 53.2). Nosocomial UTIs are a common type of complicated UTI and occur in 5% of admissions in the university tertiary care hospital setting; catheter-associated infections account for most of the infections. Catheter-associated bacteriuria is the most common source of gramnegative bacteremia in hospitalized patients.[6]

Asymptomatic bacteriuria is defined as the presence of two separate consecutive clean-voided urine specimens, both with 105 or more colony-forming units per milliliter (cfu/mL) of the same uropathogen in the absence of symptoms referable to the urinary tract.[7]

Asymptomatic bacteriuria occurs in 5% of young adult females, but rarely in males younger than 50 years. The prevalence increases to 16% of ambulatory females and 19% of ambulatory males older than 70 and up to 50% of elderly females and 40% of elderly males who are institutionalized.[7] In clinical practice, asymptomatic bacteriuria is rarely confirmed by two consecutive specimens. Asymptomatic bacteriuria may be persistent or transient and recurrent, and many patients have had previous symptomatic infection or develop symptomatic UTI soon after having asymptomatic bacteriuria. Asymptomatic bacteriuria is generally benign but occasionally may lead to serious complications.

PATHOGENESIS

Uncomplicated Infection

Most uncomplicated UTIs in healthy females begin with uropathogens (typically Escherichia coli) colonizing the rectal flora entering the urethra and then the bladder, after an interim phase of introital colonization. Colonizing uropathogens also may come from a sex partner's vagina, rectum, or penis. Hematogenous seeding of the urinary tract by potential uropathogens such as Staphylococcus aureus is the source of some UTIs, but this is more likely to occur in the setting of persistent bloodstream infection or urinary tract obstruction.

Many host behavioral, genetic, and biologic factors predispose healthy young females to uncomplicated UTI (Table 53.1).[2,8] Factors protecting individuals from UTI include the host's immune response; maintenance of normal vaginal flora, which protects against colonization with uropathogens; and removal/prevention of bladder bacteriuria by micturition.[9]

Uropathogenic E. coli, the predominant pathogens in uncomplicated UTI, are a subset of extraintestinal pathogenic E. coli that have enhanced virulence[10] (see Table 53.1).

P-fimbriated strains of E. coli are associated with acute uncomplicated pyelonephritis, and their adherence properties may stimulate epithelial and other cells to produce proinflammatory factors that stimulate the inflammatory response.[11] Other virulence determinants include adherence factors (type 1, S, and Dr fimbriae), toxins (hemolysin), immune evasion, iron acquisition (aerobactin), flagella, and serum resistance.[10,12] Bacterial determinants associated with cystitis and

Categories of Urinary Tract Infection in Adults

BOX 53.1

- Acute cystitis in females
- Recurrent cystitis in females
- Acute pyelonephritis in females and males
- Acute cystitis in males
- Complicated urinary tract infection[a]
- Asymptomatic bacteriuria

[a] This is a selected list of complicating factors. Some factors complicate urinary tract infections through several mechanisms.

Data from Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs.1997;53:583–592.

Selected List of Potential Complicating Factors for Urinary Tract Infections

BOX 53.2

- Male sex
- Pregnancy
- Poorly controlled diabetes mellitus
- Obstruction or other structural factor: Urolithiasis, malignancies, ureteral and urethral strictures, bladder diverticula, renal cysts, fistulas, ileal conduits, other urinary diversions
- Functional abnormality: Neurogenic bladder, vesicoureteral reflux
- Foreign bodies: Indwelling catheter, ureteral stent, nephrostomy tube
- Other conditions: kidney failure, kidney transplantation, immunosuppression, multidrug-resistant uropathogens, health care–associated (includes hospital-acquired long-term care facility acquired infection, prostatitis-related infection, upper tract infection in an adult other than a healthy female, other functional or anatomic abnormality of urinary tract)

Data from Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs. 1997;53:583-592.

asymptomatic bacteriuria are less characterized, and triggers for urinary symptoms are unclear.

Factors affecting the large difference in UTI prevalence between males and females include the greater distance between the anus and the urethral meatus in males, the drier environment surrounding the male urethra, and the greater length of the male urethra. Risk factors associated with UTIs in healthy males include intercourse with a female partner colonized or infected with a potential uropathogen, anal intercourse, and being uncircumcised, although these factors are often not present in males with UTI. Most uropathogenic strains infecting young males are highly virulent, suggesting that the urinary tract in healthy males is relatively resistant to infection.

Complicated Infection

The initial steps leading to uncomplicated UTI discussed earlier probably also occur in most individuals who develop a complicated UTI.
Factors that predispose individuals to complicated UTI generally do so by causing obstruction or stasis of urine flow, facilitating entry of uropathogens into the urinary tract by bypassing normal host defense mechanisms, providing a nidus for infection that is not readily treatable with antimicrobials, or compromising the host immune system (see Box 53.1).[1] UTIs are more likely to become complicated if host defense is impaired, as occurs with indwelling catheter use, VUR, obstruction, neutropenia, and immune deficiencies. Diabetes mellitus is associated with several UTI syndromes, including renal and perirenal abscesses, emphysematous pyelonephritis and cystitis, papillary necrosis, and xanthogranulomatous pyelonephritis.[12] Uropathogen virulence determinants are less important in the pathogenesis of complicated UTIs compared with uncomplicated UTIs. However, infection with multidrug-resistant uropathogens is more likely with complicated UTI, and the causative organisms are also more varied.

Factors Modulating Risk for
Acute Uncomplicated Urinary Tract Infections
in Females

TABLE 53.1

Host Determinants	Uropathogen Determinants
Behavioral: Sexual intercourse, use of spermicidal products, recent antimicrobial use, suboptimal voiding habits	Escherichia coli virulence determinants: P, S, Dr, and type 1 fimbriae; hemolysin; aerobactin; serum resistance
Genetic: Innate and adaptive immune response, enhanced epithelial cell adherence, antibacterial factors in urine and bladder mucosa, nonsecretor of ABO blood group antigens, P1 blood group phenotype, reduced CXCR1 expression, previous history of recurrent cystitis	
Biologic: Estrogen deficiency in postmenopausal females, glycosuria (including from SGLT-2 inhibitors)	

ETIOLOGIC AGENTS

Uncomplicated upper and lower UTI are caused by E. coli, present in 70% to 95% of infections, and Staphylococcus saprophyticus, present in 5% to more than 20%. Other organisms are less common (Table 53.2).[7] S. saprophyticus only rarely causes acute pyelonephritis.[13]
Among healthy nonpregnant females, the isolation of lactobacilli, enterococci, group B streptococci, and coagulase-negative staphylococci other than S. saprophyticus usually represents contamination of

the urine specimen14 unless found in voided midstream urine in high counts and pure growth in symptomatic females.

A broader range of bacteria can cause complicated UTI, many demonstrating resistance to multiple antimicrobial agents. Although E. coli is most commonly isolated, Citrobacter spp., Enterobacter spp., Pseudomonas aeruginosa, enterococci, and S. aureus account for a higher proportion of cases relative to uncomplicated UTIs (see Table 53.2).1 The proportion of infections caused by fungi, especially Candida spp., is increasing (see Chapter 55). Patients with chronic conditions, such as spinal cord injury and neurogenic bladder, are more likely to have polymicrobial and multidrug-resistant infections.

CLINICAL SYNDROMES

Acute Uncomplicated Cystitis in Young Females

Females with acute uncomplicated cystitis generally present with dysuria, frequency, urgency, or suprapubic pain. The differential diagnosis for acute dysuria in a sexually active young female is acute cystitis; acute urethritis from Chlamydia trachomatis, Neisseria gonorrhoeae, or herpes simplex virus infections; or vaginitis caused by Candida spp. or Trichomonas vaginalis.6 These three entities can usually be distinguished by the history, physical examination, and simple laboratory tests. New vaginal discharge supports urethritis or vaginitis and should prompt a vaginal exam, whereas its absence is more consistent with

TABLE 53.2

Bacterial Etiology of Urinary Tract Infections

Organisms	URINARY TRACT INFECTION (%)	
	Uncomplicated	Complicated
Gram-Negative Organisms		
Escherichia coli	70–95	21–54
Proteus mirabilis	1–2	1–10
Klebsiella spp.	1–2	2–17
Citrobacter spp.	<1	5
Enterobacter spp.	<1	2–10
Pseudomonas aeruginosa	<1	2–19
Other	<1	6–20
Gram-Positive Organisms		
Coagulase-negative staphylococci (Staphylococcus saprophyticus)	5–20+	1–4
Enterococci	1–2	1–23
Group B streptococci	<1	1–4
Staphylococcus aureus	<1	1–2
Other	<1	2

Data from Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs. 1997;53:583–592.

cystitis. Skin lesions may provide a clue that herpes simplex virus is the cause of the dysuria. Pyuria is present in almost all females with acute cystitis and in most females with urethritis caused by N. gonorrhoeae or

C. trachomatis, and its absence strongly suggests an alternative diagnosis. Hematuria (microscopic or gross) is common in females with UTI but not in females with urethritis or vaginitis.

Definitive diagnosis of UTI requires the presence of significant bacteriuria, the traditional standard for which is up to 105 uropathogens per milliliter of voided midstream urine. A minority of females with cystitis have lower colony counts, which are missed with use of the traditional definition.15 Despite their central role in the definitive diagnosis of UTI, urine cultures are generally not indicated in females with uncomplicated cystitis, in particular for females with a prior culture-confirmed UTI. For these females, history is highly reliable in establishing the diagnosis,16 the causative organisms are predictable, and the culture results usually become available only after therapeutic decisions have been made and treatment is nearly complete.

E. coli isolates from outpatients with UTI are increasingly resistant to commonly used antibiotics, including sulfonamides, amoxicillin, trimethoprim, and trimethoprim-sulfamethoxazole (TMP-SMX).17–19 In the United States, TMP-SMX resistance among E. coli isolates causing uncomplicated UTI range from 15% to 42% in different regions,17 with a similar range among European countries and Brazil.18 Many drug-resistant E. coli strains are clonal and have been hypothesized to enter new environments by contaminated products ingested by community residents.20 Because of increasing resistance to TMP-SMX and other antimicrobials, clinicians have turned to agents with more predictable activity. Nitrofurantoin is active against most E. coli isolates, with resistance rates of less than 5%. With E. coli being the most isolated organism for females with uncomplicated cystitis, nitrofurantoin is a first-line agent for this syndrome. Fluoroquinolones remain active against most E. coli strains causing uncomplicated cystitis, although resistance is increasing in most locations and use for cystitis is discouraged.17 18 21 In an antimicrobial susceptibility study of more than 12 million E. coli isolates from U.S. outpatients, fluoroquinolone resistance increased from 3% to 17% over 10 years.22 In addition, infections caused by extended-spectrum β-lactamase (ESBL)-producing strains are increasingly common, even for uncomplicated cystitis.

Recommended management of acute uncomplicated cystitis is summarized in Fig. 53.1 and Table 53.3. Updated Infectious Diseases Society of America (IDSA) guidelines emphasize the importance of considering ecologic adverse effects of antimicrobial agents (i.e., selection for colonization or infection with multidrug-resistant organisms—so-called collateral damage) when selecting a treatment regimen.21 Short-course regimens are recommended as first-line treatment for acute uncomplicated cystitis because of comparable efficacy, better compliance, lower cost, and fewer adverse effects than with longer regimens. Given the benign nature of uncomplicated cystitis along with its high frequency, the IDSA guidelines give equal weight to the risk for ecologic adverse effects and drug effectiveness in the recommendations. Nitrofurantoin is well tolerated and has good efficacy when given twice daily for 5 days, and it has a low propensity for ecologic adverse effects.23 Despite concern about the high prevalence of resistance to TMP-SMX, this combination medication remains effective for infections caused by susceptible isolates and is inexpensive and well tolerated. Fosfomycin is also considered a first-line regimen because of its low propensity for ecologic adverse effects and single-dose administration, even though it appears to be slightly inferior to TMP-SMX and fluoroquinolones, and is often considerably more expensive than other options.21 Moreover, both nitrofurantoin and fosfomycin appear to have a role as therapeutic agents effective against ESBL E. coli UTIs.24 25 Pivmecillinam, an extended gram-negative spectrum penicillin used only for treatment of UTI, is an appropriate choice for therapy in regions where it is available (primarily European countries) because of minimal resistance and propensity for collateral damage and activity against ESBL-producing organisms.26

The choice of an antimicrobial agent should be individualized based on the patient’s allergy and medication preferences, local practice patterns, prevalence of resistance in the local community (if known), availability, cost, and how comfortable the patient and provider are with increased risk for treatment failure associated with the use of an antimicrobial agent that may cause less collateral damage but is less effective than another drug.21 If first-line antimicrobial agents are not suitable because of one or more of these factors, fluoroquinolones or β-lactams are reasonable alternatives, although their use should be minimized because of concerns for increasing the risk for drug resistance.21 Thus, although fluoroquinolones (3-day duration) are highly effective in the treatment of cystitis, many experts recommend that they be considered as second-line therapy for uncomplicated cystitis to help preserve their usefulness in the treatment of other more serious infections.21 Moreover, in the United States, the Food and Drug Administration (FDA) has stated that the risks of systemic fluoroquinolones outweigh their benefits for uncomplicated cystitis.27 In general, β-lactam antibiotics have been inferior to TMPSMX or fluoroquinolones in regimens of the same duration.28

Although broad-spectrum oral β-lactams (e.g., cefixime, cefpodoxime, cefprozil, cefaclor, amoxicillin-clavulanate) demonstrate in vitro activity against most uropathogens causing uncomplicated cystitis, clinical data are sparse. Trials have shown that cure rates with 3-day regimens of amoxicillin-clavulanate29 or cefpodoxime proxetil28 were lower than a 3-day regimen of ciprofloxacin. Moreover, there are concerns about the possibility of ecologic adverse effects with oral broad-spectrum cephalosporins, as has been observed with parenteral cephalosporins. Routine posttreatment cultures in females are not indicated unless the patient is symptomatic. If the patient remains symptomatic and persistent infection is confirmed, a longer course of culture-directed therapy (usually with a fluoroquinolone) should be used. Detecting and treating asymptomatic bacteriuria in healthy females is useful only in pregnancy and before urologic instrumentation or surgery.7

Management of Acute Cystitis
Patient presents with acute cystitis

Acute
uncomplicated
cystitis

Complicated cystitis

Pregnant
Obtain culture, empiric
oral treatment with:
5-day regimen of
nitrofurantoin, a 3- to 7day regimen of
amoxicillin-clavulanate,
amoxicillin, cephalexin,
or single dose
fosfomycin (see
Table 53.3 for
dosages)

Empiric oral
treatment with:
5-day regimen of
nitrofurantoin, a 3-day
regimen of trimethoprimsulfamethoxazole
or trimethoprim, or
a single dose of
fosfomycin (see
Table 53.3 for dosages)

Nonpregnant
5- to 7-day regimen of
fluoroquinolone
(see Table 53.3
for dosages)

In all conditions, assess symptoms for persistence or recurrence within 2 weeks
No
Consider cured; no
culture needed

Yes

No

Urine culture plus
empiric oral treatment
with antibiotic to which
initially infecting
pathogen susceptible

Urine culture 1–2
weeks after therapy

Culture
negative
Culture negative
Seek other causes

Culture positive
Treat with appropriate
antibiotic for 7 days
Consider urologic

evaluation
Correct reversible
risk factors

No
Consider cured;
no culture needed

Culture
positive

Monthly screening with
cultures throughout
pregnancy
Treat any asymptomatic
bacteriuria

Treat with appropriate
antibiotic for 7 days
Correct reversible risk
factors
Follow-up urine culture
to ensure cure

Fig. 53.1 Algorithm for management of acute cystitis.

TABLE 53.3

Oral Antimicrobial Agents for Acute Uncomplicated Cystitis

Drug	Dose (mg)	Interval[a]
Nitrofurantoin		
Monohydrate/macrocrystals	100	q12h
Macrocrystals	50	q6h
TMP-SMX	160/800	q12h
Trimethoprim	100	q12h
Fosfomycin	3000	Single dose
Pivmecillinam	400	q8–12h
Cefpodoxime proxetil	100	
Amoxicillin-clavulanate	500/125	
Amoxicillin		

500

q12h
q12h
q12h

Fluoroquinolones
Ciprofloxacin
Ciprofloxacin extended release
Levofloxacin
Ofloxacin

250
500
250
200

q12h
q24h
q24h
q12h

Comment
Less active against Proteus spp.

If used in pregnancy (not approved use), avoid in first trimester.
If used in pregnancy (not approved use), avoid in first trimester.
Less effective than fluoroquinolone or TMP-SMX.
Availability limited to some European countries; not available for use in North America.
Associated with minimal resistance and propensity for collateral damage, but efficacy rates are lower than other agents.
Comparable to TMP-SMX, inferior to ciprofloxacin in 3-day regimen.28
Inferior to ciprofloxacin in 3-day regimen.29
Used only when causative pathogen is known to be susceptible or for empiric treatment of mild cystitis in pregnancy.
Avoid fluoroquinolones if possible in pregnancy, nursing mothers, or persons younger than 18 years old. Although highly effective, should be considered second-line treatment to preserve their usefulness for other infections. Moreover, in the United States, the FDA has stated that the risks of systemic fluoroquinolone antibacterial drugs outweigh their benefits for uncomplicated cystitis.

aDuration of therapy depends on the clinical setting (see text and Fig. 53.1).
FDA, U.S. Food and Drug Administration; TMP-SMX, trimethoprim-sulfamethoxazole.

Recurrent Acute Uncomplicated Cystitis
in Healthy Females
Patient with recurrent acute uncomplicated cystitis

Cure infection
Consider behavioral modification if appropriate
If spermicidal products used, switch contraceptive method
Consider postcoital urination (not proven beneficial)
Consider cranberry product (not proven beneficial)
Urologic evaluation or D-mannose not routinely indicated

Frequency: Three or more
in past year or two or
more in past 6 months

No

Yes, and patient
desires management
program

Consider application
of topical estriol if
postmenopausal

Antibiotic prophylaxis
when infections not
clearly related to coitus

Antibiotic prophylaxis
when infections temporally
related to coitus

Daily or thrice-weekly dose of
antibiotics (see Table 53.4)

Postcoital dose of
antibiotics (see Table 53.4)

Stop at
3–6 months
Manage as in Fig. 53.1
for episodes of acute
uncomplicated cystitis

Pattern
returns

No

Yes

Consider
cured

Consider
longer course
(≥1 year)

Patient-initiated treatment

for symptomatic episodes, especially if no more than two recurrences per year, patient is educated, compliant, and desires less antibiotic exposure

Short-course regimen and then follow-up as shown in Fig. 53.1 for acute uncomplicated cystitis

Fig. 53.2 Management strategies for recurrent acute uncomplicated cystitis.

Recurrent Acute Uncomplicated Cystitis in Females

Many cases of recurrent cystitis in healthy females are caused by persistence of the initially infecting strain in the fecal flora.30 Studies in mice suggest that a latent reservoir of uropathogens in the bladder epithelium that persist after the initial UTI may be one cause of recurrence,31 and indirect evidence indicates that this may occur in humans.32 If the recurrence is within 1 or 2 weeks of treatment, an antimicrobial-resistant uropathogen should be considered, and a urine culture should be performed followed by treatment with an active antimicrobial. We treat later recurrences the same as the original infection, although if the recurrence is within 6 months, we consider a first-line drug other than the one used originally, especially if TMP-SMX was used, because of the likelihood of resistance.33

Long-term management of recurrent cystitis should be aimed to improve the quality of life while minimizing antimicrobial exposure.13 Females with recurrent cystitis may benefit from behavioral modification (Fig. 53.2), such as avoiding spermicides, increasing fluid intake,34 and ensuring postcoital micturition, although it is uncertain whether these practices are truly beneficial. Data on efficacy are sparse, but targeting the adherence mechanism of Enterobacteriaceae with D-mannose powder is another antimicrobial-sparing modality used by some females to prevent UTI.35 Cranberry products are widely used to prevent recurrent UTI, but randomized, placebo-controlled trials (RCTs) have shown minimal benefits.36 Females who do not want to try or who obtain no benefit from the preceding approaches should be offered

TABLE 53.4 Antimicrobial Prophylaxis Regimens for Females With Recurrent Acute Uncomplicated Cystitis

Drug	Dose (mg)	Frequency
Continuous Prophylaxis		
Nitrofurantoin	50 or 100	Daily
TMP-SMX	40/200	Daily
TMP-SMX	40/200	Three times weekly
Trimethoprim	100	Daily
Cefaclor	250	Daily
Cefalexin (cephalexin)	125 or 250	Daily
Postcoital Prophylaxis		
Nitrofurantoin	50 or 100	Single dose
TMP-SMX	40/200	Single dose
TMP-SMX	80/400	Single dose
Cephalexin	250	Single dose

See text and Fig. 53.2 for management strategy.
TMP-SMX, Trimethoprim-sulfamethoxazole.

antimicrobial prophylaxis or have a course of antimicrobials on hand for intermittent self-treatment.

Antimicrobial prophylaxis reduces the risk for recurrent cystitis by approximately 95% (Table 53.4; see also Fig. 53.2).37 Prophylaxis should be considered for females who experience three or more infections during a 12-month period or whenever the patient thinks their life is being adversely affected by frequent recurrences. Several approaches have been used, including continuous prophylaxis, postcoital prophylaxis (best for females who experience UTI only after intercourse), and intermittent self-treatment (which is really an early treatment method).13 In postmenopausal females with recurrent UTI, intravaginal estradiol is effective, presumably by normalizing the vaginal flora, which reduces the risk for coliform colonization of the vagina.38 This approach offers an alternative to antimicrobial strategies (see Fig. 53.2).

Promising antimicrobial-sparing approaches are being developed to specifically target virulence pathways, which might prevent uropathogens from causing disease, without altering the gut commensal microbiota. Antivirulence therapeutics target processes that are critical for UTI pathogenesis but are not required for the essential processes of growth and cell division (targets of conventional antimicrobials).

Acute Uncomplicated Pyelonephritis in Females and Males

Acute pyelonephritis is suggested by fever (temperature ≥ 38°C), chills, flank pain, nausea and vomiting, and costovertebral angle tenderness. Cystitis symptoms are variably present. Symptoms may vary from a mild illness to a sepsis syndrome with or without shock and kidney failure. Pyuria is almost always present, but leukocyte casts, specific for pyelonephritis, are infrequently seen. Gram stain of the urine sediment may aid in differentiating gram-positive and gramnegative infections, which can influence empiric therapy. A urine culture, which should be performed in all females with acute pyelonephritis, will have at least 104 cfu/mL of uropathogens in nearly all patients.39

Kidney biopsy shows focal inflammation with neutrophil and monocyte infiltrates, tubular damage, and interstitial edema (Fig. 53.3).

Fig. 53.3 Acute Pyelonephritis. Kidney tissue shows a dilated tubule with neutrophils enmeshed in proteinaceous debris (“pus casts”) with adjacent interstitial inflammation. (Courtesy C. Alpers, University of Washington, Seattle.)

Fig. 53.4 Acute Pyelonephritis. Contrast-enhanced computed tomography scan shows areas of lower density caused by infection and edema (arrows). (Courtesy W. Bush, University of Washington, Seattle.)

On imaging, the infected kidney is often enlarged, and contrastenhanced computed tomography (CT) shows decreased opacification of the affected parenchyma, typically in patchy, wedge-shaped, or linear patterns (Fig. 53.4).

The availability of effective oral antimicrobials, especially fluoroquinolones, allows initial oral therapy in appropriate patients or, in those initially requiring parenteral therapy, the timely conversion from intravenous to oral therapy. Indications for hospital admission include inability to maintain oral hydration or to take medications; uncertain social situation or concern about compliance; uncertainty about the diagnosis; and severe illness with high fevers, severe pain, and marked debility. Outpatient therapy is safe and effective for select patients who can be stabilized with parenteral fluids and antibiotics in an urgent care facility and sent home with oral antibiotics under close supervision. In one populationbased study of acute pyelonephritis in adult females, only 7% were hospitalized.4

The management strategy for acute uncomplicated pyelonephritis is shown in Fig. 53.5. Many effective parenteral (Table 53.5) and oral

Acute Uncomplicated Pyelonephritis and
Complicated Urinary Tract Infection
Other Than Cystitis
Patient presents with acute
pyelonephritis or complicated urinary
tract infection (UTI) other than cystitis

Acute uncomplicated
pyelonephritis in healthy women

Hospitalize, urine
culture, blood culture

Hospitalization
indicated?

Yes

Complicated UTI

No

Empiric therapy with parenteral
regimen in Table 53.5

Urine culture, empiric therapy
with oral regimen in
Table 53.6, preferably a
fluoroquinolone

Urine culture, blood
culture, empiric
therapy with
parenteral regimen in
Table 53.5

Significant clinical improvement
during 72 hours?

Yes
Switch to or continue
oral regimen as in
Table 53.6 for total
of 7–10 days, 5–7 days
(fluoroquinolone) if mild
episode and rapid response

No
Review antimicrobial susceptibility pattern
Urologic evaluation
Correct reversible risk factors
Hospitalize if necessary

Revise treatment plan as appropriate,
treat for total of 10–14 days or longer if necessary

Follow-up
urine culture
not indicated

No data to support follow-up urine culture
in asymptomatic patient

Fig. 53.5 Management algorithm for acute uncomplicated pyelonephritis and complicated urinary tract infection other than cystitis.

(Table 53.6) regimens are available for patients with acute uncomplicated pyelonephritis. For outpatients, an oral fluoroquinolone should be used for initial empiric treatment of infection caused by gram-negative bacilli.21 TMP-SMX or other agents can be used if the infecting strain is known to be susceptible. If enterococci are suspected from the Gram stain, amoxicillin should be added to the treatment regimen until the causative organism is identified. Second- and third-generation cephalosporins also appear effective, although published data are sparse. Nitrofurantoin, fosfomycin, and pivmecillinam are not approved or recommended for the treatment of pyelonephritis because they only achieve therapeutic levels in the bladder. When antimicrobial resistance or intolerance of oral medications is a concern, one or more doses of a broad-spectrum parenteral antimicrobial is recommended until in vitro activity can be ensured.21 39

For hospitalized patients without evidence of gram-positive infection, ceftriaxone is effective and inexpensive. If enterococci are suspected based on the Gram stain, ampicillin plus gentamicin, ampicillin-sulbactam, or piperacillin-tazobactam are reasonable empiric choices. TMP-SMX should not be used as empiric monotherapy for pyelonephritis in areas with a high prevalence of resistance to this agent. Patients with acute uncomplicated pyelonephritis often can be switched to oral therapy after 24 to 48 hours, although longer durations of parenteral therapy are occasionally indicated in patients with continued high fever, severe flank pain, or persistent nausea and vomiting.

Treatment of acute uncomplicated pyelonephritis can be limited to 5 to 7 days for patients who have a rapid resolution of fever and

Parenteral Regimens for
Acute Uncomplicated Pyelonephritis and
Complicated Urinary Tract Infection a

TABLE 53.6

Drug

Dose (mg)

Interval

Drug

Ceftriaxone
Cefepime
Fluoroquinolonesb
Ciprofloxacin
Levofloxacin
Gentamicinb (± ampicillin)

1000–2000
1000–2000

q24h
q12h

200–400
250–750
3–5 mg/kg body
weight
1 mg/kg body
weight
1000
160/800
1000
3375
250–500
500
1000
1500
2500
1000

q12h
q24h
q24h

Fluoroquinolones
Ciprofloxacin
500
Ciprofloxacin
1000
extended release

TABLE 53.5

Ampicillin (+ gentamicinb)
Trimethoprim-sulfamethoxazoleb
Aztreonam
Piperacillin-tazobactam
Imipenem-cilastatinb c

Meropenemc
Ertapenemc
Ceftolozane/tazobactam
Ceftazidime/avibactam
Vancomycind

Oral Regimens for Acute
Uncomplicated Pyelonephritis and
Complicated Urinary Tract Infection a,b
Dose (mg) Interval
q12h
q24h

q8h

Levofloxacin
250–750
Trimethoprim160/800
sulfamethoxazole

q24h
q12h

q6h
q12h
q8–12h
q6–8h
q6–8h
q8h
q24h
q8h
q8h
q12h

Cefpodoxime
proxetil

200

q12h

Amoxicillinclavulanate

500/125–
875/125

q12h

aDuration

depends on clinical setting (see text and Fig. 53.5).
if possible, in pregnancy.
cRecommended if ESBL Enterobacteriacea is suspected or known.
Ertapenem is not indicated for suspected or known Pseudomonas
infection.
dRecommended if methicillin-resistant Staphylococcus aureus is suspected or known.
bAvoid,

symptoms soon after initiation of treatment. However, β-lactam regimens shorter than 14 days have been associated with unacceptably high failure rates.40 One study demonstrated superiority of a 7-day ciprofloxacin regimen over a 14-day TMP-SMX regimen, with the difference accounted for entirely by the higher rate of resistance of the uropathogens to TMP-SMX.33

A U.S. study of patients with acute pyelonephritis presenting to emergency departments demonstrated that the prevalence of fluoroquinolone-resistant and ESBL-producing strains is increasing and that such patients are often treated with empiric antimicrobial drugs that are inactive against the causative strains.41 The authors concluded that in areas with high fluoroquinolone resistance rates, where ESBL-producing Enterobacteriaceae infections have emerged, or among persons with antimicrobial drug resistance risk factors, clinicians should consider empiric treatment with a carbapenem or another agent with activity against these resistant strains.

Routine posttreatment urine cultures in asymptomatic patients are not useful, but cultures should be performed if symptoms persist or recur. Recurrent infections are treated with a 7- to 14-day course of an antibiotic to which the organism is susceptible. Symptomatic patients who have persistent infection with the same strain as the initial infecting strain warrant at least 10 to 14 days of therapy with a different antibiotic, and complicating factors should be sought and corrected if possible.

Males With Cystitis

Among premenopausal females, cystitis is more common than among similarly aged males. However, after the age of 50 to 60, rates of cystitis

Comment

Preferred for empiric treatment; avoid if possible in pregnancy, nursing mothers, or persons younger than 18 years of age.

Use only when the causative pathogen is known to be susceptible.

If used in pregnancy (not approved use), avoid in first trimester.

Data are sparse; use only when the causative pathogen is known to be susceptible.

Use only when the causative pathogen is known to be susceptible or in addition to a broadspectrum agent when empiric coverage against enterococci is desirable.

[a] A long-acting parenteral antibiotic should be given concomitantly if there are concerns about drug resistance.

[b] Duration depends on clinical setting (see text and Fig. 53.5).

in males increase, although never reaching the rates of females of equivalent age.42 Whereas cystitis in females is well studied, similar studies of male patients are lacking. Males with cystitis are often considered to be a category of complicated UTI, with male sex considered a factor that increase the risk of treatment failure or recurrence. Whether this classification is applicable to all males is unproven; many seem to respond to traditional cystitis treatment but may require a longer duration of treatment than females. Observational studies43 44 and a recent trial44a suggest that shorter-duration therapy performs similarly well to longer-duration therapy, although even the shorter-duration therapy in these studies was longer than the 1- to 5-day regimens that are effective for females with cystitis. Whether males with cystitis who have additional complicating factors (e.g., urinary retention, renal calculi, indwelling catheters) need longer-duration therapy is unknown.

Another difference between males and females with cystitis is the relative lack of predictability regarding the causative organisms. Whereas the microbiology of cystitis among females is predictable, among males there is more variability. E. coli is still the most commonly isolated pathogen, but in some series is only a plurality versus the clear majority observed in females.45 46 Because of this unpredictability, a urine culture should always be obtained to help guide therapy in male patients with cystitis.

Complicated Infections

Patients with UTI in the presence of complicating conditions may present with classic signs of cystitis and pyelonephritis but also may have vague or nonspecific symptoms, such as fatigue, irritability, nausea, headache, and abdominal or back pain. Acute cystitis in healthy individuals other than young females is more likely to involve occult renal or prostatic infection and may respond poorly to shortcourse therapy. Noninvasive tools to localize infections to the kidney or prostate are lacking, so clinical estimation of risk in a given patient is imprecise. Some patients, such as those who are diabetic or pregnant, warrant special attention because of the serious complications that can occur if treatment is inadequate. Urethritis should be excluded in dysuric sexually active males by a urethral Gram stain or a urine nucleic acid amplification test for Neisseria gonorrhoeae and Chlamydia trachomatis. Complicated UTI, just as with uncomplicated infection, is generally associated with pyuria and bacteriuria, although these may be absent if the infection does not communicate with the collecting system.

Urine culture should always be performed in patients with suspected complicated UTI. Traditionally complicated UTI is at least 10^5 cfu/mL in the urine of females and at least 10^4 cfu/mL in males, but lower counts in symptomatic persons, as demonstrated in patients with uncomplicated UTI, may well represent significant bacteriuria. This is especially true when the specimen is collected from a urinary catheter. Thus, it is reasonable to use a colony count threshold of greater than 10^3 cfu/mL of uropathogens to diagnose complicated UTI.

The wide variety of underlying conditions (see Box 53.1), diverse bacterial agents (see Table 53.2), and paucity of RCTs make generalizations about antimicrobial therapy difficult. Figs. 53.1 and 53.5 outline the management strategy for complicated cystitis and other complicated UTIs, respectively.

Correction of any underlying anatomic, functional, or metabolic defect should be attempted because antibiotics alone may not be successful.[1] For empiric therapy in patients with mild to moderate illness who can be treated with oral medication, the fluoroquinolones provide the broadest spectrum of antimicrobial activity, cover most expected pathogens, and achieve high levels in the urine and urinary tract tissue. An exception is moxifloxacin, which may not achieve sufficient concentrations in urine to be effective for complicated UTI. If the infecting pathogen is known to be susceptible, TMP-SMX or other agents are reasonable therapeutic choices. Nitrofurantoin and fosfomycin should be avoided except for cystitis in pregnancy, in which duration of treatment is 5 days or single-dose, respectively.

For initial treatment in more seriously ill, hospitalized patients, several parenteral antimicrobial agents are available (see Table 53.5). The broader spectrum agents shown in Table 53.5 are preferable for health care–associated infections. S. aureus is more common in complicated UTIs, and, if suspected, the therapeutic regimen should have activity against S. aureus. Studies show that a high proportion of S. aureus isolates, even in the community, are methicillin resistant (MRSA), so vancomycin should be included in the empiric treatment regimen if S. aureus is suspected. Factors that must be considered in the management of complicated UTI include the increasing prevalence of resistance to fluoroquinolones in institutional settings and the frequency of enterococcal infections.

The antimicrobial regimen can be modified when the infecting strain has been identified and antimicrobial susceptibilities are known. Patients receiving parenteral therapy can be switched to oral treatment after clinical improvement. Few studies evaluate duration of treatment in populations with complicated UTIs. However, it is desirable to limit the duration of treatment, especially for milder infections, to reduce the selection pressure for drug-resistant flora. In one study, clinical and microbiologic success rates after treatment were almost identical in patients with acute pyelonephritis or complicated UTI treated with a 5-day course of levofloxacin or a 10day course of ciprofloxacin.47 These data suggest that a 5- to 10-day regimen is reasonable for most patients with complicated UTI, depending on their severity of illness and clinical response; shorter regimens, such as a 5-day regimen of a urinary fluoroquinolone, are likely to be sufficient in patients who are less severely ill, are infected with uropathogens susceptible to the antibiotic used, and have a rapid response to treatment. A recent large retrospective study of male veterans with UTI found no difference in recurrence rates with 7 days of treatment versus longer, with a trend toward more Clostridium difficile infections in those treated longer.43 A clinical trial of V in veterans with UTI but without fever confirmed non-inferiority of 7 versus 14 days of antibiotics.44a At least 10 to 14 days of therapy is recommended in patients who have a delayed response. Routine posttreatment cultures are not indicated unless the patient is symptomatic, except in pregnant patients (see Fig. 53.1). In males, early recurrence of UTI with the same species suggests a prostatic source of infection and warrants a 4- to 6-week regimen of either a fluoroquinolone (preferable) or TMP-SMX, depending on the antimicrobial susceptibility of the infecting strain.

Chronic Kidney Disease

Because of the wide variety of underlying diseases and comorbidities, prior instrumentation of the urinary tract, and differences in age and sex, the incidence of UTI in patients with CKD is not known.48 Moreover, there are few data on urine concentrations of antimicrobials used for the treatment of UTI in patients with CKD.49 Studies in animals suggest that (1) urine drug concentrations are necessary to sterilize urine, (2) effective tissue concentrations are necessary to treat pyelonephritis, and (3) serum concentrations of antimicrobials are correlated with the drug concentrations in kidney tissue. Thus, for patients with CKD who have a therapeutic serum drug level and adequate perfusion of the kidney parenchyma, the delivery of therapeutic concentrations of both the parenchyma and the urine should be adequate, but some oral agents for cystitis may not deliver adequate concentrations to the urine.49 For patients with a low glomerular filtration rate (GFR) and pyelonephritis or cystitis, the agents listed in Tables 53.5 and 53.6 for pyelonephritis and complicated cystitis should be adequate to treat these infections if the organism is susceptible.49 As noted previously, β-lactams are not as effective as fluoroquinolones, even in patients with normal kidney function.28,29 Doses of ciprofloxacin or levofloxacin should be adjusted for GFR; moxifloxacin is not recommended for UTI treatment. Nitrofurantoin and sulfamethoxazole are not recommended in patients with reduced GFR, although trimethoprim concentrations appear to be adequate.48 Likewise reduced kidney function (such as CKD stage 3 or higher) significantly decreases the excretion of fosfomycin, which also should not be used in such patients.

Catheter-Associated Infections

Approximately 15% to 25% of patients in general hospitals have a urethral catheter inserted at some time during their stay, and approximately 5% to 10% of long-term care facility residents are managed with urethral catheterization, in some cases for years. The incidence of bacteriuria associated with indwelling catheters is 3% to 10% per day of catheterization, and the duration of catheterization is the most important risk factor for the development of catheter-associated bacteriuria. Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients, often associated with catheter obstruction or trauma. Complications of long-term catheterization (≥30 days) include almost universal bacteriuria, often with multiple antibiotic-resistant flora, and (in addition to cystitis, pyelonephritis, and bacteremia, as seen with short-term catheterization) frequent febrile episodes, catheter obstruction, stone formation associated with urease-producing uropathogens, and local genitourinary infections. Other rare complications include fistula formation and bladder cancer. An increase in mortality risk has been reported with catheter-associated bacteriuria, but it is difficult to distinguish the role of the catheter because most deaths occur in patients who have severe underlying disease.

Most episodes of catheter-associated bacteriuria are asymptomatic and do not require routine screening or treatment because treatment does not reduce the complications of bacteriuria and can lead to antimicrobial resistance.7 Moreover, the presence or absence of pyuria does not differentiate symptomatic from asymptomatic urinary infection.7 Symptomatic UTIs, often caused by many multidrug-resistant uropathogens, warrant broad-spectrum therapy, as described previously. In a symptomatic catheterized patient, a urine culture specimen should be obtained from a freshly placed catheter if the catheter has been in place for a few days because the catheter biofilm may result in spurious culture results. Moreover, clinical outcomes are improved if the catheter is replaced at the time of antimicrobial therapy.50 The recommended duration of antimicrobial treatment for patients who have prompt resolution of symptoms is 7 days, and 10 to 14 days if response is delayed.51

Preventive measures are indicated to reduce the morbidity, mortality, and costs of catheter-associated infection. Effective strategies include avoidance of a catheter when possible and, when the catheter is necessary, sterile insertion, prompt removal, and strict adherence to a closed collecting system.6,51 Bundling of preventive steps may be useful.52,53 Meta-analyses have shown that rates of catheter-associated bacteriuria, at least in patients catheterized for less than 2 weeks, are higher in patients with an indwelling urethral catheter than in those with intermittent or suprapubic catheterization.54 Likewise, condom catheterization is preferable to indwelling urethral catheterization in appropriately selected males.54 Although highly effective in reducing catheter-associated bacteriuria rates, prophylactic systemic antimicrobial agents are generally not recommended for routine use because of concerns about selection for antimicrobial resistance. Antimicrobialcoated catheters appear to be effective in reducing catheter-associated bacteriuria in patients catheterized for less than 2 weeks, but these have not been shown to be effective in reducing symptomatic infection.

The most common organisms causing bacterial prostatitis are gramnegative bacilli, including E. coli, Proteus spp., Klebsiella spp., P. aeruginosa, and, less frequently, enterococci and S. aureus. The pathogenesis of prostatitis is believed to be related to reflux of infected urine from the urethra into the prostatic ducts. Prostatic calculi, commonly found in adult males, may provide a nidus for bacteria and protection from antibacterial agents.

Acute bacterial prostatitis is rare. Patients present with dysuria, frequency, urgency, obstructive voiding symptoms, fever, chills, and myalgias. The prostate is tender and swollen, and the prostate exam should be limited to assessment of size and tenderness to avoid precipitating bacteremia. The patient will usually have pyuria and a positive urine culture. Patients who are severely ill require hospitalization and parenteral antibiotics, but many patients can be treated in the outpatient setting with oral fluoroquinolones. The recommended duration of treatment is 14 to 30 days.57 Rarely, abscess formation may occur, which should be treated by source control with the assistance of a urologist.

Chronic bacterial prostatitis is characterized by recurrent UTIs with the same uropathogen with intervening asymptomatic periods. The prostate typically is normal to palpation during asymptomatic periods. Chronic bacterial prostatitis is characterized microscopically by the presence of at least 10 leukocytes per high-power field in expressed prostatic secretions or postmassage voided urine in the absence of significant pyuria in first-voided and midstream urine specimens, as well as a uropathogen colony count at least 10-fold higher in the expressed prostatic secretions or postmassage voided urine compared with the first-voided midstream urine. In addition, macrophage-laden fat droplets (oval fat bodies) are usually prominent in the prostatic secretions.

These tests, however, are infrequently performed by urologists. Cure rates, which historically have been low, are 60% to 80% with the fluoroquinolones, which are the antibiotics of choice. The optimal duration of treatment is unknown, but 4 to 6 weeks is recommended by some authorities,57 whereas others recommend up to 3 months. Some patients require long-term, low-dose suppressive therapy to prevent symptomatic UTIs. Surgical intervention is only rarely considered and is associated with high morbidity.

Spinal Cord Injury

Kidney cortical and corticomedullary abscesses and perirenal abscesses occur in 1 to 10 per 10,000 hospital admissions.58 Patients usually present with fever, chills, back or abdominal pain, and costovertebral angle tenderness, but they may have no urinary symptoms or findings if the abscess does not communicate with the collecting system, as often occurs with a cortical abscess. Bacteremia may be primary (cortical abscess) or secondary (corticomedullary or perirenal). The clinical presentation may be insidious and nonspecific, especially with perirenal abscess, and the diagnosis may not be made until admission to a hospital or at autopsy. CT is recommended to establish the diagnosis and location of a renal or perirenal abscess (Fig. 53.6). Empiric antibiotic therapy should be broad and cover S. aureus and other uropathogens causing complicated UTI (see Fig. 53.5 and Table 53.5) and modified once urine culture results are known.

A renal cortical abscess (kidney carbuncle) is usually caused by S. aureus, which reaches the kidney by hematogenous spread. Treatment with antibiotics is usually effective, and drainage is not required unless the patient is slow to respond. A renal corticomedullary abscess, in contrast, usually results from ascending UTI in association with an underlying urinary tract abnormality, such as obstructive uropathy or VUR, and is usually caused by common uropathogenic species such as E. coli and other gram-negative bacilli. Such abscesses may extend deep into the renal parenchyma, perforate the renal capsule, and form

Spinal cord injury alters the dynamics of voiding and often requires the use of bladder drainage with catheters. The diagnosis of UTI in patients with spinal cord injuries is based on the combination of symptoms and signs (which are often nonspecific), pyuria, and significant bacteriuria. Uropathogens are usually present in quantities of at least 105 cfu/mL. Fluoroquinolones are the empiric oral agents of choice in patients with mild to moderate infection, although many uropathogens, even in the outpatient setting, are resistant to this class of antibiotic, and parenteral antibiotics may be needed.

Treatment of asymptomatic bacteriuria in patients with spinal cord injuries is not of proven benefit and increases the risk for infection with antimicrobial-resistant uropathogens.7,55 Likewise, antibiotic prophylaxis is generally not recommended, although it may be considered for select outpatients with frequent symptomatic UTIs for whom there are no correctible risk factors. Recent studies have shown that use of a hydrophilic-coated catheter for intermittent catheterization is associated with a reduction in the incidence of symptomatic UTI in patients with spinal cord injury.56

Prostatitis

Prostatitis occurs in up to 25% of males during their lifetime, but it is caused by acute or chronic bacterial infection in a minority.57

Kidney Abscess

Fig. 53.6 Renal Abscess. Contrast-enhanced computed tomography scan shows an abscess in the medulla of the kidney (arrowhead) with penetration and extension into the perinephric space (arrows). (Courtesy L. Towner.)

Fig. 53.7 Emphysematous Pyelonephritis. A plain radiograph in this febrile patient with diabetes reveals diffuse gas formation throughout both kidneys (outlined by arrows) and gas dissecting in the left retroperitoneal space (arrowheads). (Courtesy W. Bush, University of Washington, Seattle.)

a perirenal abscess. Treatment with antimicrobial agents without drainage may be effective if the abscess is small and if the underlying urinary tract abnormality can be corrected. Aspiration of the abscess may be necessary in some patients, and nephrectomy may occasionally be required in patients with diffuse renal involvement or with severe sepsis. Perirenal abscesses usually occur in the setting of obstruction or other complicating factors (see Box 53.1) and result from ruptured intrarenal abscesses, hematogenous spread, or spread from a contiguous infection. Causative uropathogens are those usually found in complicated UTIs (see Table 53.2), including S. aureus and enterococci; polymicrobial infections are common. Anaerobes or Mycobacterium tuberculosis may be causative (see Chapter 54). A previously high mortality rate has been lowered with earlier diagnosis and therapy. In contrast to the other types of renal abscesses, drainage of pus is the cornerstone of therapy and nephrectomy may be indicated.

of pyelonephritis, and there may be a flank mass. Dehydration and ketoacidosis are common. Pyuria and a positive urine culture are usually present. Gas is usually detected by a plain abdominal radiograph or ultrasound (Fig. 53.7). CT is the diagnostic modality of choice, however, because it can localize the gas better than ultrasound. Accurate localization of gas is important because gas also may form in an infected obstructed collecting system or renal abscess; although serious, these conditions do not carry the same poor prognosis and are managed differently. Parenteral broad-spectrum antibiotics and percutaneous catheter drainage with relief of obstruction may be adequate for less severely ill patients, but nephrectomy is warranted for those who are more severely ill and those less severely ill who do not respond to the preceding steps. Medical treatment is associated with mortality of 60% to 80%, which is lowered to 20% or less with surgical intervention (e.g., nephrectomy, percutaneous drainage).

Papillary Necrosis

Kidney Malacoplakia

More than half of patients who develop papillary necrosis have diabetes, almost always in conjunction with a UTI, but the condition also complicates sickle cell disease, analgesic abuse, and obstruction. Kidney papillae are vulnerable to ischemia because of the sluggish blood flow in the vasa recta, and relatively modest ischemic insults may cause papillary necrosis. The clinical features are those typical of pyelonephritis. In addition, passage of sloughed papillae into the ureter may cause renal colic, renal impairment or failure, or obstruction with severe urosepsis. Papillary necrosis in the setting of pyelonephritis is associated with pyuria and a positive urine culture. Causative uropathogens are those typical of complicated UTI. CT is the preferred diagnostic procedure. Radiologic findings include an irregular papillary tip; dilated calyceal fornix; extension of contrast material into the parenchyma; and a separated crescent-shaped papilla surrounded by contrast called the ring sign (see Chapter 51, Fig. 51.8). Broadspectrum antibiotics are indicated. Papillae obstructing the ureter may require removal with a cystoscopic ureteral basket or relief of obstruction by insertion of a ureteral stent.

Malacoplakia is a chronic granulomatous disorder of unknown etiology involving the genitourinary, gastrointestinal, skin, and pulmonary systems.60 It is characterized by an unusual inflammatory reaction to a variety of infections and is manifested by the accumulation of macrophages containing calcified bacterial debris called MichaelisGutmann bodies (Fig. 53.8). The underlying disorder appears to be a monocyte-macrophage bactericidal defect. The diagnosis is made by histologic examination of involved tissue. Genitourinary malacoplakia, most often involving the bladder, is usually associated with gramnegative UTI. Patients with kidney malacoplakia generally have fever, flank pain, pyuria and hematuria, bacteriuria, and, if both kidneys are involved, impaired renal function. CT usually shows enlarged kidneys with areas of poor enhancement, and the condition may be indistinguishable from other infectious or neoplastic lesions. On occasion, the malacoplakia may extend through the kidney capsule into the perinephric space, simulating a renal carcinoma (see Fig. 53.8). Treatment consists of therapy with a broad-spectrum antimicrobial, attempted correction of any underlying complicating conditions, and improvement of renal function. Nephrectomy is recommended for advanced unilateral disease. When the disease is bilateral or occurs in a transplanted kidney, the patient’s prognosis is very poor.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a fulminant, necrotizing, lifethreatening variant of acute pyelonephritis caused by gas-forming organisms, including E. coli, Klebsiella pneumoniae, P. aeruginosa, and Proteus mirabilis.59 Up to 90% of cases occur in diabetic patients, and obstruction may be present. Symptoms are suggestive

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a poorly understood, uncommon but severe chronic destructive granulomatous inflammation of

*

B

A

Fig. 53.8 Renal Malacoplakia. (A) Malacoplakia involving most of the kidney (arrows) with extension through the capsule (asterisks). A small portion of normal kidney is present associated with hydronephrosis secondary to obstruction by the malacoplakia. (B) The kidney tissue shows many macrophages containing intracytoplasmic inclusions (arrows identify two particularly well-demarcated macrophages with Michaelis-Gutmann bodies). (Courtesy L. Truong, Baylor College of Medicine, Houston, and N. Sheerin, Guy's Hospital, London.)

Asymptomatic Bacteriuria

Fig. 53.9 Xanthogranulomatous Pyelonephritis. Contrast-enhanced computed tomography scan with an inflammatory mass outlined by arrows. Pathologic diagnosis confirmed xanthogranulomatous pyelonephritis. (Courtesy W. Bush, University of Washington, Seattle.)

the kidney parenchyma associated with obstruction and infection of the urinary tract.61 The renal parenchyma is replaced with a diffuse or segmental cellular infiltrate of foam cells, which are lipid-laden macrophages. The process also may extend beyond the kidney capsule to the retroperitoneum. Its pathogenesis appears to be multifactorial, with infection complicating obstruction and leading to ischemia, tissue destruction, and accumulation of lipid deposits. Patients with xanthogranulomatous pyelonephritis are characteristically middleaged females and have chronic symptoms such as flank pain, fever, chills, and malaise. Flank tenderness, a palpable mass, and irritative voiding symptoms are common. The urine culture is usually positive with E. coli, other gram-negative bacilli, or S. aureus. CT generally shows an enlarged nonfunctioning kidney, often the presence of calculi and low-density masses (xanthomatous tissue), and, in some cases, involvement of adjacent structures (Fig. 53.9). It may be difficult to distinguish from neoplastic disease. Broad-spectrum antimicrobials are indicated, but total or partial nephrectomy is usually necessary for cure.

Asymptomatic bacteriuria is common and generally benign.7 Pyuria is almost universally present, especially in elderly people, and is a predictor for subsequent symptomatic UTI in some groups. Causative uropathogens are the same as those causing UTIs in the same population.

Testing for and treatment of asymptomatic bacteriuria is generally not warranted.7 In young females with recurrent UTI, asymptomatic bacteriuria may paradoxically be protective against symptomatic recurrence and treatment may increase the risk for such recurrences.62 Two exceptions to this are pregnant patients and patients undergoing urologic surgery; in both these groups, screening for and treatment of asymptomatic bacteriuria is recommended to prevent subsequent complications.7 Current management strategies in patients with a renal transplant, including long-term antimicrobial prophylaxis, help prevent both asymptomatic bacteriuria and symptomatic UTI. It is not clear, however, whether testing for or treatment of asymptomatic bacteriuria in such patients is worthwhile.7 Some authorities advise treatment of asymptomatic bacteriuria found in patients with anatomic or functional abnormalities of the urinary tract, diabetic patients, and patients with urea-splitting bacteria (e.g., P. mirabilis, Klebsiella spp.).

Evidence-based guidelines for evaluation and treatment of asymptomatic bacteriuria in these populations are needed.

Asymptomatic bacteriuria in catheterized patients in hospitals and long-term care facilities, although thought to be generally benign, represents a large reservoir of antimicrobial-resistant urinary pathogens that increases the risk for cross-infection among catheterized patients and results in frequent inappropriate antimicrobial use.51

IMAGING OF THE URINARY TRACT

Urologic consultation and evaluation of the urinary tract should be considered in patients who present with symptoms or signs of obstruction, urolithiasis, flank mass, or urosepsis. Similarly, such an evaluation should be considered for those patients with presumptive uncomplicated or complicated UTI who have not had a satisfactory clinical response after 72 hours of treatment, to exclude complicating factors. A kidney ultrasound can detect the size and contour of the kidneys and bladder, the presence of a renal mass or abscess, certain renal and ureteral calculi, hydronephrosis suggestive of obstructive uropathy, and elevated postvoid residual urine.63 A plain abdominal radiograph (kidneys, ureters, bladder [KUB]) can identify radiopaque calculi along the genitourinary tract, especially proximal and distal ureteral stones that can be missed on ultrasound. Kidney ultrasound and KUB are less sensitive than CT for detection of many conditions in patients with complicated UTI. Any finding suggesting mass or complex fluid collection should prompt follow-up imaging with CT. CT offers fine anatomic detail and is thus the superior study for evaluation of focal inflammation, renal or perirenal abscess and masses, and both radiopaque and radiolucent stones. However, CT also carries the greatest risk profile, exposing the patient to both intravenous contrast and ionizing radiation.63 Non–contrast-enhanced spiral CT is a rapid, safe, and sensitive method for evaluating patients with suspected kidney stones. Radionuclide imaging procedures have no role in the evaluation of adults with UTI, although they are useful in children with pyelonephritis (see Chapter 62).

Excretory urography and cystoscopy in females with recurrent cystitis rarely demonstrate abnormalities or alter management3 and therefore are not recommended. Likewise, imaging studies in young females with acute pyelonephritis are also generally not cost-effective and have a low diagnostic yield, although it is reasonable to obtain such studies after two episodes of pyelonephritis or if any complicating factor is present (see Box 53.1). Imaging studies and cystoscopy are unnecessary in a male who has had a single UTI with no obvious complicating factors and whose infection responds promptly to treatment.

SELF-ASSESSMENT QUESTIONS

1. Which of the following antimicrobials is not recommended for first-line use for uncomplicated cystitis by the Infectious Disease Society of America treatment guidelines?
A. Fosfomycin
B. Ciprofloxacin
C. Trimethoprim-sulfamethoxazole
D. Nitrofurantoin

2. What approach has not been shown to be effective in the management of recurrent cystitis in females?
A. Postcoital antimicrobial prophylaxis
B. Daily antimicrobial prophylaxis
C. Intermittent self-treatment
D. Periodic screening and treatment of asymptomatic bacteriuria

3. Which of the following antimicrobials should be avoided in the treatment of prostatitis?
A. Ciprofloxacin
B. Nitrofurantoin
C. Levofloxacin
D. Trimethoprim-sulfamethoxazole

4. In which of the following conditions is screening for and treatment of asymptomatic bacteriuria indicated?
A. Elderly males and females
B. Catheterized males and females
C. Pregnant patients and patients undergoing urologic instrumentation
D. After treatment for acute pyelonephritis

REFERENCES

1. Nicolle LE. A practical guide to the management of complicated urinary tract infection. Drugs. 1997;53(4):583–592.
2. Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med. 1996;335(7):468–474.
3. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am. 1997;11(3):551–581.
4. Scholes D, Hooton TM, Roberts PL, Gupta K, Stapleton AE, Stamm WE. Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med. 2005;142(1):20–27.
5. Foxman B, Barlow R, D’Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol. 2000;10(8):509–515.
6. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med. 1993;329(18):1328–1334.
7. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the infectious diseases Society of America. Clin Infect Dis. 2019;68(10):1611–1615.
8. Sobel JD. Pathogenesis of urinary tract infection. Role of host defenses. Infect Dis Clin North Am. 1997;11(3):531–549.
9. Johnson JR. Microbial virulence determinants and the pathogenesis of urinary tract infection. Infect Dis Clin North Am. 2003;17(2):261–278 (viii).
10. Lundstedt AC, McCarthy S, Gustafsson MC, et al. A genetic basis of susceptibility to acute pyelonephritis. PLoS One. 2007;2(9):e825.
11. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269–284.
12. Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am. 1997;11(3):735–750.
13. Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366(11):1028–1037.
14. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. N Engl J Med. 1982;307(8):463–468.
15. Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. N Engl J Med. 2013;369(20):1883–1891.
16. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA. 2002;287(20):2701–2710.
17. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in Escherichia coli outpatient urinary isolates: final results from the North American urinary tract infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents. 2006;27(6):468–475.
18. Schito GC, Naber KG, Botto H, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents. 2009;34(5):407–413.
19. Karlowsky JA, Lagace-Wiens PR, Simner PJ, et al. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD surveillance study. Antimicrob Agents Chemother. 2011;55(7):3169–3175.
20. Manges AR, Johnson JR. Food-borne Origins of Escherichia coli causing extraintestinal infections. Clin Infect Dis.
21. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103–120.
22. Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary Escherichia coli isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother. 2012;56(4):2181–2183.
23. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med. 2007;167(20):2207–2212.

24. Rodriguez-Bano J, Alcala JC, Cisneros JM, et al. Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Arch Intern Med. 2008;168(17):1897–1902.

25. Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamaseproducing Escherichia coli-related lower urinary tract infections. Int J Antimicrob Agents. 2007;29(1):62–65.
26. Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrugresistant bacteria. J Antimicrob Chemother. 2014;69(2):303–308.
27. U.S. Food and Drug Administration. Drug safety communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. www.fda.gov/Drugs/DrugSafety/ucm500143.htm. Accessed 3/14/2021.
28. Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA. 2012;307(6):583–589.
29. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA. 2005;293(8):949–955.
30. Stapleton A, Stamm WE. Prevention of urinary tract infection. Infect Dis Clin North Am. 1997;11(3):719–733.
31. Anderson GG, Dodson KW, Hooton TM, Hultgren SJ. Intracellular bacterial communities of uropathogenic Escherichia coli in urinary tract pathogenesis. Trends Microbiol. 2004;12(9):424–430.
32. Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ. Detection of intracellular bacterial communities in human urinary tract infection. PLoS Med. 2007;4(12):e329.
33. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA. 2000;283(12):1583–1590.
34. Hooton TM, Vecchio M, Iroz A, et al. Effect of increased daily Water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. JAMA Intern Med. 2018;178(11):1509–1515.
35. Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol. 2014;32(1):79–84.
36. Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clin Infect Dis. 2011;52(1):23–30.
37. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. Urol Clin North Am. 2008;35(1):1–12.
38. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014;124(6):1147–1156.
39. Johnson JR, Russo TA. Acute pyelonephritis in adults. N Engl J Med. 2018;378(12):1162.
40. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis. 1999;29(4):745–758.
41. Talan DA, Takhar SS, Krishnadasan A, et al. Fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing Escherichia coli infections in patients with pyelonephritis, United States(1). Emerg Infect Dis. 2016;22(9).
42. Ahmed H, Farewell D, Jones HM, Francis NA, Paranjothy S, Butler CC. Incidence and antibiotic prescribing for clinically diagnosed urinary tract infection in older adults in UK primary care, 2004-2014. PLoS One. 2018;13(1):e0190521.
43. Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary tract infection in male veterans: treatment patterns and outcomes. JAMA Intern Med.

173(1):62-68.
44. Germanos GJ, Trautner BW, Zoorob RJ, et al. No clinical benefit to treating male urinary tract infection longer than seven days: an outpatient Database study. Open Forum Infect Dis. 2019;6(6):ofz216.
44a.Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR Effect of 7 vs 14 days of antibiotic therapy on resolution of symptoms among afebrile men with urinary tract infection: a randomized clinical trial. JAMA. 2021;326(4):324–331.

References

45. Marsh KJ, Mundy L, Holter JJ, Johnson JR. Analysis of urine-specific antibiograms from veterans to guide empiric therapy for suspected urinary tract infection. Diagn Microbiol Infect Dis. 2019;95(4):114874.
46. Montelin H, Forsman KJ, Tangden T. Retrospective evaluation of nitrofurantoin and pivmecillinam for the treatment of lower urinary tract infections in men. PLoS One. 2019;14(1):e0211098.
47. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology. 2008;71(1):17–22.
48. Funfstuck R, Ott U, Naber KG. The interaction of urinary tract infection and renal insufficiency. Int J Antimicrob Agents. 2006;28(suppl 1):S72–S77.
49. Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. Clin J Am Soc Nephrol. 2006;1(2):327–331.
50. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases Society of America. Clin Infect Dis. 2010;50(5):625–663.
51. Tambyah PA, Oon J. Catheter-associated urinary tract infection. Curr Opin Infect Dis. 2012;25(4):365–370.
52. Saint S, Greene MT, Krein SL, et al. A Program to prevent catheterassociated urinary tract infection in acute care. N Engl J Med. 2016;374(22):2111–2119.

53. Niel-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. Cochrane Database Syst Rev. 2005;3:CD004203.
54. Saint S, Kaufman SR, Rogers MA, Baker PD, Ossenkop K, Lipsky BA. Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc. 2006;54(7):1055–1061.
55. Cardenas DD, Hooton TM. Urinary tract infection in persons with spinal cord injury. Arch Phys Med Rehabil. 1995;76(3):272–280.
56. Li L, Ye W, Ruan H, Yang B, Zhang S, Li L. Impact of hydrophilic catheters on urinary tract infections in people with spinal cord injury: systematic review and meta-analysis of randomized controlled trials. Arch Phys Med Rehabil. 2013;94(4):782–787.
57. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010;50(12):1641–1652.
58. Dembry LM, Andriole VT. Renal and perirenal abscesses. Infect Dis Clin North Am. 1997;11(3):663–680.
59. McHugh TP, Albanna SE, Stewart NJ. Bilateral emphysematous pyelonephritis. Am J Emerg Med. 1998;16(2):166–169.
60. Dobyan DC, Truong LD, Eknoyan G. Renal malacoplakia reappraised. Am J Kidney Dis. 1993;22(2):243–252.
61. Li L, Parwani AV. Xanthogranulomatous pyelonephritis. Arch Pathol Lab Med. 2011;135(5):671–674.
62. Cai T, Mazzoli S, Mondaini N, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis. 2012;55(6):771–777.
63. Dielubanza EJ, Schaeffer AJ. Urinary tract infections in women. Med Clin North Am. 2011;95(1):27–41.

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Tuberculosis of the Urinary Tract

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DEFINITION

More than a century after Mycobacterium tuberculosis (MTB) was first described by Robert Koch, tuberculosis (TB) remains a global health problem and among the leading causes of death from infectious disease worldwide.1 As per the World Health Organization (WHO) Global Tuberculosis Report in 2018, an estimated 10 million people developed TB, of whom 4 million people with TB remained undiagnosed and untreated.2 Infection with MTB is responsible for nearly 1.3 million deaths each year. TB is the most common opportunistic infection in people with human immunodeficiency virus (HIV).3 In HIV-endemic areas, as many as 75% of patients with urogenital TB (UG-TB) are coinfected with HIV. TB is also common in patients with chronic kidney disease (CKD). In some endemic areas, TB has been reported to occur in up to 8.7% of patients on hemodialysis, 12.3% of kidney allograft recipients,4 and 9.3% of children with nephrotic syndrome.5 Although the global incidence is estimated to be declining by 1.6% and mortality by 4.1% per year, few countries are likely to meet the United Nations (UN) Sustainable Development Goals target to end the epidemic by 2030.

Drug-resistant forms of tuberculosis are currently among the world’s deadliest pathogens. Data from 2017 show that among nearly 0.55 million cases of rifampicin-resistant TB, 80% had multidrugresistant (MDR) TB (defined as resistance to rifampicin and isoniazid) and 8.5% of patients with MDR-TB had extensively drug-resistant (XDR) TB (with XDR-TB defined as resistance to rifampicin, isoniazid, quinolones, and aminoglycosides).6

The common sites of extrapulmonary involvement by MTB are lymph nodes, urinary tract, genital tract, bone, adrenal glands, and the central nervous system. UG-TB may remain asymptomatic and undiagnosed in up to 20% of individuals with active pulmonary TB. Kidney involvement may also occur as part of miliary TB. Because UG-TB can easily be overlooked, a high index of suspicion is necessary for early diagnosis in endemic areas. Delayed diagnosis may result in irreversible organ damage and even end-stage kidney failure.7

ETIOLOGY

TB is caused by the M. tuberculosis complex (MTBC). Mycobacterium tuberculosis is a nonmotile, nonsporing, rod-shaped, slightly curved, obligate aerobe bacterium (Fig. 54.1). It is weakly gram-positive and acid- and alcohol-fast. The cell wall has a high content of mycolic acid that makes the organism resistant to acids, alkalis, antibiotics, osmotic agents, and intracellular events. Lipoarabinomannan (LAM) forms a part of the mycolic acid in the cell wall and its identification in urine is useful for diagnosis. The most superficial layer consists of glycolipids and polypeptide (Fig. 54.2). The polypeptides are isolated and purified to make the skin testing antigen, which is called purified protein derivative (PPD) (Table 54.1). Although most TB, including genitourinary TB, is caused by MTB, other mycobacteria, such as M. avium-intracellulare, M. kansasii, M. bovis, M. fortuitum, and M. szulgai, may cause clinical disease, especially in immune-compromised hosts. Among the atypical mycobacteria, M. chelonei abscessus belongs to the group of “rapid growers” and causes abscesses after injection or percutaneous procedures, especially in patients with diabetes.8

PATHOGENESIS

Acc. V Spot Magn Det WD Exp
30.0 kV 3.0 15549x SE 7.4 0

2 µm
jhc

Fig. 54.1 Scanning Electron Microscopy of Mycobacterium Tuberculosis. The bacillus is a straight or slightly curved rod about 2 to 4 µm long and 0.3 to 0.5 µm wide. (High magnification × 15,549). (Courtesy Ray Butler MS, CDC. Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention. Atlanta, GA.)

The most common routes of transmission are:

1. Inhalation of infected droplets from patients with active pulmonary TB (95%)
2. Ingestion of dairy products infected with M. bovis from cattle
3. After therapeutic intravesical bacillus Calmette-Guérin (BCG) instillation
4. Contiguous spread to nearby organs
5. Lymphatic or hematogenous spread
6. Congenital, sexual, or accidental inoculation (rare)

The clinical and pathologic manifestations of TB depend on the virulence of the organism and the effectiveness of the host response. In 95% of people, after primary infection, the bacilli multiply locally and evoke a local response to form a primary granuloma called the Ghon complex. The immune responses result in either eradication, containment as latent TB infection (LTBI), or active disease. The WHO has defined LTBI

Diagrammatic Representation of Mycobacterial Cell Wall
Surface layer of
glycolipids / polypeptides

Mycolic acid layer

Arabinogalactan layer

Peptidoglycan layer

Lipid bilayer (cell wall)
Cytoplasm of
Mycobacterium tuberculosis

Fig. 54.2 Diagrammatic representation of mycobacterial cell wall.

TABLE 54.1 Cell Wall Characteristics Affecting Survival of Mycobacterium tuberculosis

Composition of Cell Wall	Factors for Survival
Mycolic acid	Resist proteolysis and uptake into phagolysosomes
Lipoarabinomannan	Detected by CD1 T cells that may assist the immune response
Muramyl dipeptide	Stimulate T cell responses (granuloma formation) that may assist clearance
Glycolipids	Inhibit macrophage function
Inert lipids and surface proteins	Dormant survival inside phagocytes

as a state of persistent immune response to stimulation by MTB antigens with no evidence of clinically manifest active TB. The Ghon complex may be found in the lungs, tonsils, gut, or any organ. The organisms from the primary focus drain to a regional lymph node or nodes, causing their enlargement. This triad of the primary Ghon focus, lymphangitis, and lymphadenitis is known as the primary complex and is self-limited in 90% to 95% of cases. Progression occurs in the remainder, leading to local or systemic dissemination of mycobacteria via lymphatics or the bloodstream.[9] Because of the slow replication rate, its intracellular location in macrophages, and acquired immune responses, it may take 1 to 2 years after primary infection for symptoms and signs to manifest. Reactivation of LTBI may occur in 5% to 15% of people and progress to active TB. Up to 10% of patients with UG TB have active pulmonary TB, and 50% have evidence of previous TB on chest radiographs.

Bacilli from the regional lymph node enter the bloodstream through the thoracic duct resulting in silent dissemination to various sites, including the kidney cortex (Fig. 54.3). Here, the bacilli elicit an inflammatory response, resulting in granuloma formation that may heal and form a microscopic scar, remain dormant for many years, or rupture into the proximal tubule of the nephron. The bacilli in the nephron are trapped at the level of the loop of Henle, where they multiply. The relatively poor blood flow, hypertonicity, and high ammonia concentration in the kidney medulla impair the immune response and favor the formation of medullary granulomas, leading to chronic tubulointerstitial nephritis, fibrosis, or papillary necrosis. The center of these granulomas (tuberculomas), which contains macrophages, may undergo coagulative necrosis and form ulcers or cavities filled with cheese-like caseous material (Fig. 54.4A). Extensive caseous destruction of the kidney parenchyma occurs with formation of lobules and cavities (see Fig. 54.4B). The dissemination of infection to the kidney pelvis can cause tuberculous pyelonephritis. This may burst into perirenal tissue to form perinephric abscess or into the calyx causing pyonephrosis. With progressive fibrosis and scarring of the uretero-pelvic junction, dilation of pelvis and calyces may occur. Extensive necrosis replaces the kidney parenchyma with caseous material. Various patterns of calcification may be seen in imaging (Fig. 54.5). Calcification commences intracellularly because of the accumulation of phosphate ions from the disintegration of nucleoproteins and entry of calcium ions from cell membrane damage. These dystrophic calcific lesions may harbor live or dormant mycobacteria and such dystrophic lesions are considered active disease and not signs of healing. Dystrophic calcification may result in a nonfunctioning kidney (autonephrectomy) with dystrophic calcification called putty or cement kidney. Kidney TB can be briefly classified as:

✓ • ✓ Stage 1: nondestructive form (TB of parenchyma)
✓ • ✓ Stage 2: small-destructive form (TB papillitis)
• ✓ Stage 3: destructive form with one or two caverns (cavernous kidney TB)
✓ • ✓ Stage 4: widespread destructive form (polycavernous kidney TB)

Involvement of the ureter is common and frequently affects the lower third and ureteropelvic junction leading to obstructive uropathy.

Pathogenesis of Urinary Tuberculosis
Tonsil

Primary complex
(Ghon focus)

Lung
Regional
lymph node

Dormant

Gastrointestinal
tract

Active

Hematogenous
spread
Kidney
Bacilli trapped
in glomerular
capillaries

Thoracic
duct
Cortical
granuloma

Cortical granuloma
Cortical
granuloma

Active

Dormant

Rupture into
proximal
tubule

Bacilli trapped
in loop of Henle
Abscess

Medullary
granuloma
Ulcer

Rupture into
Bacilluria
collecting system
Spread into
contiguous structures
(submucosal/lymphatic)
Fig. 54.3 Pathogenesis of urinary tuberculosis.

Ureteric involvement leads to inflammation, edema, granulomatous ulceration, and fibrosis, leading to irregular ureteric strictures (Fig. 54.6A), segmental dilation (“corkscrew” ureter), or fibrosis resulting in a shortened and rigid ureter (“pipe-stem” ureter).

The bladder may develop hyperemia near the ureteral orifice, followed by superficial ulcers and granulomatous changes involving all layers (pancystitis). Healing by fibrosis at the ureteral orifice results in a refluxing “golf-hole” ureter. Extensive fibrosis of the bladder wall results in a thick, small-capacity bladder called a “thimble” bladder (see Fig. 54.6B). Bladder infection also may rarely result from instillation of BCG in the bladder as part of treatment of superficial bladder carcinomas. Rare complications of bladder TB include vesicovaginal, vesicocolic, and enterovesical fistulae and bladder perforation. TB of the bladder can be classified into four stages[10]:

✓•✓ Stage 1: infiltrative bladder TB (tubercles in bladder wall)
✓•✓ Stage 2: ulcerous bladder TB (erosion of bladder mucosa)
✓•✓ Stage 3: interstitial cystitis (painful bladder syndrome)
✓•✓ Stage 4: contracted bladder (obliteration)

Involvement of the genital tract is also common. Men with TB of the urinary tract have epididymitis, prostatitis, seminal vesiculitis, orchitis, cold abscesses, or discharging scrotal sinuses. In women, genital tract involvement is less common, but, if present, usually presents as salpingitis, often diagnosed during investigation for infertility.

A

B

Fig. 54.4 Kidney Tuberculosis (Cut Section). (A) Cut section of kidney shows areas of cavitation filled with white chalky material (caseation necrosis). (B) Cavitating lesions (arrows) caused by tuberculosis in cut section of kidney (autopsy). (Courtesy Department of Pathology, Amrita Institute of Medical Sciences, Kochi, Kerala, India.)

A

B

Fig. 54.5 Types of calcification. (A) Curvilinear pattern (orange arrow), amorphous and speckled pattern (blue arrow), ureteric calcification (yellow arrow). (B) Contrast-enhanced computed tomography image showing contracted densely calcified right kidney and normally functioning left side (density on right side was the same before and after contrast).

TB can be transmitted from the donor to recipient through kidney transplantation, and the risk can be minimized by thorough evaluation of the donor.11

CLINICAL MANIFESTATIONS

UG-TB can present at any age, but most patients are 20 to 40 years of age, with a male-to-female ratio of 2:1. It is relatively uncommon in children because of the long latency period. It may be asymptomatic and detected incidentally during investigations for other illnesses. Clinical presentation may include a range of manifestations (Table 54.2), but a high index of suspicion enables early diagnosis. Risk factors for TB include one or more of the following:

1. Close contact with sputum-positive individuals
2. Residence in an endemic area
3. Overcrowding/social deprivation/vagrancy
4. Immunosuppression (HIV/infection/diabetes mellitus)
5. CKD
6. Vitamin D deficiency
7. Malnutrition and other debilitating illnesses

Asymptomatic Presentation

In some countries, one-quarter of the population may have latent MTB.11 Almost 25% of patients have no clinical or laboratory evidence of any abnormality, and the diagnosis of urinary TB is made on investigation for other diseases, during surgery, or at autopsy. Another 25% may have asymptomatic urinary abnormalities, particularly pyuria or hematuria. Nonspecific constitutional symptoms like fever, weight loss, and night sweats are uncommon. UG-TB should be suspected when conventional urine cultures are repeatedly negative in spite of empiric antibiotic therapy for suspected UTI. The urine pH may be acidic with persistent pyuria and negative routine bacterial cultures (acid-sterile pyuria). Genital involvement in males may be with chronic epididymitis or prostatitis that does not resolve with standard antibiotics.11

C

C

F

A

B

Fig. 54.6 Ureteric and Bladder Changes. (A) Multiple ureteric strictures (arrows), caliectasis (C), and fuzzy calyx (F). (B) Cystogram showing irregular, small capacity bladder or “thimble bladder.”

TABLE 54.2

Clinical Features of Urinary

Features

Frequency (%)

Symptoms

Asymptomatic

25

Asymptomatic urinary abnormalities
Lower urinary tract symptoms (most common)

25

Male genital tract involvement

75

Female genital tract involvement
Constitutional symptoms

<5

Miscellaneous

—

Detected during autopsy, surgery, or investigations for other diseases
Persistent pyuria, microscopic abnormalities, hematuria
Frequency, urgency, dysuria, incontinence, nocturia,

suprapubic pain, perineal
pain
Epididymitis, hemospermia,
infertility, reduced semen
volume
Amenorrhea, infertility,
vaginal bleeding, pelvic pain
Fever, reduced appetite,
anorexia, weight loss, night
sweats
Urolithiasis, hypertension,
acute kidney injury, chronic
kidney disease, abdominal
colic, abdominal mass

Tuberculosis

40

<20

Lower Urinary Tract Symptoms

Of the patients who are symptomatic, lower urinary tract symptoms, such as frequency, urgency, dysuria, nocturia, frank pyuria, or hematuria, occur in more than 75% of patients. Increased urinary frequency is the earliest and most common symptom. Recurrent bouts of painless gross macroscopic hematuria should alert the clinician to the possible diagnosis of urinary TB, although glomerular diseases such as immunoglobulin A (IgA) nephropathy also should be considered. Macroscopic

hematuria in urinary TB is a result of bleeding from the ulcerating lesions, inflammation of the urothelium, or rupture of a blood vessel in the vicinity of a cavity. Episodes of frank pyuria also may be a manifestation of kidney TB and indicate either secondary bacterial infection or drainage of a caseous focus into the collecting system. In advanced disease, frequency and urgency of micturition related to reduced bladder capacity, incomplete emptying, increased susceptibility to infection, and secondary vesicoureteral reflux (VUR) may also occur.

Kidney Tuberculosis

Patients with kidney TB may be asymptomatic with only abnormal urinalysis. With advancing kidney TB, the clinical presentations are nonspecific symptoms and signs such as lower urinary symptoms, flank pain, colic, and hematuria. Long-standing kidney parenchymal involvement may result in tubular proteinuria, which is often in the subnephrotic range. The kidneys are of normal size and show diffuse interstitial nephritis, with noncaseating or caseating granulomas. MTB can be identified by molecular tests in nearly 75% of biopsy samples. The overall incidence of kidney failure reported in the literature is 24%. The mechanisms of kidney failure are12:

- Kidney parenchymal infection causing obliterative endarteritis
- Extensive dystrophic calcification
- Secondary kidney amyloidosis
- Multiple ureteric strictures with postobstructive atrophy
- Tubulointerstitial nephritis
- Destruction of kidney parenchyma by caseation

Nephrotic proteinuria occurs rarely, and it could be because of mesangioproliferative glomerulonephritis or serum amyloid A (SAA) protein–associated secondary amyloidosis. Chronic inflammation of the kidney pelvis can also lead to squamous metaplasia or carcinoma.

Ureteral Tuberculosis

Nonspecific manifestations like hematuria or abdominal colic occur because of ureteric obstruction associated with kidney stones, blood clots, or sloughed kidney papillae. Secondary infection with Escherichia coli is also common.

Genital Involvement

In males, the most common genital involvement is epididymitis, which manifests with scrotal discomfort, mass, or cold abscess or may be asymptomatic. When the cold abscess ruptures, a nonhealing posterior scrotal sinus discharging caseous material may form. Thickening of the vas deferens may result in a “beaded” texture. TB of the prostate may manifest with lower urinary tract symptoms and perineal pain. The prostate may be hard or boggy. Penile and urethral TB may manifest with strictures, fistulas, ulcers, or papulonecrotic skin lesions. Hemospermia, reduction of semen volume, and infertility are other manifestations of genital involvement. Direct spread of MTB to a sexual partner is also possible. Only 5% of females with kidney TB also have genital TB. The major manifestation of genital involvement in females is infertility resulting from adherent salpingitis. Secondary amenorrhea, vaginal bleeding, and pelvic pain caused by inflammation may occur.

A

Other Manifestations

Anemia is seen in less than 20% of patients with nonmiliary disease, but the frequency is higher in those with CKD stages 3 to 5. A few patients may develop nephrogenic diabetes insipidus or renal tubular acidosis. Hyporeninemic hypoaldosteronism may result from the tubulointerstitial injury secondary to obstructive uropathy.13 Hypertension is unusual in kidney TB, but intimal proliferation of vessels near inflamed areas may lead to segmental ischemia and renin release and hypertension.14 Relief of obstruction or removal of a nonfunctioning kidney causing hypertension may be necessary in rare instances. Constitutional symptoms, such as fever, weight loss, night sweats, fatigue, and anorexia, occur in less than 20% of patients and indicate active infection in other organs or secondary bacterial infection of the urinary tract. All patients who present with constitutional symptoms must be carefully examined to identify pulmonary, lymph node, or skeletal TB. The chest radiograph may show evidence of active or healed tuberculous lesions in more than half of cases. Rarely, hypercalcemia may be present because of increased synthesis of calcitriol in the granulomas.

PATHOLOGY

The pathologic process of urinary TB may take the form of a miliary, granulomatous, or ulcerocavernous lesion depending on the virulence of the organism and host response. In the miliary form, which is seen particularly in immunosuppressed individuals, the cortex is studded with yellowish white, hard, pinhead-sized nodules that on microscopy show several coalescent granulomas with central caseation. In early disease and in those with effective cell-mediated response, granulomas are seen in the kidney parenchyma, characterized by macrophages with engulfed bacilli, surrounded by epithelioid cells and Langhans giant cells (Fig. 54.7). Surrounding this, a cuff of lymphocytes and plasma cells are seen.15 Healing occurs by fibrosis and scarring. In the more common ulcerocavernous form, yellow nodules consisting of pinhead-sized caseous foci are often seen on the outer surface. On cut section, granulomas and ulcers in the kidney pyramid or medullary cavities may be seen. Larger cavities filled with amorphous, soft, chalk-like eosinophilic material (caseous material) communicating with the collecting system also may be seen (see Fig. 54.2A). Other gross findings include multiple ulcers in the infundibular region of the calyces, calyceal stenosis, caliectasis (see Fig. 54.6A), ulcers, or strictures of the ureter with hydronephrosis, pyonephrosis, subcapsular collections, and perinephric abscesses. The bladder may show ulcers or be grossly fibrotic and contracted. In advanced cases, extensive caseating necrosis, replacing the normal kidney architecture, may be seen,

B

Fig. 54.7 Histologic Changes. (A) Acid fast bacilli in tissue (Ziehl Neelsen stain; ×1000 magnification). (B) Needle biopsy of kidney showing granuloma formation (blue arrows) and multinucleated Langhans giant cells (white arrows). (A, Courtesy Dr. George Kubica, Centers for Disease Control and Prevention. B, Courtesy Department of Pathology, Medical College, Kottayam, India.)

which may undergo calcification. The presence of caseous necrosis or calcification suggests activity of the disease and is not to be taken as a sign of healing. Kidneys also may be enlarged from amyloidosis.

DIAGNOSIS

Early and accurate diagnosis of UG-TB is important for successful treatment outcomes, and a high index of suspicion is necessary. Elderly patients, as well as those exposed to or who have had infection in the past, immunocompromised individuals, and patients with TB elsewhere are at high risk. Although the gold standard for specific diagnosis of TB is by identifying MTB from a clinical sample, it may not be possible in all cases because of the paucibacillary nature of the disease. No single specific diagnostic test exists, and a range of microbiological, molecular, histopathologic, and imaging tests are available for the diagnosis.

Smear Microscopy

Microscopic examination of urine for acid-fast bacilli (AFB) using Ziehl-Neelsen (ZN) or auramine staining has been a first-line diagnostic test for UG-TB for the past 70 years. Bacterial load of 5000 organisms/mL is needed for positive smear and at least three early morning urine samples should be analyzed. Diagnostic yield from urine sample is only less than 40%. WHO recommends that conventional fluorescence microscopy may be replaced by light-emitting diode (LED) microscopy.16 Contamination of urine with environmental, nonpathogenic mycobacteria such as M. smegmatis may give false-positive results.

ureteroscopy, hysteroscopy, and laparoscopy) can be used for detecting anatomic abnormalities, localizing lesions, and obtaining biopsy tissue samples.

Urine Culture

Imaging

Culture of specimens for MTB is the gold standard for the diagnosis of active TB with a sensitivity of 65% and specificity of 100%. Traditional culture requires about 6 to 12 weeks for a result. The WHO has recommended automated liquid mycobacteria growth indicator tube (MGIT) culture as the gold standard where positive results can be available within 2 weeks.17 Because the organism is intermittently excreted, at least three, but preferably five, consecutive early morning specimens of urine should be cultured.

All imaging findings may be normal in patients with early UG-TB, and findings are based on the presence of cavities, strictures, or calcifications. Imaging of the urinary tract helps to;

1. Localize the site of disease
2. Assess the extent of tissue destruction
3. Monitor response to treatment
4. Identify complications
5. Guide the needle to target sites for procuring samples for histologic, microbiological, and molecular analyses.

Tuberculin Skin Test

TST or Mantoux test is done by administering intradermally 0.1 mL of PPD of MTB, and the extent of induration caused by the injection is read after 48 to 72 hours. The test can be positive in active TB infection, LTBI, and those who have received BCG vaccination. This test is now rarely used.

Polymerase Chain Reaction

The sensitivities and specificities of polymerase chain reaction (PCR) on urinary samples are nearly 95% and 90%, respectively. A real-time quantitative PCR assay for amplifying MTB DNA and the gene for rifampicin resistance (GeneXpert MTB/RIF) is commercially available and is recommended by WHO. It is a rapid, affordable, near-point-ofcare test for detecting MTB and rifampicin resistance simultaneously and can also be used for testing urine. An expanded new version called Xpert XDR allows for detection of resistance to isoniazid, injectable agents, and fluoroquinolones as well.18 GeneXpert MTB/RIF assays may give false-positive test results in treated patients because the MTB DNA lingers in tissues even after eradication of live mycobacteria. Novel, battery-operated, portable, single-module, near-patient/point-of-care versions of the GeneXpert system (GeneXpert Omni, GeneXpert Edge) are also available.

Whole-Blood Interferon-γ Release Assays

The test is based on quantifying the interferon (IFN)-γ released from the white blood cells that have been exposed to the mycobacterial antigens. Available as the QuantiFERON TB Gold and T Spot test, these assays can identify latent or active TB, replacing the traditional tuberculin test, and are reported to have a sensitivity and specificity of more than 90%.[19,20] They can be performed in a single patient visit and are not altered by prior BCG vaccination.

Urine Tuberculosis Lipoarabinomannan Assay

Lipoarabinomannan forms part of the cell wall glycolipid of MTB bacterium and can be detected in the urine of patients with active or disseminated infection with kidney involvement. This immunochromatographic assay is recommended by the WHO for the diagnosis of HIV-associated TB in people with CD4+ lymphocyte counts of less than 200 cells/µL. The usefulness of this assay for diagnosing UG-TB has not yet been evaluated.[21]

Histopathology

Conventional needle biopsies are usually not done for diagnosis of kidney TB. However, ultrasound-guided fine-needle aspiration/biopsy from the lesion is useful in defining the granulomatous nature of the lesion. Histologic diagnosis is made by identifying the pathologic triad of caseating necrosis, loose aggregates of epithelioid histiocytes, and Langhans giant cells. Endoscopic examination (cystourethroscopy,

Plain Radiographs

Plain radiographs of the chest may show abnormal changes caused by active TB or healed TB in up to 50% of patients with UG-TB.[22] In a plain radiograph of the abdomen, various types of calcification can be identified:

1. Amorphous, granular, or curvilinear calcification, within the kidney parenchyma: indicates early stages
2. Diffuse granular opacification or “cumulus cloud calcification”: often associated with active, granulomatous infection
3. Dense, punctate calcification: found in healed tuberculomas
4. Homogeneous, moderately dense, ground glass–like calcification: indicates calcified caseous tissue referred to as putty kidney
5. Triangular/ring-like calcifications: represents papillary necrosis
6. Lobar pattern with calcific rims outlining the periphery of distorted renal lobes: pathognomonic of TB.
7. Faint upper ureteral calcification along with any other kidney calcification: good marker of kidney TB.

Ultrasonography

In the early stages and in diffuse, infiltrative kidney TB, ultrasonography may appear normal. Granulomas are seen as small, hypoechoic intrarenal masses. In more extensive disease, changes similar to acute focal bacterial nephritis or chronic pyelonephritis may be seen. Large abscesses or tuberculomas distorting the kidney contour may be mistaken for tumors or cysts. Smaller parenchymal lesions, mucosal thickening, stenosis of the calyces, and ulcers can be identified by high-resolution ultrasonograms[23] (Fig. 54.8A–B). Various degrees of calcification, hydronephrosis, perinephric collections, bladder capacity, bladder emptying, and associated structural abnormalities in the genital tract can also be identified by ultrasonography.

Intravenous Urography

Intravenous urography (IVU) provides a simultaneous assessment of urinary tract anatomy and drainage. The important changes are:

1. Minimal calyceal dilation and loss of calyceal sharpness (early change) (see Fig. 54.6A)
2. Irregularity, fuzzy or feathery calyx (“moth-eaten” calyx)
3. Calyceal erosion and “phantom calyx”
4. Upward-pointing “hiked-up” pelvis
5. Kinking of the kidney pelvis (because of traction from a strictured infundibulum and parenchymal fibrosis): Kerr’s kink sign
6. Irregular ureter and areas of stricture and dilation: corkscrew ureter
7. Diffusely thickened ureters: pipestem ureter
8. Distal ureteric narrowing at ureterovesical junction

9. Small-capacity, thick-walled bladder with an elevated bladder base: thimble bladder (see Fig. 54.6B)

P
C

P

A

B

Fig. 54.8 High-Resolution Ultrasonography. (A) Sloughed, necrosed papilla (P) in the calyx. (B) Transverse ultrasound scan of kidney showing thickened mucosa (arrows) and calcification of calyces (C) and pelvis (P). There are calcifications of the wall of the calyx and pelvis (arrowheads). A parenchymal cavity (C) is also shown. (From Vijayaraghavan SB, Kandasamy SV, Arul M, et al. Spectrum of high resolution sonographic features of urinary tuberculosis. J Ultrasound Med. 2004;23[5]: 585–594.)

Computed Tomography Scan and Computed Tomography Urography

These imaging modalities are better than IVU and show abnormalities in greater detail. Computed tomography (CT) is a sensitive imaging modality to detect calcification, which is present in more than 50% of patients (see Fig. 54.5). Multidetector CT urography technology (MDCTU) using reformatted images such as multiplanar reconstruction and maximum intensity projection is replacing IVU for the assessment of kidney and urinary tract lesions.

Positron Emission Tomography–Computed Tomography Imaging

Positron emission tomography (PET) imaging using 2-deoxy-2-(fluorine-18)fluoro-d-glucose (18F-FDG) provides functional information about sites with active inflammatory and immune cells that use glucose during metabolism. Anatomic and functional information is obtained by acquiring 18F-FDG PET and CT data in a single scan. FDG PET-CT imaging does not help distinguish TB from cancer, thereby limiting its utility for specific diagnosis of UG-TB.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has a limited role because the sensitivity is low for detecting early lesions and abnormalities. For definitive diagnosis of tuberculosis, one major or two minor criteria are required.24

Major criteria include:

✓•✓ Granulomatous lesion in biopsy specimen
✓•✓ AFB in urine or tissue by smear or culture
✓•✓ Positive PCR

Minor criteria include:
IVU/CT findings suggestive of GU-TB
Hematuria
Raised erythrocyte sedimentation rate (ESR)
Pulmonary changes of old tuberculosis

LTBI is common and can become reactivated even decades later.

Currently, three tests are recommended by the WHO for detecting LTBI25:

1. Tuberculin skin test (TST)
2. QuantiFERON-TB Gold
3. T-SPOT TB

✓•✓
✓•✓

✓•✓
✓•✓

Differential Diagnosis

UG TB mimics numerous diseases. Chronic nonspecific urinary tract infections may be confused with kidney TB, especially because secondary bacterial infection may complicate 20% of cases of kidney TB. Absence of response to usual antibiotics should raise suspicion of urinary TB. Conditions causing recurrent painless hematuria, such as IgA nephropathy and schistosomiasis, are often misdiagnosed as TB in endemic areas. In interstitial cystitis, lower urinary tract symptoms similar to tuberculous cystitis may occur, but the urinalysis does not show gross pyuria, and cultures for AFB are negative.

On radiologic examination, chronic pyelonephritis, kidney papillary necrosis, medullary sponge kidney, calyceal diverticulum, renal carcinoma, xanthogranulomatous pyelonephritis, and multiple small kidney calculi need to be differentiated from TB. In a few reported cases of pseudotuberculous pyelonephritis, caseating granulomas resembling TB were observed in the kidney parenchyma, but no mycobacteria or other microorganisms were detected in the kidney tissue or urine culture.

MANAGEMENT OF UROGENITAL TUBERCULOSIS

The aims of management are to eradicate the infection, treat complications, and manage comorbidities/risk factors. The general precautions to prevent toxicity and adverse reactions in patients with CKD and dialysis are appropriate dose modification and administering drugs after hemodialysis.

Antituberculous drugs form the mainstay of treatment (Table 54.3).

The latest recommendation by the WHO for treatment of drugsensitive organisms is a 2-month intensive phase of quadruple therapy with first-line drugs (such as rifampicin, isoniazid, pyrazinamide, and ethambutol) daily, followed by a 4-month continuation phase of two drugs (rifampicin and isoniazid). The response in terms of resolution/ improvement of systemic urinary symptoms and kidney function is assessed at 8 weeks. In immunosuppressed individuals, the continuation phase is extended to a total of 9 months. As with pulmonary TB, this regimen gives a cure rate of 90%.

In the case of drug-resistant UG-TB, there are scarce data and no clinical trials. As recommended by WHO for MDR pulmonary tuberculosis, an intensive 4- to 6-month course of therapy monitored by an experienced TB physician is necessary. The drug combinations may include five to six drugs initially as follows: gatifloxacin/moxifloxacin, ethionamide/prothionamide, kanamycin/amikacin, high-dose clofazimine/isoniazid with ethambutol, and pyrazinamide. This is followed by a 5-month continuation phase of clofazimine, ethambutol, pyrazinamide, and gatifloxacin or moxifloxacin.[26]

In situations where the incidence of TB is high, LTBI is treated with isoniazid monotherapy for 6 months or rifampicin plus isoniazid daily for 3 months or rifapentine and isoniazid weekly for 3 months. In areas with lower incidence and for prevention, 6 to 9 months of isoniazid monotherapy or weekly rifapentine plus isoniazid for 3 months or rifampicin with or without isoniazid for 3 months is recommended.

Newer drugs and repurposed drugs are used in MDR TB and XDR TB. Some drugs are still being examined in clinical trials (Table 54.4).

Surgical Treatment of Urogenital Tuberculosis

Surgical treatment as an adjunct to drugs is required in patients during or after TB drug therapy. Surgery is required for the following clinical settings:

1. Drainage for obstructed pelvicalyceal system
2. Drainage of abscesses
3. Reconstruction of ureters
   - ✓ •✓ Ureterocalicostomy
   - ✓ •✓ Reimplantation of ureters
   - ✓ •✓ Ileal replacement of ureter
4. Reconstructive surgery of the bladder (bladder augmentation)
5. Nephrectomy

Treatment Regimens in Special Situations

should be closely monitored. In those with acute hepatitis unrelated to TB or its therapy, it would be safer to defer chemotherapy until the acute hepatitis has resolved. If immediate treatment of TB during acute hepatitis is mandatory, streptomycin plus ethambutol for 3 months followed by isoniazid and rifampin for 6 months is advised. Excessive alcohol consumption should be avoided.

Patients With Chronic Kidney Disease

Because streptomycin and ethambutol are excreted by the kidney, dosage modification of these drugs is necessary when GFR is less than 60 mL/min/1.73 m^2. For ethambutol, the full dose is administered every 24 to 36 hours if GFR is 10 to 50 mL/min/1.73 m^2 and every

48 hours if GFR is less than 10 mL/min/1.73 m2. Monthly questioning for symptoms of visual dysfunction (alterations in visual fields, acuity, blue-green vision) and periodic ophthalmic examination may identify early ethambutol toxicity, at the stage of potential reversibility. Streptomycin is used only rarely now because of ototoxicity. It is avoided in older individuals, and the dose is 15 mg/kg every 48 to 72 hours if GFR is 10 to 50 mL/min/1.73 m2 and every 72 to 96 hours if GFR is less than 10 mL/min/1.73 m2. In patients with CKD, isoniazid, rifampin, and pyrazinamide, which are eliminated by the biliary route, can be given in normal dosages. In patients on dialysis, it is ideal to administer these drugs under supervision after each dialysis session.

Kidney Allograft Recipients

No clear-cut recommendations exist for GU-TB in native kidneys after transplantation. It is preferable to complete at least 6 weeks of therapy for all types of TB and reassessment before considering transplantation. Ideally, the patient could be considered for kidney transplantation after 6 months of treatment. Rifampin is avoided in patients receiving a calcineurin inhibitor (CNI) because enzyme induction may make maintenance of adequate CNI blood levels difficult. For patients with a kidney allograft, a suitable treatment regimen is with isoniazid and ethambutol for 18 months (with dose adjusted for GFR), combined with ofloxacin 200 mg twice daily for the first 9 months and pyrazinamide 750 mg twice daily for the first 3 months.[27] If rifampin is used in those receiving a non–CNI-based immunosuppressive regimen, the maintenance dose of prednisolone should be doubled.

Human Immunodeficiency Virus and Tuberculosis

In patients with HIV who are already on antiretroviral treatment (ART), conventional 6-month treatment with 4 drugs for the first 2 months followed by 2 drugs for the remaining 4 months is sufficient. In patients with HIV infection who are not on ART, antituberculous drugs are continued for 9 months. If HIV and TB are diagnosed simultaneously, antituberculous drugs are started first, followed by ART after 15 days if the CD4 count is less than 50 cells/μL and after 30 days if the CD4 cell count is less than 100 cells/μL.

Women During Pregnancy and Lactation

Patients Who Do Not Respond to Treatment

Most antituberculous drugs are safe for use during pregnancy and lactation. However, streptomycin is ototoxic to the fetus and should be avoided. It is not necessary to isolate the baby from the mother unless the mother has active pulmonary tuberculosis. The baby should receive BCG immunization and isoniazid prophylaxis. Rifampin reduces the efficacy of oral contraceptives, and females should be advised to use alternative methods of contraception.

Failure of clinical or radiologic improvement with treatment may signify poor compliance, inadequate regimen and/or dosage, incorrect diagnosis, delayed response, MDR TB, XDR TB, or the paradoxical reaction known as immune reconstitution inflammatory syndrome. This syndrome is characterized by unexpected worsening of symptoms or appearance of new lesions, including lymphadenopathy, serosal effusions, and pleural infiltrates. This syndrome is more common in those receiving ART for coexisting HIV and TB infections.[28]

Patients With Liver Disease

In chronic liver disease, pyrazinamide is contraindicated. Isoniazid and two of the nonhepatotoxic drugs (streptomycin and ethambutol) can be used for 8 to 12 months. If rifampin is used, liver function

Newer Therapies

The recent introduction of two new drugs, bedaquiline and delamanid, for rifampicin-resistant tuberculosis and ongoing studies on

TABLE 54.3

Antituberculous Drugs: Dosage, Actions, and Side Effects a
Dose
Modification
GFR (50–10
mL/min)

Dose
Modification
GFR (<10
mL/min)

Drug

Dose
Form

Dosage

Mode of Action

Side Effects

Remarks

Isoniazid
(INH)b

Tablet: 100,
300 mg

PO: 5 mg/kg/
day (max 300
mg/day)

Bactericidal for groups I and II Nil
Interferes with mycolic acid
synthesis

66%

Hypersensitivity
Peripheral neuritis
Hepatitis

Administer
pyridoxine 50 mg/
day

Rifampin
(rifampicin)b

Tablet/
capsule:
150, 300,
450 mg

PO: 10 mg/kg/
day (max 600

mg/day)

Bactericidal for groups I, II,
Nil
and III
Interferes with protein
synthesis by inhibiting RNA
polymerase

Nil

Febrile reactions
Acute interstitial
nephritis
Hepatitis

Dose adjustment when
using calcineurin
inhibitors or oral
contraceptives
May be used in
pregnancy and
lactation

Pyrazinamideb

Tablet: 400,
500 mg

PO: 25 mg/kg/ Bactericidal for semidormant
day (max: 2 g/ Mycoplasma tuberculosis
day)

Nil

50%c

Hyperuricemia
Hepatotoxicity
Photosensitivity

Primary hepatic
metabolism
Monitor liver functions
and uric acid

Ethambutol

Tablet: 100,
400 mg

PO: 15–25 mg/ Bacteriostatic
kg (max 2.5 g/ Bactericidal in high
day)
concentrations
Inhibits cell wall synthesis

75%c

Avoid or 50%c

Optic neuritis
Primarily renal
(monitor for color

excretion
vision)
May be used during
pregnancy and
lactation

Streptomycin

Injection: 1,
0.75 g

IM: 15–25 mg/ Bactericidal
kg/day (max Inhibit protein synthesis
1 g)
Age >60 y: 75%
dose

50%c

25%c

Ototoxicity
Vestibulotoxicity
Hypokalemia
Hypomagnesemia

Therapeutic drug
monitoring advised
Peak level for
efficacy
Trough level for
toxicity

Amikacin

IM/IV:
ampoules,
500, 1000
mg

15 mg/kg/day
Bactericidal
(max 1 g/day) Inhibit protein synthesis

50%c

25%c

Ototoxicity
Vestibulotoxicity
Hypokalemia
Hypomagnesemia

Cleared by
hemodialysis
Supplement dose
after HD or give
regular full dose
after dialysis
Avoid
coadministration of
loop diuretics
TDM recommended

Levofloxacin

PO: tablet,
750–1000 mg/
250, 500,
day
750 mg
IV: ampoules,
500–750
mg

Bactericidal
Inhibit protein synthesis—
DNA gyrase

50%c (500–
750 mg q36h)

25%c (250–
500 mg q48h)

Severe upper GI
symptoms
Prolonged QTc
Arthralgia
Tendon rupture

Hepatic and renal
elimination
Used in liver disease
More effective than
ciprofloxacin and
ofloxacin

Moxifloxacin

PO: Tablet,
400 mg
IV: infusion,
400 mg in
100 mL

400 mg/day

Bactericidal

Nil

Nil

Severe upper GI
symptoms
Prolonged QTc
Arthralgia
Tendon rupture

Not removed by HD

Capreomycin

IM/IV: 1-g
vial

15 g/kg/day

Strongly bactericidal
(max 1 g/day) Inhibits protein synthesis
on 5–7 days/
wk

75%

25%c

Nephrotoxicity
Ototoxicity
Hypokalemia
Hypomagnesemia
Hepatotoxicity
when combined
with other
anti-TB drugs

Used only for MDR
TB

TABLE 54.3

Antituberculous Drugs: Dosage, Actions, and Side Effects a—cont’d
Dose
Modification
GFR (50–10
mL/min)

Drug

Dose
Form

Dosage

Mode of Action

Ethionamide

PO

15–25 mg/
kg/day (max
1 g/day in
2 divided
doses)

Weakly bactericidal
Nil
Blocks mycolic acid synthesis

Cycloserine

PO

15–25 mg/kg/
day

Bacteriostatic

50%c

Dose
Modification
GFR (<10
mL/min)

Side Effects

Remarks

50%

Hepatotoxic
Severe GI
symptoms
Hypothyroidism
Gynecomastia

Not to be combined

with cycloserine

25%[c]

Neurotoxicity
Seizures
Peripheral
neuropathy

Maintain peak level
<35 µg/mL
Cleared by dialysis
Avoid in pregnancy
and lactation

[a]The

main drugs are listed with dosage form, dosage, mode of action, side effects,
and dose modifications in those with low glomerular filtration rate.
M. tuberculosis exists as three subpopulations. Group I is extracellular, occurs
mainly in cavitating lesions, and responds to streptomycin, isoniazid,
and rifampin. Group II resides intracellularly in macrophages, replicates
slowly, and responds to pyrazinamide, isoniazid, or rifampin. Group III
organisms exist within closed caseous lesions, survive better in neutral pH,
replicate slowly, and respond best to rifampin.
[b]Prescribed dose to be given after hemodialysis.
[c]Dose reduction and/or increasing dosing intervals.
GFR, Glomerular filtration rate; GI, gastrointestinal; HD, hemodialysis; IM,
intramuscular; IV, intravenous; MDR TB, multidrug-resistant TB; PO, orally,
QTc, corrected QT interval on electrocardiogram; TB, tuberculosis; TDM,
therapeutic drug monitoring.

TABLE 54.4
Name of
Drug

Newer Drugs: Clinical Pharmacology

Class/Mechanism of Action

Dose/Route of
Administration

Side Effects

Remarks

Bedaquiline

Diarylquinoline
Inhibits mycobacterial ATP synthase
Core drug in rifampicin resistant tuberculosis
All-oral regimen
Capable of killing both actively replicating
and nonreplicating persistent mycobacteria
in cells

Oral/400 mg once daily QT prolongation
for 2 wk, followed by
Hepatitis
200 mg three times/wk GI toxicity
for 24 wk (total 26 wk)

Recommended by WHO for treatment

of MDR TB
May be used in pregnancy

Delamanid

Nitrodihydroimidazooxazole
Inhibits mycolic acid synthesis

Oral/100 mg twice daily
for 24 wk

QT prolongation
GI toxicity

Recommended by WHO
Drug of choice for children <6 y with
rifampicin-resistant tuberculosis
Avoid in pregnancy

Pretomanid

Nitroimidazole

Oral 200 mg once daily

Peripheral neuropathy (81%)
Headache (28%)
Skin rash (21%)

Experimental
No human trials yet

Clofazimine

Active against inactive nonreplicating
mycobacterium

Oral 100–200 mg once
daily

Red discoloration of skin,
eyes, body fluids
Photosensitivity
GI toxicity

Avoid in pregnancy

Linezolid/
sutezolid

Oxazolidinone/antibiotic

Oral or IV 600 mg once
daily or 1200 mg once
daily for 14 d

Myelosuppression
GI toxicity
Optic neuritis
Peripheral neuropathy

Avoid in pregnancy

Telacebec

Imidazopyridine (IPA) compound
Oral
Mycobacterial respiratory chain inhibitor
Targets MTB cellular energy production by inhibiting (with high specificity) cytochrome bc1 complex

—

Completed phase II trial

Delpazolid

Oxazolidinone
Inhibits protein synthesis
Binding to domain V of rRNA

Ongoing phase II trials

GI, Gastrointestinal; MDR TB, multidrug-resistant tuberculosis; MTB, Mycobacterium tuberculosis; WHO, World Health Organization.

rifapentine, clofazimine, and pretomanid may alter the treatment landscape in the future (see Table 54.4).29 There is growing interest in the use of repurposed drugs such as linezolid and clofazimine. The second novel drug, delamanid, is recommended by WHO as the drug of choice for treating children younger than 6 years with rifampicinresistant TB.30

A single interstitial injection of autologous bone marrow–derived mesenchymal stem cells (MSCs) into the bladder showed considerable reduction of inflammation as well as a reduction in the development of fibrosis and bladder wall deformity in animal models.31

SELF-ASSESSMENT QUESTIONS

1. All of the following are features of immune reconstitution inflammatory syndrome (IRIS) except:
A. Development of new lesions
B. Worsening of symptoms
C. Severity inversely proportional to the load of organisms
D. Common in MDR TB
E. Common in patients with simultaneous treatment of coexisting HIV infection
2. The following antituberculous drugs act as bactericidal agents when used in therapeutic does except:
A. Rifampicin
B. Isoniazid
C. Amikacin
D. Ethambutol
E. Pyrazinamide
3. The following symptoms point to suspicion of kidney tuberculosis except:
A. Recurrent painless macroscopic hematuria
B. Acid, sterile pyuria
C. Sterility in women/epididymitis in men
D. Lack of constitutional symptoms
E. Icterus
4. Which of the following antituberculous drug combinations require dose modifications in patients with kidney failure?
A. Isoniazid and rifampin
B. Streptomycin and ethambutol
C. Pyrazinamide and rifampin
D. Isoniazid and pyrazinamide
5. Which drug is uniformly effective against all three groups of Mycobacterium tuberculosis—group I (extracellular), group II (intracellular), and group III (closed caseous lesions)?
A. Isoniazid
B. Rifampicin
C. Pyrazinamide
D. Ethambutol
E. Streptomycin

REFERENCES

1. World Health Organization (WHO). The Top 10 Causes of Death; 2019. https://www. who.int/news-room/fact-sheets/detail/the-top10-causes-of-death.
2. WHO. Global Tuberculosis Report 2018; 2018. https://www. who.int/tb/ publications/global_report/en/.
3. WHO. Tuberculosis Report. Geneva: WHO; 2016.
4. John GT. Infections after renal transplantation in India. Indian J Nephrol. 2013;13:14.
5. Gulati S, Kher V, Gulati K, Arora P. Tuberculosis in childhood nephrotic syndrome in India. Pediatr Nephrol. 1977;11:695–698.
6. Furin J, Cox H, Pai M. Tuberculosis. Lancet. 2019;393(10181):1642–1656.
7. Kulchavenya E, Naber K, Bjerklund Johansen TE. Urogenital tuberculosis: classification, diagnosis, and treatment. Eur Urol. 2016;15:112–121.
8. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989;370:546–547.
9. Simmons JD, Stein CM, Seshadri C, et al. Immunological mechanisms of human resistance to persistent mycobacterium tuberculosis infection. Nat Rev Immunol. 2018;18:575–589.
10. Kulchavenya EV, Shevchenko SY, Cherednichenko AG. Diagnosis and treatment of cystitis: more questions than answers? Urologiia. 2016;5:37–42.
11. Mourad G, Soullilon IP, Chong G, et al. Transmission of mycobacterium TB with renal allografts. Nephron. 1985;41:82–85.
12. Oliverira JL, Silva Junior GB, Daher EF. Tuberculosis associated chronic kidney disease. Am J Trop Med Hyg. 2011;84:843–844.
13. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int. 1980;17:118–134.
14. Marks LS, Poutasse EF. Hypertension from renal tuberculosis: operative cure predicted by renal vein rennin. J Urol. 1973;109:149–152.
15. Kulchavenya E, Kholtobin D, Shevchenko S. Challenges in urogenital tuberculosis. World J Urol. 2019.
16. Pang Y, et al. GeneXpert MTB/RIF assay in the diagnosis of urinary tuberculosis from urine specimens. Sci Rep. 2017;7:6181.
17. Walzl G, et al. Tuberculosis: advances and challenges in development of new diagnostics and biomarkers. Lancet Infect Dis. 2018;18:e199–e210.
18. WHO. The Use of Next-Generation Sequencing Technologies for the Detection of Mutations Associated with Drug Resistance in Mycobacterium Tuberculosis Complex: Technical Guide; 2018. https://apps.who.int/ iris/bitstream/ handle/10665/274443/WHO-CDS-TB- 2018.19-eng.pdf.

19. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection – United States, 2010. MMWR Recomm Rep. 2010;59(RRO5):1–25.
20. Pai M, Gokhale K, Joshi R, et al. Mycobacterium tuberculosis infection in health workers in rural India: comparison of whole blood interferon gamma assays with tuberculin skin testing. JAMA. 2005;293:2746–2755.
21. Xie Y, Chakrovarty D, Armstrong S, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. N Engl J Med. 2017;377:1043–1054.
22. WHO. The Use of the Lateral Flow Urine Lipoarabinomannan Assay (Lf-Lam) for the Diagnosis and Screening of Active Tuberculosis in People Living with HIV; 2015. http://apps.who.int/iris/bitstream/ handle/10665/193633/9789241509633_eng.pdf ?sequence=1.
23. Vijayaraghavan SB, Kandasamy SV, Arul M, et al. Spectrum of high resolution sonographic features of urinary tuberculosis. J Ultrasound Med. 2004:585–594.
24. Merchant S, Bharati A, Merchant N. Tuberculosis of the uro-genital system — urinary tract tuberculosis: renal tuberculosis. II. Indian J. Radiol. Imaging. 2013;23:64–77.
25. Martin C, Castaigne C, Vierasu I, et al. Prospective serial FDG PET/ CT during treatment of extrapulmonary tuberculosis in HIV-infected patients: an exploratory study. Clin Nucl Med. 2018;43:635–640.

26. Banyal S, Malik P, Tuli HS, Mukherjee TK. Advances in Nanotechnology for diagnosis and treatment of tuberculosis. Curr Opin Pulm Med. 2013;19(3):289–297.
27. Sundaram M, Adhikary SD, John GT, Kekre NS. Tuberculosis in renal transplant recipient. Indian J Urol. 2008;24:396–400.
28. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV- infected patients receiving antituberculosis and antiretroviral therapy. J Infect. 2006;53:357–363.
29. WHO. Latent TB Infection: Updated and Consolidated Guidelines for Programmatic Management; 2018. WHO www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/.
30. Liu C, et al. Quantification of circulating mycobacterium tuberculosis antigen peptides allows rapid diagnosis of active disease and treatment monitoring. Proc Natl Acad Sci USA. 2017;114:3969–3974.
31. Muneer A, Macrae B. Sriram Krishnamoorthy & Alimuddin Zumla Urogenital tuberculosis — epidemiology, pathogenesis and clinical features. Nat Rev Urol. 2019;16:573–598.

55

Fungal Infections of the Urinary Tract

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Funguria is a frequent finding in hospitalized patients. The organisms found in urine are almost always Candida spp., although several other yeasts and, less often, molds and endemic fungi, can be found (Table 55.1). Candiduria is not a symptom, a sign, or a disease, but frequently it is a perplexing phenomenon for the physician to address. Most patients with candiduria are asymptomatic and have colonization of the bladder or an indwelling urinary catheter. The most difficult diagnostic problem is determining when infection, rather than colonization, is present. Diagnostic tests to define colonization or infection have not been standardized, and neither have studies to localize the site of infection to either the bladder or the kidneys. In contrast to the situation with candiduria, growth in urine of organisms such as Blastomyces dermatitidis, Aspergillus spp., and Cryptococcus neoformans almost always reflects disseminated infection. This chapter outlines an approach to the diagnosis and treatment of candiduria and other less common fungal urinary tract infections (UTIs).

CANDIDA

Epidemiology

Candida spp. are common inhabitants of the perineum but are not found in urine in appreciable numbers in healthy hosts. A variety of predisposing factors allow these commensals microorganism to grow in the urine and in some cases to cause infection of the bladder or the upper urinary tract. These factors are frequently encountered in hospitalized patients, especially those in the intensive care unit (ICU).1 In a cross-sectional survey of positive urine cultures obtained from hospitalized patients, Candida spp. were found in almost 10% of specimens and were the third most common microorganism isolated from urine.2

Risk factors for candiduria, but not specifically for Candida UTI, include increased age, female sex, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus3,4 (Table 55.2). In a large surveillance study, urinary drainage devices, mostly indwelling urethral catheters, were present in 83% of 861 patients who had candiduria.3 In a multicenter study of patients in an ICU, independent risk factors associated with candiduria were older than 65 years, female sex, diabetes mellitus, prior antibiotic use, mechanical ventilation, parenteral nutrition, and length of hospital stay before ICU admission.4 Candiduria uncommonly leads to candidemia, confirming that most often candiduria reflects colonization, not infection.3 When candiduria is found in patients with candidemia, the strains often have been shown to be unrelated by molecular techniques.5 Prospective controlled studies assessing risk factors for well-documented Candida UTI have not been performed because firm diagnostic criteria specifically for infection have not been established. However, clinical experience suggests that UTI is more common in diabetic patients and in those with urinary tract obstruction.

Pathogenesis

Candida can cause urinary tract disease by either the hematogenous or the ascending route. The pathogenesis of hematogenous seeding of Candida to the kidney has been studied with animal models.6 Multiple microabscesses develop throughout the cortex, with the yeasts penetrating through the glomeruli into the proximal tubules, where they are shed into the urine (Fig. 55.1). Healthy animals eventually clear the infection, but immunocompromised animals do not. Consistent with these studies, kidney microabscesses have been identified at autopsy in many patients with candidemia or invasive candidiasis. For ascending infection with Candida, obstruction is an important factor in many patients. Virulence factors that control adherence and biofilm formation are likely important.6,7

A unique syndrome seen early after kidney transplantation is graft site candidiasis, which appears to result from contamination of the donor kidney during the harvest procedure.8 Arteritis with aneurysm formation and rupture can result from direct fungal invasion into the arterial wall. Most patients lose the graft, and mortality is high.

Microbiology

C. albicans accounts for 50% to 70% of all Candida urinary isolates, and C. glabrata for about 20% of isolates.3 Candida tropicalis and Candida parapsilosis are less common, and other species are rarely isolated. Certain populations of patients have a predominance of C. glabrata isolated from cultures of urine; these include older adults, those who have diabetes, kidney transplant recipients, and persons who have had prior exposure to fluconazole. To prescribe appropriate treatment it is important to know the species causing candiduria. Resistance to fluconazole, the primary agent used for the treatment of Candida UTI, is common among isolates of C. glabrata and in all isolates of Candida krusei. In contrast, almost all isolates of C. albicans, C. tropicalis, and C. parapsilosis are susceptible to fluconazole.

Clinical Manifestations

Most patients with candiduria are asymptomatic, and, indeed, most do not have infection. A large prospective surveillance study of patients with candiduria noted that less than 5% of patients with candiduria had any symptoms suggesting UTI.3 When patients have symptomatic cystitis or pyelonephritis, symptoms are indistinguishable from those noted with bacterial infections. Cystitis is manifested by dysuria, frequency, urgency, and suprapubic discomfort; patients with upper tract infection can present with fever, chills, and flank pain. Urinary tract obstruction can occur from formation of a bezoar or fungal ball in the bladder or the collecting system.

Patients who have had seeding of the kidney parenchyma during an episode of candidemia manifest the symptoms associated with invasive candidiasis, such as chills, fever, and hypotension, and not symptoms suggesting UTI.

TABLE 55.1

Infections

Fungal Genitourinary Tract

Fungal Infection	Prostate	Bladder	Kidney
Candidiasis	++	++++	++++
Cryptococcosis	++	+/−	+++
Blastomycosis	+++	+	++
Histoplasmosis	+	+/−	++
Coccidioidomycosis	+	+/−	++
Aspergillosis	+/−	+/−	++
Mucormycosis	+/−	+/−	++

Shown is the relative frequency of the site of infection for various fungal organisms.

TABLE 55.2

Risk Factors for Candiduria

Type	Risk Factors
A Kidney (hematogenous)	Neutropenia, recent surgery, central venous catheter,

parenteral nutrition, antibiotics, dialysis
Lower urinary tract
Indwelling bladder catheter, older age, female, diabetes, obstruction, antibiotics, urinary tract instrumentation
Upper urinary tract
Older age, diabetes, antibiotics, obstruction, urinary tract instrumentation (e.g., nephrostomy tube, ureteral stent)

B

Diagnosis

Major diagnostic difficulties are encountered in trying to differentiate contamination of a urine specimen from colonization of the bladder or an indwelling urethral catheter from invasive infection of the bladder or kidney. Contamination is most easily differentiated by simply repeating the urine culture a day later to determine whether candiduria persists. It may be necessary to obtain the second urine specimen by sterile bladder catheterization if the patient is unable to accomplish a clean-catch collection. In those patients who have an indwelling urethral catheter, the catheter should be replaced and a second urine specimen collected the next day. For either of these circumstances, if the repeated culture yields no yeasts, no further diagnostic studies or therapeutic interventions are needed.

Distinguishing colonization from infection is not straightforward. Compared with bacterial UTIs, in which the diagnosis is based on appropriate symptoms combined with the findings of pyuria and quantitative bacterial counts, no studies have established the importance of quantitative urine cultures or pyuria for the diagnosis of Candida UTI.

The role of quantitative urine cultures to differentiate upper tract infection from bladder colonization was assessed by investigators in the 1970s and unfortunately showed broad ranges of colony counts for both colonization and infection.9 In patients who did not have indwelling catheters, documented kidney infection was found with colony counts as low as 104 yeast colony-forming units per milliliter (cfu/mL). For patients who had indwelling catheters, colony counts between 2 × 104 and 105 cfu/mL or more were noted and there was no correlation with biopsy-proven kidney infection.

The techniques routinely used in most clinical laboratories for the detection of bacteria will also detect Candida in urine. However, C. glabrata grows more slowly than other species, and colonies may not appear for 48 hours, which is often after routine cultures of urine have been discarded. Laboratories should be notified if C. glabrata is a likely pathogen.

Fig. 55.1 Hematogenous Candidiasis Involving the Kidney. (A) Multiple small abscesses are seen throughout the kidney. (B) Histopathologic demonstration of a microabscess caused by Candida albicans in the cortex of the kidney (methenamine silver stain; yeast shown in graybrown; magnification ×100).

Pyuria is often not a helpful diagnostic criterion for infection in patients with candiduria. Concomitant bacteriuria, frequently noted in patients with candiduria, may be responsible for pyuria, and when an indwelling bladder catheter is present, pyuria is routinely noted. In patients who do not have an indwelling bladder catheter or bacteriuria, the presence of pyuria is helpful.

Imaging procedures, including abdominal ultrasound and computed tomography (CT), are essential to document obstruction at any level in the urinary tract and to determine the presence of fungus balls in bladder or kidney (Fig. 55.2). In some patients, it is helpful to perform cystoscopy and biopsy of the bladder wall to determine whether inflammation is present and evaluate the extent of invasion (Fig. 55.3).

Treatment With Systemic Antifungal Agents

Most patients who have candiduria do not need treatment with an antifungal agent. For patients who are asymptomatic, treatment should be given only to those who are at high risk for development of candidemia or in whom the presence of candiduria, regardless of symptoms, is likely to represent disseminated infection. The guidelines for the management of candidiasis published by the Infectious Diseases Society of America recommend treatment for patients about to undergo urologic procedures, infants with very low birth weight, and neutropenic patients10 (Table 55.3). Patients who have candiduria and who are to undergo a urologic procedure are at increased risk for development of candidemia and should be treated with an antifungal agent a few days before and after the procedure. Candiduria in

Fig. 55.2 Fungus Balls in the Pelvis of the Kidney. Several fungus balls (dark round “holes” in the contrast dye) are seen in the ureter and pelvis of the right kidney, causing hydronephrosis.

Fig. 55.3 Candida Cystitis. Cystoscopic appearance of extensive cystitis caused by Candida krusei.

neutropenic patients and in infants with very low birth weight has a high probability of representing disseminated candidiasis; thus these groups should be treated with an antifungal drug. Asymptomatic candiduria in the kidney transplant patient does not warrant systemic antifungal treatment unless obstruction is present; a urologic procedure, including stent removal, is planned; or symptoms suggestive of local or systemic infection develop.[10,11]

In non–high-risk patients who have asymptomatic candiduria, removal of an indwelling urinary catheter will eradicate candiduria in many patients.[3] If catheterization cannot be discontinued, the existing catheter should be removed and a new one inserted. This will often eradicate candiduria transiently, but it is highly likely that the organisms will return within a short time. It is not known if a suprapubic catheter is less likely to be colonized than an indwelling urethral catheter. Relief of obstruction, whether it is present in the upper or lower urinary tract, is essential for the long-term eradication of Candida from the urinary tract.

Patients who have symptoms suggestive of cystitis or pyelonephritis, and in whom bacteria and Candida are found in the urine culture specimen, should be treated initially with an antibacterial agent. If no bacteria are present, treatment with an antifungal drug is appropriate. Eradication of the organism with antifungal therapy is more likely if the indwelling catheter is removed.[12] Oral fluconazole, which is an azole antifungal agent and is excreted as active drug in the urine, is the agent of choice (see Table 55.3). A loading dose of 400 mg should be given, followed by 200 mg daily for 14 days.[10,13] Fluconazole does not effectively treat C. krusei infections, and many C. glabrata infections also do not respond to fluconazole.

The possibility of drug-drug interactions should be evaluated before fluconazole is prescribed. Phenytoin, warfarin, cyclosporine, tacrolimus, and sulfonylurea agents are a few of the drugs for which serum concentrations will increase and may reach toxic levels after the addition of fluconazole. Azoles should be used with caution in patients taking drugs that prolong the QTc interval.

The other available azole agents, itraconazole, voriconazole, posaconazole, and isavuconazole, are not excreted into the urine as active drug. Whether tissue concentrations might be high enough to treat invasive kidney or bladder infections is not known, but there is little clinical experience to suggest that they will be effective.

Intravenous (IV) amphotericin B deoxycholate is effective in treating Candida UTI but should be reserved for patients who have upper tract infection or for whom fluconazole therapy has failed, which will be predominantly those who have C. glabrata infection. Because of its inherent nephrotoxicity, IV amphotericin B deoxycholate must be used judiciously in patients who have kidney dysfunction. The recommended dosage is 0.3 to 0.6 mg/kg/day for 1 to 7 days, although this may be extended to 2 weeks for those who have complicated upper tract infection.[10] The dose used depends on kidney function and number of days infusions will be given; for example, some clinicians have had success with 0.3 mg/kg/day for 3 days, whereas others use a single dose of 0.6 mg/kg.[13] Infusion-related side effects are seen in some patients, even when low doses are used, and can include rigors, fever, nausea, vomiting, and headache.

TABLE 55.3

Treatment Recommendations for Candiduria and Candida Urinary Tract Infections

Infection

Treatment

Other/Alternative Therapy

Asymptomatic
candiduria

Urologic surgery

Treat a few days before and after the procedure with fluconazole 200–400 mg/day
POor
amphotericin B deoxycholate 0.3–0.6 mg/kg/day IV
Treat as for disseminated candidiasis/candidemia with fluconazole 12 mg/kg/day
Treat as for disseminated candidiasis/candidemia with an echinocandin

Low-birthweight infant
Neutropenic patient
Cystitis

Preferred: fluconazole 200 mg/day PO × 14 days[a]

Alternatives include amphotericin B deoxycholate 0.3–0.6 mg/kg/day IV × 1–7 days
or
flucytosine 25 mg/kg q6h PO × 7–10 days[b]

Pyelonephritis

Preferred: fluconazole 200–400 mg/day PO × 14
days

Alternatives include amphotericin B deoxycholate 0.3–0.6 mg/kg/day IV × 1–7 days
with or
without flucytosine 25 mg/kg q6h PO or flucytosine 25 mg/kg q6h PO × 14 days

Kidney
(hematogenous)

Treat as for disseminated candidiasis/candidemia —
with an echinocandin or fluconazole

Fungus balls

Surgical removal plus fluconazole 200–400 mg/
day PO until resolved

Alternatives include surgical removal plus amphotericin B deoxycholate 0.3–0.6
mg/kg/day
IV with/without flucytosine 25 mg/kg q6h PO
Irrigation through nephrostomy tube with amphotericin B deoxycholate 25–50 mg in
200–500 mL sterile water

Prostatitis
Surgical drainage plus fluconazole 400 mg/day PO Alternatives include surgical
drainage plus amphotericin B deoxycholate 0.3–0.6 mg/kg/day IV

Epididymo-orchitis
until resolution noted on imaging studies
aFluconazole

dosage in kidney failure: creatinine clearance (CrCl) 20 to 50 mL/min, reduce dose by 50%; CrCl <20 mL/min, reduce dose by 75%.
dosage in kidney failure: CrCl 20 to 40 mL/min, reduce dose to 25 mg/kg q12h; CrCl <20 mL/min, reduce dose to 25 mg/kg q24h.
IV, Intravenous; PO, orally; q6h, every 6 hours.

bFlucytosine

Lipid formulations of amphotericin B are not recommended for treatment of fungal UTI. The decreased nephrotoxicity that results from the addition of the lipid component likely also precludes the drug's effectiveness by failing to achieve adequate levels in the urinary tract.13

One of the few uses of flucytosine is for the treatment of Candida UTI. Flucytosine is excreted into the urine in high concentrations but should be used only when fluconazole is not tolerated or the organism is fluconazole resistant. The usual dosage of flucytosine in patients who have normal creatinine clearance is 25 mg/kg orally every 6 hours for 7 to 10 days.13 Most species of Candida, with the exception of C. krusei, are susceptible to flucytosine, but resistance emerges quickly when this agent is used alone. Serious adverse effects of flucytosine include bone marrow suppression and hepatotoxicity. These effects are dose related, and the risk increases greatly with kidney failure (see Table 55.3).

The echinocandins (caspofungin, micafungin, and anidulafungin) have minimal or no excretion into the urine as active drug. The tissue concentrations achieved with these agents may be adequate to treat invasive Candida infections of the bladder or kidney, but this is not clear. Both success and failure have been reported when echinocandins are used to treat Candida UTI.14–16 Currently, echinocandins are not recommended for the treatment of Candida UTI but can be tried if all else fails in patient with C. glabrata UTI.

Local Antifungal Administration

Continuous bladder infusion of amphotericin B deoxycholate 50 mg in 1 L of sterile water through a triple-lumen catheter is sometimes used to treat Candida bladder infection. Bladder irrigation clears candiduria more quickly than systemic antifungal agents.17 However, the effect is brief, and recolonization occurs within 1 to 2 weeks. Bladder irrigation is rarely ordered, but it is sometimes useful for patients who have recalcitrant bladder infection with azole-resistant C. krusei or C. glabrata.

In the patient with kidney obstruction caused by a fungus ball, irrigation through a percutaneous nephrostomy tube with amphotericin B deoxycholate is recommended, in addition to systemic antifungal therapy with fluconazole.10 Absorption of amphotericin B does not occur, and direct infusion is not nephrotoxic. Surgical or endoscopic removal of the fungus ball is essential to eradicate the infection.

Localized Candida Infections

Prostatitis and prostatic abscess caused by Candida spp. manifest with symptoms that are similar to those of bacterial prostatic infection. The initial manifestation may be urinary retention; physical examination reveals a tender prostate, and imaging can show either discrete abscesses or diffuse inflammation. Treatment is drainage, if an abscess is present, and fluconazole, which achieves excellent concentrations in the prostate, for several months until the infection has resolved.18

Epididymo-orchitis is less common and usually manifests as a tender scrotal mass. Surgical drainage or orchiectomy is required, along with fluconazole therapy until resolution has occurred.

OTHER YEASTS

Rarely, yeasts such as Saccharomyces cerevisiae and Trichosporon asahii cause UTI, but the most important non-Candida yeast that infects the genitourinary (GU) tract is Cryptococcus neoformans. Cryptococcosis occurs primarily in immunosuppressed hosts. In autopsy series, kidney involvement has been noted in 25% to 50% of patients who died of cryptococcosis, but GU tract symptoms were rare. The prostate is frequently infected and can be a reservoir for persistent C. neoformans infection. Isolated prostatitis and epididymo-orchitis have been reported in the absence of systemic cryptococcosis.[19] The diagnosis is usually made after biopsy of a mass or nodule; granulomatous inflammation is typically seen. Treatment of localized GU tract cryptococcal infection is fluconazole 400 mg/day for 6 to 12 months.

ASPERGILLUS AND OTHER MOLDS

The urinary tract is an uncommon site of infection with molds. However, individual case reports have noted GU infections caused by a variety of molds, including the Mucorales (e.g., Rhizopus, Mucor) and Aspergillus.20 21 The most common mold infection is aspergillosis. Hematogenous spread to the kidney with invasive disease in immunosuppressed patients results in numerous kidney microabscesses and infarcts. This may be an incidental finding at autopsy in patients with disseminated infection; in other patients, infection is localized to the GU tract.21 Urinary tract obstruction from masses of fungal elements is not uncommon. Treatment is surgical removal of the obstructing mass, often nephrectomy, and systemic antifungal therapy for the specific mold. Mortality is extremely high when GU involvement is accompanied by disseminated infection.

ENDEMIC FUNGI

All of the major endemic mycoses have been reported to infect the GU tract. For all of these organisms, infection is by hematogenous spread to the GU tract. For upper tract infection, treatment is the same as that for disseminated infection. The treatment of focal infection, which is more likely to involve the lower GU tract,

often requires surgical removal of the infected tissue and antifungal therapy.

B. dermatitidis has the greatest propensity to cause symptomatic infection. In patients with disseminated blastomycosis, involvement of the GU tract occurs in as many as a third of cases and usually manifests as prostate or epididymal infection.22 In most patients, this involvement is discovered incidentally when urine cultures yield the organism or a biopsy is performed for a prostatic or epididymal mass.

Symptomatic GU tract involvement with histoplasmosis is uncommon. However, at autopsy, kidney lesions are often found in patients who have disseminated histoplasmosis.23 Patients are usually asymptomatic in regard to urinary symptoms. Individual cases of testicular abscesses, epididymitis, and prostate nodules have been reported.

Coccidioidomycosis rarely causes symptomatic UTI. However, autopsy series of cases of disseminated coccidioidomycosis have noted kidney involvement in more than 50% of cases. and Coccidioides spp. can be grown in urine culture in patients with disseminated infection.24 Localized infection, manifesting as abscesses or mass lesions of the epididymis or prostate, has also been reported caused by Coccidioides spp.

SELF-ASSESSMENT QUESTIONS

1. Which of the following Candida spp. is isolated most often in patients with candiduria?
A. C. glabrata
B. C. parapsilosis
C. C. albicans
D. C. krusei
E. C. tropicalis

2. The presence of pyuria is a helpful diagnostic test for Candida UTI when there is:
A. An indwelling bladder catheter in a symptomatic patient
B. An indwelling bladder catheter in an asymptomatic patient
C. Concomitant bacteriuria and candiduria in an asymptomatic patient
D. Concomitant bacteriuria and candiduria in a symptomatic patient
E. No indwelling bladder catheter and no bacteriuria

3. The dose of which of the following antifungal agents used to treat fungal UTI should be reduced in patients who have a creatinine clearance below 40 to 50 mL/min?
A. Amphotericin B
B. Flucytosine
C. Caspofungin

D. Liposomal amphotericin B
E. Voriconazole
4. The antifungal agent of choice for treating a Candida albicans UTI is:
A. Amphotericin B
B. Fluconazole
C. Flucytosine
D. Voriconazole
E. Caspofungin

REFERENCES

1. Sobel JD, Fisher JF, Kauffman CA, et al. Candida urinary tract infections: epidemiology. Clin Infect Dis. 2011;52(suppl 6):S433–S436.
2. Bouza E, San Juan R, Munoz P, et al. A European perspective on nosocomial urinary tract infections. I. Report on the microbiology workload, etiology, and antimicrobial susceptibility (ESGNI-003 study). Clin Microbiol Infect. 2001;7:523–531.
3. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. Clin Infect Dis. 2000;30:14–18.
4. Alvarez-Lerma F, Nolla-Salas J, Leon C, et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med. 2003;29:1069–1076.
5. Drogari-Apiranthitou M, Anyfantis I, Galani I, et al. Association between candiduria and candidemia: a clinical and molecular analysis of cases. Mycopathol. 2017;182:1045–1052.
6. Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev. 2010;23:253–273.
7. Fisher JF, Kavanaugh K, Sobel JD, et al. Candida urinary tract infection: Pathogenesis. Clin Infect Dis. 2011;52(suppl 6):S437–S451.
8. Debska-Slizien A, Chrobak L, Bzoma B, et al. Candida arteritis in kidney transplant recipients: case report and review of the literature. Transpl Infect Dis. 2015;17:449–455.
9. Kauffman CA, Fisher JF, Sobel JD, et al. Candida urinary tract infection: diagnosis. Clin Infect Dis. 2011;52(suppl 6):S452–S456.
10. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409–417.
11. Aslam S, Rotstein C, the AST Infectious Disease Community of Practice. Candida infections in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transpl. 2019;33:e13623.
12. Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. Clin Infect Dis. 2000;30:19–24.

13. Fisher JF, Sobel JD, Kauffman CA, et al. Candida urinary tract infection: treatment. Clin Infect Dis. 2011;52(suppl 6):S457–S466.
14. Malani A. Failure of caspofungin for treatment of Candida glabrata candiduria: case report and review of the literature. Infect Dis Clin Pract. 2010;18:271–272.
15. Gabardi S, Martin S, Sura M, et al. Micafungin treatment and eradication of candiduria among hospitalized patients. Int Urol Nephrol. 2016;48:1881–1885.
16. McMorris TE, Smith WJ, Kupiec K, et al. Micafungin therapy for symptomatic candiduria in hospitalized patients: a review of 14 cases. Infect Dis Clin Pract. 2017;25:88–93.
17. Leu HS, Huang CT. Clearance of funguria with short-course antifungal regimens: a prospective, randomized, controlled study. Clin Infect Dis. 1995;20:1152–1157.
18. Finley RW, Cleary JD, Goolsby J, et al. Fluconazole penetration into the human prostate. Antimicrob Agents Chemother. 1995;39:553–555.
19. Kiertiburanakul S, Sungkanuparph S, Buabut B, et al. Cryptococcuria as a manifestation of disseminated cryptococcosis and isolated urinary tract infection. Jpn J Infect Dis. 2004;57:203–205.
20. Alexander BD, Schell WA, Siston AM, et al. Fatal Apophysomyces elegans infection transmitted by deceased donor renal allografts. Am J Transpl. 2010;10:2161–2167.
21. Albin OR, Soper N, Khurana I, et al. Invasive genitourinary aspergillosis in a patient with chronic lymphocytic leukemia treated with venetoclax: case report and review of the literature. Open Forum Infect Dis. 2019;6(11).
22. Bradsher RW, Bariola JR. Blastomycosis. In: Kauffman CA, Pappas PG, Sobel JD, Dismukes WE, eds. Essentials of Clinical Mycology. 2nd ed. New York: Springer; 2011:337–348.

23. Kauffman CA. Histoplasmosis. A clinical and laboratory update. Clin Microbiol Rev. 2007;20:115–132.
24. Sohail MR, Andrews PE, Blair JE. Coccidioidomycosis of the male genital tract. J Urol. 2005;173:1978–1982.

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The Kidney in Schistosomiasis

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INTRODUCTION

Schistosomiasis is a parasitic disease usually acquired by teenagers, often leading to complications that may extend into the fourth and fifth decades of life. It was known to the ancient Egyptians as "the bloody urine disease"[1] and is also known as bilharziasis in honor of its discoverer, Theodor Bilharz, the German physician who practiced in Egypt in the 1850s.

The life cycle of the parasite is shown in Fig. 56.1. Infection is acquired through contact with contaminated waters in ponds and slow-flowing canals. Cercariae enter through the skin or mucous membranes and migrate through the lymphatics and blood circulation into the portal or perivesical venous system, where they mature into sexually differentiated adult worms and live in almost continuous copulation. Females leave the males only to lay eggs, and, traveling against the blood flow, reach the rectal or bladder mucosa. The ova are driven out by visceral contraction during defecation or urination. Contact with fresh water within a couple of days allows the eggs to hatch, releasing miracidia, which infect specific snails. In this intermediate host, the organisms mature asexually into cercariae, which are eventually released to search for their definitive host, which is usually humans and occasionally apes and cattle. The snail demography defines the endemicity and frequency of schistosomiasis in different geographic regions and is influenced by temperature and humidity.[2]

About 230 million inhabitants (about 50% children) of 78 countries on five continents are infected, and an additional 700 million are at risk. Of the infected persons, 60% are symptomatic, 10% have serious sequelae, and 1% die of the disease each year, mainly in China, the Philippines, Brazil, northern Senegal, and Uganda. There has been a significant decline in prevalence during the second half of the past century, as a result of mass treatment with tartar emetic during the 1960s, the use of praziquantel during the 1980s, and the World Health Organization (WHO)-sponsored global mass praziquantel treatment program starting in the late 1990s. This has resulted in eradication of schistosomiasis from Japan and the Lesser Antilles islands; transmission was halted in Tunisia and significantly reduced in China, Egypt, Morocco, Saudi Arabia, Brazil, Venezuela, and Puerto Rico. However, certain schistosomal strains—up to 82% in Senegal—are resistant to praziquantel. Such strains are responsible for incremental prevalence in several countries and even spread to adjacent geographic regions in East and West Africa.

Of seven species that affect humans, three are responsible for almost all major morbidity from the disease: Schistosoma haematobium throughout Africa and adjacent regions; Schistosoma mansoni in Africa, South America, and the Caribbean; and Schistosoma japonicum in the Far East (Fig. 56.2).

S. haematobium affects the genitourinary (GU) tract, whereas S. mansoni and S. japonicum typically affect the colon and rectum and

spread upstream through the portal venous system to the liver, leading to periportal fibrosis. All three species may cause "metastatic" lesions when ova are driven by the bloodstream to the lungs, brain, spinal cord, heart muscle, eyes, and other sites.[3] Overall morbidity is variable and depends on the virulence of the infective strains, host resistance, environmental factors, and standards of primary medical care. For example, chronic lower urinary tract disease among infected subjects was reported a few decades back to vary from 2% in Nigeria in the west of Africa to 52% in Tanzania in the east.[4] An even wider range (0.6%–67%) was reported among children in subSaharan Africa.[5]

The kidneys are secondary targets of both S. hematobium and S. mansoni infection. New cases of S. mansoni–associated nephropathy are reported mainly in South America6,7 and of S. hematobium–associated urogenital disease in Africa.8

PATHOGENESIS

Schistosomes cause morbidity through two major mechanisms: (1) local reactions around the ova deposited in different tissues and (2) systemic effects attributed to the host’s response to circulating antigens released from the worms or the ova (Fig. 56.3).4,9

The local reaction is a granulomatous cell-mediated immune response to soluble egg antigens diffusing out of trapped ova through micropores in the eggshell. The initial response is innate, being driven by tissue macrophages, and involves natural killer cells, neutrophils, and complement. This is followed by a specific immune response orchestrated by T helper (Th) lymphocytes. The schistosomal granuloma is composed of mononuclear cells, eosinophils, neutrophils, basophils, and fibroblasts, which are recruited and activated by a variety of Th lymphokines and by specific chemoattractants of parasitic origin (Fig. 56.4). These cells are involved in the elimination of the parasite by direct phagocytosis (monocytes), lymphocytotoxicity (T lymphocytes), antibody-dependent cytotoxicity (eosinophils), and antibody- and complement-dependent cytotoxicity (neutrophils).

Later, the granuloma is modulated by gradual switching from Th1 to Th2 activation, largely mediated by a change in the monokine profile that favors release of modulatory cytokines, which are associated with a phenotypic change of the committed tissue macrophages. At this stage, the intensity of the inflammatory reaction is reduced, and progressive fibrosis is induced largely through the release of interleukin (IL)-5, IL-10, IL-13, somatostatin, and transforming growth factor (TGF)-β. Data from murine models incriminate additional T-cell subsets in promoting fibrosis, including Th9, Th17, and T-follicular helper cells (Tfh).10 Further on, tolerance to the parasite is achieved by an established population of regulatory T (T-reg) cells, which develop under the combined influence of host- and ova-derived mediators.

With the final extinction of the inflammatory reaction, granulomas in

Life Cycle of Schistosomes
Human

Ova

Water

Miracidia

Adult worms
Human

Cercaria
Fig. 56.1 Life cycle of schistosomes.

Global Distribution of Schistosomiasis

Snail

CLINICAL MANIFESTATIONS

Schistosomal lesions in the urinary system mirror the two major pathogenetic mechanisms. On one hand, there are local lesions, mostly affecting the lower urinary tract, caused by the local granulomatous response to S. haematobium ova.[15] One may also observe lesions caused by immune complex deposition in the glomeruli, usually associated with hepato-intestinal S. mansoni and, less commonly, urogenital S. haematobium infections.[15] Although glomerular lesions can be readily induced by S. japonicum in experimental animals,[16] this species does not seem to cause significant kidney disease in humans.

Lower Urinary Tract Schistosomiasis

S. haematobium

S. mansoni

S. japonicum

Fig. 56.2 World map showing the geographic distribution of the main pathogenic schistosomes.

the bladder, lower ureters, and seminal vessels heal with fibrosis and dystrophic calcification.[11,12]

The systemic immune response is primarily a humoral reaction to circulating schistosomal antigens, which originate mainly from the worm's digestive enzymes (gut antigens), with a less significant contribution of tegument and oval proteins. The gut antigens consist of a positively charged glycoprotein and a negatively charged proteoglycan (circulating cationic antigens and circulating anionic antigens, respectively). These antigens are present in most of the schistosomal immune complex–mediated lesions, particularly in glomeruli.[13] The antibody response is biphasic, driven by the successive Th1 and Th2 stages of lymphocyte activation. In the Th1 stage, B cells tend to produce immunoglobulin M (IgM), IgG1, and IgG3 under the influence of IL-2. During the Th2 phase, IgG2, IgG4, and IgA predominate; these have a limited ability to fix complement and may even block its deposition, hence their importance in modulating the granulomas.[14]

The lower urinary tract and adjacent genital structures are the primary sites of S. haematobium infection. Clinical disease starts by the coalescence of multiple granulomas that form small pseudotubercles in the bladder mucosa (Fig. 56.5). These may consolidate to form sessile, occasionally pedunculated masses or ulcerate, leading to painful terminal hematuria, the most typical presenting symptom. Hematuria may vary from microscopic (40%–100% in different reports) to gross (0%–97%).[17] Ulcers eventually heal by fibrosis, with calcified granulomas under the atrophic and dirty mucosa, leading to the characteristic cystoscopic appearance of sandy patches and also the radiologic appearance of linear bladder calcifications in 2% to 62% of cases.[17] Similar lesions may occur in the lower ureters, bladder neck, seminal vesicles, and other organs in the vicinity (Fig. 56.6).

The bladder lesions predispose to secondary bacterial infection, particularly with Pseudomonas or Proteus spp., usually after diagnostic or therapeutic instrumentation. Proteus infection is notorious for favoring stone formation, which further complicates the scenario.

The subsequent fibrotic process may involve the bladder neck, leading to outflow obstruction, or the vesicoureteral junction, leading to ureteral obstruction or vesicoureteral reflux. Involvement of the detrusor is late and may lead to an atonic or a hyperirritable bladder. Eventually, the bladder becomes a deformed, contracted, and calcified organ that accommodates a very small amount of urine that is difficult to void.

Immune Response to Schistosomal Infection
Local immune response
NKC

Systemic immune response

IL-12

Glomerular lesions
APC
Chemokines

Soluble
egg antigens

Circulating
worm antigens

Impaired
clearance

Parasitic
antigens

ThO
IL-1,6

IL-4

Th1

Th2

Neutrophil
Alternative
pathway

B
Interleukins

IL-2

Classical
pathway

IL-13
Antibodies

CD8
Eosinophil

Basophil

Immune
complexes

IgA

Granuloma

Fig. 56.3 Immune Response to Schistosomal Infection. The local immune response to deposited ova leading to granuloma formation is shown on the left; all cells shown in the diagram, in conjunction with antibodies or complement, participate in eventual parasite elimination (see text). The systemic immune response is shown on the right; note the important role of impaired clearance of schistosomal antigens and immunoglobulin A (IgA) in the development of glomerular lesions. APC, Antigen-presenting cell; IL, interleukin; NKC, natural killer cell.

Bladder Cancer

Chronic bilharzial cystitis is precancerous. The typical tumor is a squamous cell carcinoma,[18] although a time trend to predominance of transitional cell carcinoma was reported in a large series of close to 10,000 Egyptian patients with bladder cancer.[19] The tumor, particularly when of the squamous cell type, remains localized for a long time before spreading to the surrounding pelvic tissues or a distant site, thanks to the occlusion of lymphatics by the preceding fibrotic process.

Products of S. hematobium ova are directly incriminated in oncogenesis.[20,21] The major impact is on the BCL2 gene, which leads to epithelial proliferation and inhibition of apoptosis. This is coupled by inhibition of the tumor suppressor genes P27, TP53, and others. Other oncogenic factors in schistosoma-associated bladder cancer include disturbance of the urinary microbiome and secondary bacterial infection.[21]

Development of malignancy is suspected when the symptoms of chronic cystitis worsen, along with recurrence of hematuria many years after the initial presentation and the passage of small pieces of necrotic tissue with urine (necroturia). A characteristic radiologic sign is the irregular “eating up” of the bladder calcification on a plain radiograph (Fig. 56.7). Cystoscopy shows the tumor and provides the means for a histologic diagnosis.

Fig. 56.4 Schistosoma haematobium Granuloma. Note the egg’s terminal spike (arrow), which identifies S. haematobium, and the distortion of shell by proteases and oxidants released by the local neutrophil infiltration. (Hematoxylin-eosin stain, ×500.)

Upstream Consequences

Although ureteral strictures and calcifications are common, the hypertrophied upper ureteral musculature usually overcomes the lower obstruction, thereby limiting the upstream consequences. Nevertheless, hydronephrosis and progressive kidney failure may

A

B

C

D

Fig. 56.5 Hand-Painted Cystoscopic Appearances in Urinary Schistosomiasis. (A) Pseudotubercles. (B) Sessile mass covered by pseudotubercles. (C) Ulcer surrounded by pseudotubercles. (D) Sandy patches.
(Courtesy Professor Naguib Makar.)

develop when there is extensive ureteral scarring, in the presence of stones or secondary bacterial infection, or when the vesicoureteral junction is incompetent (Fig. 56.8). The frequency of upper urinary tract disease from S. haematobium is variably reported from different geographic regions—for example, from less than 10% in Niger to 48% in Cameroon.4

Interstitial Nephritis

Progressive kidney scarring is the eventual outcome of complicated S. haematobium infection, resulting from obstruction, reflux, and bacterial infection. Granulomas have occasionally been seen in the kidney interstitium but tend to be discrete and of no functional significance (Fig. 56.9).

The typical pathologic picture is that of a deformed kidney with calyceal dilation, distortion, and atrophic parenchyma. Dense interstitial infiltration, fibrosis, and periglomerular scarring are present. The glomeruli may show ischemic collapse or other schistosomal lesions, such as proliferative glomerulonephritis (GN) or amyloidosis.

The clinical picture is that of chronic tubulointerstitial nephritis (see Chapter 65), often associated with residual manifestations of lower urinary tract involvement. Hypertension is a late feature, being checked by concomitant tubular salt wasting. Anemia and osteodystrophy may be disproportionately severe because of the associated secondary distal tubular acidosis and nutritional deficiency in endemic areas.

Immune-mediated tubulointerstitial nephritis has been described with S. mansoni in humans.22,23 Tubular dysfunction associated with hepatosplenic schistosomiasis includes salt wasting, impaired concentrating ability,24 and Type I renal tubular acidosis.24,25 Because these were also reported in chronic liver disease from other causes, their specificity to schistosomal etiology remains questionable.

Glomerulonephritis

Immune complex–mediated GN has been described in experimental16 and human15 infection, mainly with S. japonicum and S. mansoni. The latter species accounts for most clinically significant disease in humans. S. haematobium GN is rare, transient, and usually subclinical.26

Schistosomal gut antigens are present in circulating immune complexes and in the immune deposits in mesangial, subendothelial, and intramembranous locations. The presence of liver fibrosis is critical because it results in impaired hepatic clearance of schistosomal antigens and immune complexes. These are mostly generated within the portal venous system, which accommodates the adult worms.

Most patients are 20- to 40-year-old men with evidence of hepatosplenic schistosomiasis. This is often discovered accidently during a physical or ultrasonographic abdominal examination in an asymptomatic case. Less frequently, these patients may complain of abdominal distension, edema, upper gastrointestinal (GI) bleeding, or manifestations of chronic liver disease. Kidney involvement is asymptomatic in up to 40% of those, being identified by accidental or surveillance urinalysis, which may display various grades of proteinuria, or abnormal sediment. Some 15% of those with hepatosplenic schistosomiasis have overt GN, with proteinuria and microhematuria on presentation and with or without the nephrotic syndrome, hypertension, and impaired kidney function. Liver function test results are often normal. A polyclonal gammopathy is seen in most cases, whereas a monoclonal IgM response is seen in those with associated hepatitis C virus (HCV) infection and cryoglobulinemia. Rheumatoid factor activity and antiDNA antibodies are detected in 5% to 10% of cases, particularly in association with Salmonella infection (see later discussion), but they do not correlate with clinical severity. Rheumatoid factor seropositivity is detected in much higher titers when HCV infection is associated.27

A

Fig. 56.7 Schistosomal bladder cancer.

B

Fig. 56.6 Plain radiographic Appearances in Schistosoma haematobium Infection. (A) Faint linear calcification of the bladder wall (arrows). (B) Dense calcifications of contracted bladder and seminal vesicles.

Six histologic classes of schistosomal GN are recognized (Table 56.1 and Fig. 56.10).[15 27] Class I (mesangial proliferative), class III (membranoproliferative), and class IV (focal segmental proliferative and sclerosing) result from the deposition of immune complexes representing different stages in the evolution of pure schistosomal hepatosplenic disease. The main deposits in class I are schistosomal antigens, IgM, and C3; and in class III and class IV, IgG and IgA, usually without schistosomal antigens. The IgA deposits parallel the severity of proteinuria and mesangial proliferation. Impaired hepatic clearance and increased mucosal synthesis of IgA have been documented in many of those patients.[28] Whereas class I lesions are seen in most asymptomatic cases, class III and class IV are usually symptomatic and progressive, even with eradication of the parasitic infection.

Class II (diffuse proliferative and exudative) is associated with urinary or biliary coinfection with Salmonella strains, usually Salmonella paratyphi A in Africa and Salmonella typhimurium in Brazil, which are attached to specific receptors in the tissues of adult schistosomes. C3 and Salmonella antigens have been detected in the glomerular capillary walls and the mesangium. In these patients the clinical presentation is typical of acute postinfectious GN, associated with manifestations of Salmonella-related toxemia (fever, exanthema, and severe anemia).

Fig. 56.8 Ascending cystogram showing right megaureter caused by vesicoureteral reflux.

Serum amyloid A (AA) protein deposits are detected by special stains or electron microscopy in up to 15% of biopsy samples from patients with class III and class IV, whereas AA-amyloidosis may be the predominant lesion (class V) in less than 5% of patients with clinically overt schistosomal GN. It occurs with heavy, often mixed infection regardless of the anatomic site. Minimal amyloid deposits do not seem to alter the clinical presentation or prognosis, but typical class V lesions are grossly nephrotic and relentlessly progressive.

Class VI lesion was described in patients with hepatosplenic schistosomiasis and HCV infection.27 The lesion consists of a mixture of mesangial proliferation, amyloid deposition, fibrinoid necrosis, and cryoglobulinemic thrombi in the glomerular capillaries with tubular casts. Patients have chronic hepatitis, cirrhosis, nephrotic syndrome, cryoglobulinemic skin vasculitis, polyarthritis, and rapidly progressive kidney failure associated with severe protein-calorie malnutrition.

Other histologic lesions have described in chronic schistosomiasis, yet a cause-and-effect relationship has not been established.

A frequently debated lesion is membranous nephropathy, which is believed to be a chance association of primary membranous nephropathy and schistosomiasis.29 Collapsing glomerulopathy has been described in a patient with APOL1 genotype infected with Schistosoma mansoni,30 which was blamed as a triggering factor in a predisposed patient.

COINFECTION

Fig. 56.9 Schistosomal Chronic Interstitial Nephritis. Note the dense cellular infiltration and fibrosis, atrophic dilated tubules, and thickened vessels. Three glomeruli heavily infiltrated with amyloid are seen on the right side (arrows); a schistosomal granuloma is seen in the lower left corner (arrowhead). (H&E stain; original magnification ×75.)

TABLE 56.1

Patients living in endemic areas may acquire one or more superimposed infections that can perturb schistosomal pathogenicity and modify its presentation. Mutually, schistosomiasis may modify the course of the confounding infection. The first reported coinfection is that of schistosomiasis and salmonellosis,31 discussed earlier as class II schistosomal glomerulopathy. Likewise, class VI is attributed to coinfection with HCV.27

The list of other infections known to interact with schistosomiasis is expanding (Box 56.1). Some of the documented coinfections, namely those with plasmodium, filaria, tuberculosis, and staphylococci, are clinically significant. However, they were not reported to modify the known kidney lesions of schistosomiasis alone.

Classification of Schistosomal Glomerulonephritis
Immunofluorescence

Etiologic
Agent

Histology

I

Mesangial proliferative IgM, C3, schistosomal
GN
antigens

S. haematobium,
S. mansoni, S.

japonicum

II

Diffuse proliferative
exudative GN

S. haematobium, Salmonella infections
S. mansoni, plus
Salmonella spp.

III

Membranoproliferative IgG, IgA, C3, schistosomal
GN
antigens

S. mansoni (S.
haematobium?)

7%–20% of asymptomatic Hepatosplenomegaly, No
patients and in 80%
nephrotic syndrome,
of patients with overt
hypertension,
kidney disease
kidney failure

IV

Focal segmental
glomerulosclerosis

IgM, IgG (occasionally IgA)

S. mansoni

11%–38%

Hepatosplenomegaly, No
nephrotic syndrome,
hypertension, kidney
failure

V

Amyloid

AA protein

S. mansoni, S.
haematobium

16%–39%

Hepatosplenomegaly, No
nephrotic syndrome,
hypertension, kidney
failure

VI

Cryoglobulinemic GN

IgM, C3

S. mansoni +
Unknown
hepatitis C virus

C3, Salmonella antigens

AA, Amyloid A; GN, glomerulonephritis; Ig, immunoglobulin.

Prevalence

Treatment of
Clinical Findings Kidney Disease

Class

27%–60% of
asymptomatic patients,
10%–40% of patients
with kidney disease

Microhematuria,
proteinuria

May respond to
antiparasitic
treatment

Acute nephritic
syndrome, toxemia,
reduced serum C3

May respond to
treatment of
Salmonella and
schistosomal
infections

Hepatosplenomegaly, Interferon plus ribavirin,
nephrotic
corticosteroids,
syndrome, purpura,
immunosuppression,
vasculitis, arthritis,
plasma exchange
hypertension, kidney
failure

A

C

B

D

E

F

Fig. 56.10 Schistosomal Glomerulopathy. (A) Mesangial proliferative glomerulonephritis (GN), H&E stain (class I). (B) Schistosoma- and Salmonella-associated exudative GN, H&E stain (class II). (C) Membranoproliferative (mesangiocapillary) GN type I, H&E stain (class III). (D) Focal segmental glomerulosclerosis, Masson trichrome stain (class IV). (E) Green birefringence under polarized light in a glomerulus with mesangial proliferation in a patient with mixed Schistosoma haematobium and Schistosoma mansoni infection, Congo red stain (class V). (F) Amyloid deposits and cryoglobulin capillary thrombi (red stain) in a glomerulus displaying focal mesangial proliferation in a patient with schistosomal hepatic fibrosis and associated hepatitis C virus infection (class VI).

Clinically Relevant Coinfection with Schistosomiasis

BOX 56.1

Viral
- Hepatitis B virus
- Hepatitis C virus
- Human immunodeficiency virus
- Human papillomavirus

Bacterial
- Tuberculosis
- Staphylococci
- Salmonella

Parasitic
- Plasmodium
- Filaria

schistosomiasis are at significantly increased risk (odds ratio [OR], 2.9 in Zimbabwe32 and 4.0 in Tanzania33) of acquiring and subsequently transmitting HIV to their sexual partners. Data on males with S. hematobium infection or either sex with S. mansoni infection are inconsistent. There are no published data on S. japonicum and HIV coinfection.

The immunologic perturbation induced by schistosomiasis seems to accelerate the progression and spread of HIV infection.34 HIV coinfection impairs the immune response, resulting in alteration of the granulomatous process involving schistosomes, yet without known clinical sequelae. However, HIV-infected patients are more vulnerable to reinfection with schistosomes upon new exposure after successful eradication.35

There is some concern about the unexplained 3- to 16-fold increase of HIV viral load after treatment of schistosomiasis by praziquantel.36 Fortunately, this effect is spontaneously reversible in a few weeks, and the benefit of eradicating the confounding parasitic infection on the clinical course and spread of HIV infection is unquestionable.36

Hepatitis B Virus

On the other hand, there is evidence that coinfection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or human papilloma virus (HPV) may augment schistosomal morbidity:

Human Immunodeficiency Virus

Several studies have established an epidemiologic link between schistosomiasis and HIV infection. Females with lower urinary tract

Vulnerability of patients with hepatosplenic schistosomiasis to coinfection with HBV is well documented in hospital-based,37 but not in community-based,38 studies, perhaps because of the selection of complicated cases in the former. Such coinfection augments the liver injury induced by schistosomiasis,39 leading to increased incidence of abnormal liver function (46.6%), jaundice (23.3%), hepatocellular carcinoma (17.8%), and liver-related mortality (23.3%).40 It is unknown whether schistosoma and HBV coinfection influences the nature or severity of the kidney lesions associated with either.

B

Human Papilloma Virus

The association of HPV infection with nonschistosomal squamous cell carcinoma of the bladder was reported in 1994.41 Three years later, an in-situ hybridization study in South Africa did not show evidence of such infection in 25 patients with bilharzial squamous cell bladder cancer.42 However, because of the confirmed association of HPV with cervical carcinoma in patients with genital schistosomiasis,43 debate continues whether it may also be a confounding risk factor for bilharzial bladder cancer.

A

B

Diagnosis

Schistosoma haematobium Urinary Tract Disease

The clinical diagnosis of lower urinary tract schistosomiasis is easily made, particularly in patients with the typical pattern of painful terminal hematuria after exposure to fresh river waters in an endemic area. Diagnosis is more difficult when the history of exposure is less convincing (e.g., swimming pools) or when the clinical presentation is atypical (e.g., bacterial pyelonephritis, typhoid, or amyloidosis).

The diagnosis is made by finding ova in a fresh urine sample, which is easy because of their abundance, large size, and typical appearance (see Fig. 56.4). Live ova, containing mobile miracidia, indicate active infection, whereas dead, calcified ova may continue to be shed from fibrotic lesions for many months or even years.

Serologic diagnosis is based on finding circulating schistosomal antigens or antibodies.44 The circumoval precipitin test is most frequently used in clinical laboratories. Serologic diagnosis is useful for diagnosis in the absence of ova, which occurs with old infections when the worms are sterile but continue to release their antigens. Serologic tests are also useful in assessing the response to treatment because titers usually become negative within 3 to 6 months of complete eradication of infection.

A polymerase chain reaction (PCR) real-time assay is available for detection of the dra-1 S. hematobium antigen in the serum.45 Because of its high cost, its clinical use is limited to early detection of infection in expatriates visiting endemic areas.

The radiologic appearances of bladder and seminal vesicle calcification are so typical that no further confirmatory tests are needed in an endemic area. Cystoscopic findings are equally pathognomonic although seldom required. Early pseudotubercles are easily distinguished from mycobacterial infection by their size and the surrounding mucosal pathologic changes. The presence of sandy patches with associated masses, polyps, and even neoplasms confirms the diagnosis.

Tissue biopsy confirms the parasitic nature of the lesions. Different imaging techniques (e.g., ultrasound,46 intravenous urography, voiding cystography) are useful in the diagnosis of upstream complications, including obstruction and reflux (see Chapters 61 and 62).

The main differential diagnosis for urinary schistosomiasis is tuberculosis, which also causes hematuria, strictures, back pressure, and chronic kidney disease (CKD). This differential can be resolved with appropriate parasitologic and bacteriologic techniques (see Chapter 54).

SCHISTOSOMA MANSONI GLOMERULONEPHRITIS

Overt glomerular disease in patients with hepatosplenic schistosomiasis is suspected in those who develop hypertension, nephrotic or nephritic syndrome, or CKD. Occult glomerular disease is indicated by the presence of abnormal urinary sediment or kidney function. Although kidney biopsy is essential for diagnosis and classification, no lesion is pathognomonic unless schistosomal antigens are detected, which is unusual in clinically overt cases when sought with conventional immunofluorescence.

Fig. 56.11 Stool smears showing living (A) and dead (B) Schistosoma mansoni ova. Species are identified by the lateral spike (arrows).

Identification of S. mansoni eggs in the stools (Fig. 56.11) or submucosal rectal biopsy samples supports the diagnosis. Serologic tests for schistosomal gut antigens[47] and molecular tests for Sm1-7 encoding DNA[48] are usually positive. However, it is important to remember that these tests only indicate schistosomal infection and do not necessarily implicate schistosomes as causing the kidney disease.

Several biomarkers have been proposed for the detection of kidney injury in schistosomiasis. So far, none of these has reached a reliable, more specific, and noninvasive alternative to kidney biopsy.[49]

Concomitant Salmonella or HCV infection can be detected by appropriate microbiologic tests. The various serologic abnormalities described are of limited diagnostic value, except the high rheumatoid factor, monoclonal IgM expansion, and low C4 that are typical of class VI.

Other glomerular disorders associated with hepatic fibrosis, such as secondary IgA nephropathy and hepatic glomerulosclerosis, should be considered in the differential diagnosis. However, in both these conditions, the kidney disease is relatively milder, mainly with microhematuria at presentation but rarely with nephrotic-range proteinuria or impaired kidney function. The glomerular deposits are mostly mesangial, in contrast to those seen in schistosomiasis, in which subendothelial and intramembranous deposits may also be present.

TREATMENT

Schistosoma haematobium Urinary Tract Disease

S. haematobium is susceptible to antimony compounds, organophosphates (metrifonate), and niridazole. However, the standard drug of choice is praziquantel, with a cure rate greater than 85% and the least toxicity. It is administered as a single oral dose of 40 mg/kg body weight, which may be repeated 2 weeks later if there is evidence of active disease. The drug has a low toxicity profile, mainly a mild to moderate transient elevation of hepatic transaminases. In infections resistant to praziquantel, the antimalarial Artemisia annua may be used as an alternative with equal effectiveness.[50] Antiparasitic treatment cures the early bladder disease but has no effect on sandy patches or other fibrotic lesions. Ureteral distension with radiologic evidence of hydronephrosis may be reversed in a few weeks after successful treatment.

Antibacterial therapy usually controls acute episodes of cystitis and pyelonephritis. However, it must be combined with simultaneous eradication of parasitic infection if still active, especially when the urinary bacterial infection is because of typhoid (Salmonella typhi).

Chronic fibrotic lesions are difficult to treat. Surgery or the placement of stents may be necessary for the relief of an obstructive lesion. However, particular caution is required in dealing with the vesicoureteral junction to avoid induction of reflux. Several plastic procedures are available to restore the distorted ureteral, bladder, or urethral anatomy. Associated bacterial infections may require long-term low-dose antibiotics.

Chronic dialysis in such patients can be difficult because of the negative effects of the associated schistosomal lesions in the liver, lungs, and other organs and the comorbid impact of undernutrition, viral infection, or malignant disease. The same factors can compromise outcomes of kidney transplantation, with the additional risk for urinary leakage, which is many-fold higher than usual because of the presence of fibrotic granulomas and anatomic distortion in the bladder wall. Reinfection with S. haematobium also has been described.51

Schistosoma Mansoni Glomerulonephritis

S. mansoni is more resistant to treatment and may require higher doses of praziquantel (40–60 mg/kg body weight) or the use of oxamniquine (single dose of 15 mg/kg body weight in South America or two doses of 15 mg/kg body weight given 12 hours apart in Africa). Research is underway to overcome oxamniquine resistance, which is limiting its use in many geographic regions.52 Nevertheless, eradication of the parasite can be curative only in classes I and II. In the latter, it must be combined with antibiotics for the control of Salmonella infection (usually quinolones, macrolides, or third-generation cephalosporins). Antischistosomal and immunosuppressive therapy are ineffective in all other classes of schistosomal GN.15 These tend to progress to kidney failure in about 35% of cases 5 years after initial diagnosis.6

Chronic dialysis may be complicated by the risk for bleeding from esophageal or gastric varices after anticoagulation. Endoscopy is essential before the start of regular hemodialysis, with prophylactic sclerotherapy if necessary. Although peritoneal dialysis is viable for some, it is relatively contraindicated in those with significant ascites.

Kidney transplantation is a viable option in those who develop kidney failure, in the absence of major risk factors such as viral infection, undernutrition, or hepatic insufficiency. Uncomplicated residual hepatic fibrosis in the recipient does not seem to significantly modify the pharmacokinetics of immunosuppressive agents, but variations in cyclosporine blood levels can occur, perhaps secondary to altered GI absorption.53 The severity of chronic liver disease may have a considerable impact on donor selection, choice of immunosuppression, and the eventual outcome.

Recurrence of schistosomal GN after transplantation has been described in a few patients,53 suggesting the persistent release of antigens from living worms.54 Although it is not an evidence-based practice, many authorities recommend the administration of a single dose of praziquantel before transplantation to recipients known to have been previously infected with the parasite.

SELF-ASSESSMENT QUESTIONS

1. A 45-year-old male recent Egyptian immigrant to Canada presents with a 4-week history of pyrexia, abdominal discomfort, asthenia, and increasing generalized edema. His medical history includes two treatment courses for intestinal schistosomiasis. Examination shows significant pallor, facial puffiness, a faint macular itchy eruption on the forearms and abdominal wall, and bilateral soft pedal edema. Temperature is 38.7°C (101.7°F), and blood pressure is 100/70 mm Hg. The liver edge is felt 2 cm below the right costal margin, firm

and moderately tender. The spleen is felt 5 cm below the left costal margin and acutely tender. Urinary protein is 14 g/g creatinine, and the sediment shows 20 to 25 white blood cells, 8 to 10 red blood cells, and a few blood casts per high-power field. Peripheral blood hemoglobin is 8.6 g/dL; leukocyte count is 14,300/μL, of which 85% are neutrophils with left shift. Rheumatoid factor is positive at 48 IU/L, C-reactive protein is 128 units, and C3 is 54 mg/dL. Aspartate aminotransferase is 75 IU/mL, alanine aminotransferase is 62 IU/mL, and γ-glutamyl transferase is 123 IU/mL. Serum albumin is 1.8 g/dL, serum creatinine is 2.1 mg/dL, and blood urea nitrogen is 73 mg/dL. Which of the following is the most likely explanation for the patient's recent illness?

A. Ascending pyelonephritis complicating neglected urinary schistosomiasis
B. Schistosoma-associated Salmonella bacteremia
C. Active hepatitis viral infection on top of hepatointestinal schistosomiasis
D. Schistosoma-associated secondary immunoglobulin A nephropathy
E. Cryoglobulinemic vasculitis

2. A 50-year-old male Nigerian patient presents with severe burning during micturition, with passage of blood and necrotic tissue with urine for 2 weeks. He received treatment for urinary schistosomiasis

30 years previously and for recurrent urinary bacterial infection many times after that. Examination shows an ill man, with bilateral edema of the left lower limb. The left kidney is palpable and slightly tender. Rectal examination reveals a mass indenting the anterior rectal wall. Midstream urine examination shows a protein/creatinine ratio of 4 g/g, and uncountable red blood and pus cells. Serum creatinine is 4.3 mg/dL, and blood urea nitrogen is 103 mg/dL. The most likely cause of his edema is:

A. Schistosomal glomerulonephritis
B. Schistosoma-associated chronic pyelonephritis
C. End-stage postobstructive kidney disease
D. Infiltrative bladder cancer
E. Advanced prostatic cancer

3. A 38-year-old female Brazilian patient presents with painful swelling of the small joints of her hands, right knee, and left shoulder; bilateral soft lower limb swelling; and a raised brownish-purple macular skin eruption over the tibial shins. She has been under medical follow-up for compensated chronic hepatosplenic schistosomiasis. Urine examination shows a protein-to-creatinine ratio of 5.2 g/g, and the sediment shows many red blood cells, few leukocytes, and red blood cell and granular casts. Serum creatinine is 2.1 mg/dL; blood urea nitrogen is 26 mg/dL; serum albumin is 2.7 g/dL; serum C3 is 86 mg/dL; and C4 is 3.2 mg/dL. Rheumatoid factor is 256 IU/mL. Alanine aminotransferase is 128 IU/L, aspartate aminotransferase is 9 IU/L, and γ-glutamyl transferase is 396 IU/L. Which of the following is the most likely diagnosis?

A. Acute schistosomiasis
B. Autoimmune hepatitis
C. Schistosomal glomerulonephritis
D. Concomitant virus-induced cryoglobulinemia
E. Superimposed rheumatoid arthritis

REFERENCES

1. Ghalioungui P. Magic and Medical Science in Ancient Egypt. London: Hodder and Stoughton; 1963.
2. Yang GJ, Vounatsou P, Zhou XN, et al. A review of geographic information system and remote sensing with applications to the epidemiology and control of schistosomiasis in China. Acta Trop. 2005;96:17–29.
3. Abdel-Wahab MF. Schistosomiasis in Egypt. Boca Raton, FL: CRC Press; 1982.
4. Barsoum RS. Schistosomiasis. In: Davison AM, Cameron JS, Grunfeld JP, et al., eds. Oxford Textbook of Clinical Nephrology. 3rd ed. Oxford: Oxford University Press; 2005:1173–1184.
5. Kayange NM, Smart LR, Tallman JE, et al. Kidney disease among children in sub-Saharan Africa: systematic review. Pediatr Res. 2015;77(2):272–281.
6. Neves PDMM, Jorge LB, Cavalcante LB, et al. Schistosomiasis-associated glomerulopathy: clinical aspects, pathological characteristics, and renal outcomes. Clin Nephrol. 2020;93(5):251–261.
7. Dos-Santos WLC, Sweet GMM, Azevêdo LG, et al. Current distribution pattern of biopsy-proven glomerular disease in Salvador, Brazil, 40 years after an initial assessment. J Bras Nefrol. 2017;39(4):376–383.
8. Chiamah OC, Ubachukwu PO, Anorue CO, et al. Urinary schistosomiasis in Ebonyi state, Nigeria from 2006 to 2017. J Vector Borne Dis. 2019;56(2):87–91.
9. Wahl SM, Frazier-Jessen M, Jin WW, et al. Cytokine regulation of schistosome-induced granuloma and fibrosis. Kidney Int. 1997;51:1370–1375.
10. Zheng B, Zhang J, Chen H, et al. T-Lymphocyte-Mediated liver Immunopathology of schistosomiasis. Front Immunol. 2020;11:61.
11. Barsoum RS. Schistosomiasis and the kidney. Semin Nephrol. 2003;23:4–41.
12. Hartgers FC, Smits HH, van der Kleij D, Yazdanbakhsh M. Innate, adaptive and regulatory responses in schistosomiasis: relationship to allergy. Chem Immunol Allergy. 2006;90:157–175.
13. deWater R, Van Marck EA, Fransen JA, Deelder AM. Schistosoma mansoni: ultrastructural localization of the circulating anodic antigen and the circulating cathodic antigen in the mouse kidney glomerulus. Am J Trop Med Hyg. 1988;38:118–124.
14. Abdel-Badie I, Barsoum RS. B-lymphocyte immunoglobulin surface expression in schistosomal glomerulopathy. Med J Ahmed Maher Hosp. 1999;1:1.
15. Barsoum RS. Schistosomal glomerulopathies. Kidney Int. 1993;44:1–12.
16. Houba V. Experimental renal disease due to schistosomiasis. Kidney Int. 1979;16:30–43.
17. Gryseels B. The relevance of schistosomiasis for public health. Trop Med Parasitol. 1989;40:134–142.
18. Mostafa M, Sheweita I, O’Connor P. Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev. 1999;12(1):97–111.
19. Gouda I, Mokhtar N, Bilal D, et al. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. J Egypt Natl Canc Inst. 2007;19:158–162.
20. Abd El-Aa1 A, Bayoumy I, Basyoni M, et al. Genomic instability in complicated and uncomplicated Egyptian schistosomiasis haematobium patients. Mol Cytogenet. 2015;8:1.
21. Zaghloul MS, Zaghloul TM, Bishr MK, et al. Urinary schistosomiasis and the associated bladder cancer: update. J Egypt Natl Canc Inst. 2020;32:44.
22. Nessim I, Francis M, Abdel-Rahman H, et al. Tubular proteins (TP) in hepatosplenic schistosomiasis (HSS). In: Proceedings of the 2nd International Congress of Geographical Nephrology. Egypt: Hurghada; 1993.
23. Duarte DB, Vanderlei LA, RKdA B, et al. Renal function in hepatosplenic schistosomiasis – an assessment of renal tubular disorders. PLoS One. 2014;9(12):e115197.
24. Duarte DB, Meneses GC, Lima DB, et al. Aquaporin-2 and NKCC2 expression pattern in patients with hepatosplenic. Schistosomiasis. 2020;25(9):1140–1144.

25. Scheiner B, Lindner G, Reiberger T, et al. Acid-base disorders in liver disease. J Hepatol. 2017;67:1062–1073.

26. Ezzat E, Osman R, Ahmed KY, Soothill JF. The association between Schistosoma haematobium infection and heavy proteinuria. Trans R Soc Trop Med Hyg. 1974;68:315–317.
27. Barsoum R. The changing face of schistosomal glomerulopathy. Kidney Int. 2004;66:2472–2484.
28. Barsoum R, Nabil M, Saady G, et al. Immunoglobulin A and the pathogenesis of schistosomal glomerulopathy. Kidney Int. 1996;50:920–928.
29. Araújo SA, Neves PDMM, Wanderley DC, Reis MAD, et al. The immunohistological profile of membranous nephropathy associated with chronic Schistosoma mansoni infection reveals a glomerulopathy with primary features. Kidney Int. 2019;96(3):793–794.
30. Neves PD, Bridi RA, Ramalho JA, et al. Schistosoma mansoni infection as a trigger to collapsing glomerulopathy in a patient with high-risk APOL1 genotype. PLoS Negl Trop Dis. 2020;14(10):e0008582.
31. Hathout Sel -D, Abd el-GhaffarY, Awny AY. Salmonellosis complicating schistosomiasis in Egypt. A new clinical appreciation. Am J Trop Med Hyg. 1967;16(4):462–472.
32. Kjetland EF1, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. AIDS. 2006;20(4):593–600.
33. Downs JA, van Dam GJ, Changalucha JM, et al. Association of schistosomiasis and HIV infection in Tanzania. Am J Trop Med Hyg. 2012;87(5):868–873.
34. Secor WE. The effects of schistosomiasis on HIV/AIDS infection, progression and transmission. Curr Opin HIV AIDS. 2012;7:254–259.
35. Ganley-Leal LM, Mwinzi PN, Cetre-Sossah CB, et al. Correlation between eosinophils and protection against reinfection with Schistosoma mansoni and the effect of human immunodeficiency virus type 1 coinfection in humans. Infect Immun. 2006;74(4):2169–2176.
36. Mbabazi PS, Andan O, Fitzgerald DW, et al. Examining the relationship between urogenital schistosomiasis and HIV infection. PLoS Negl Trop Dis. 2011;5(12):e1396.
37. Al-Freihi HM. Prevalence of hepatitis B surface antigenemia among patients with Schistosoma mansoni. Ann Saudi Med. 1993;13(2):121–125.
38. Al-Shamiri AH, Al-Taj MA, Ahmed AS. Prevalence and co-infections of schistosomiasis/hepatitis B and C viruses among school children in an endemic areas in Taiz, Yemen. Asian Pac J Trop Med. 2011;4(5):404–408.
39. Abruzzi A, Fried B, Alikhan SB. Coinfection of schistosoma species with hepatitis B or hepatitis C viruses. Adv Parasitol. 2016;91:111–231.
40. Du H. Relationship between advanced schistosomiasis and HBV infection. Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi. 2013;25(1):115–117.
41. Lemmer LB, Fripp PJ. Schistosomiasis and malignancy. S Afr Med J. 1994;84(3):211–215.
42. Cooper K, Haffajee Z, Taylor L. Human papilloma virus and schistosomiasis associated bladder cancer. Mol Pathol. 1997;50:145–148.
43. Swai B, Poggensee G, Mtweve S, et al. Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. BMC Infect Dis. 2006;6:134.
44. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the diagnosis of human schistosomiasis. Clin Microbiol Rev. 2015;28(4):939–967.
45. Cnops L, Soentjens P, Clerinx J, Van Esbroeck M. A Schistosoma haematobium-specific real-time PCR for diagnosis of urogenital schistosomiasis in serum samples of international travelers and migrants. PLoS Negl Trop Dis. 2013;7:e2413.
46. Bocanegra García C, Pintar Z, Serres X, Mendioroz J, et al. Ultrasound findings and associated factors to morbidity in Schistosoma haematobium infection in a highly endemic setting. Trop Med Int Health. 2018;23(2):221–228.
47. Midzi N, Butterworth AE, Mdluza T, et al. Use of circulating cathodic

antigen strips for the diagnosis of urinary schistosomiasis. Trans T Soc Trop Med Hyg. 2009;103:45.

48. Sandoval N, Siles-Lucas M, Pérez-Arellano JL, et al. A new PCRbased approach for the specific amplification of DNA from different Schistosoma species applicable to human urine samples. Parasitology. 2006;133:581.

References

49. Duarte DB, Lacerda MCSR, Ribeiro YJP, et al. Kidney biomarkers in tropical infections: an update. Pathog Glob Health. 2020;114(6):302–308.
50. Utzinger J, Tanner M, Keiser J. ACTs for schistosomiasis: do they act? Lancet Infect Dis. 2010;10(9):579–581.
51. Mahmoud KM, Sobh MA, El-Agroudy AE, et al. Impact of schistosomiasis on patient and graft outcome after renal transplantation: 10 years' followup. Nephrol Dial Transplant. 2001;16:2214–2221.

52. Valentim CL, Cioli D, Chevalier FD, et al. Genetic and molecular basis of drug resistance and species-specific drug action in schistosome parasites. Science. 2013;342(6164):1385–1389.
53. Azevedo LS, de Paula FJ, Ianhez LE, et al. Renal transplantation and schistosomiasis mansoni. Transplantation. 1987;44:795–798.
54. Kron M, Gordon C, Bauers T, et al. Persistence of schistosoma japonicum DNA in a kidney-liver transplant recipient. Am J Trop Med Hyg. 2019;100(3):584–587.

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Glomerular Diseases Associated With Infection

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More than 250 years ago, dark, scanty urine was observed during convalescence from scarlatina infection. Richard Bright and others identified nephritis symptoms in patients with scarlet fever in the nineteenth century. In the early 1900s, von Pirquet proposed that nephritis occurring after scarlet fever resulted from antibodies that were pathogenic, an insight that unlocked the field of immune-mediated kidney disease. We now recognize that many infectious organisms can induce a spectrum of glomerular lesions via differing pathogenetic mechanisms, including immune complex deposition, direct kidney cell infection and injury, and sequelae of ongoing chronic inflammation (Table 57.1). Glomerular injury may occur secondary to resolved or ongoing infection; therefore, the preferred term is infection-related glomerulonephritis (GN).1 As demographics, health care access, and public health conditions change, there are alterations in the epidemiology, clinical presentation, morphology, and therapeutic approaches to infectionrelated glomerulonephritides.2 Table 57.2 shows the glomerular lesions associated with specific microorganisms.

BACTERIAL INFECTIONS

Poststreptococcal Glomerulonephritis

Etiology and Pathogenesis

Poststreptococcal GN (PSGN) is an immune complex–mediated lesion occurring after infection with a nephritogenic bacterial strain. Poststreptococcal GN traditionally was considered a complication of group A β-hemolytic streptococci infections of the skin (M types 49, 55, 57, 60) or upper respiratory tract (M types 1, 2, 4, 12), but PSGN can result from infections caused by other M type streptococci and other groups (particularly group C Streptococcus zooepidemicus). There are three immunologic mechanisms likely involved in streptococcalassociated GN: passive entrapment and deposition of circulating immune complexes, in situ immune complex formation associated with nephritogenic planted bacterial antigens or intrinsic antigens displaying molecular mimicry, and deposition of nephritogenic bacterial antigens that activate plasmin resulting in local complement activation.3-6

Two nephritogenic streptococcal antigens are thought to be involved in PSGN immune complex formation: nephritis-associated plasmin receptor (NAPlr), characterized as glyceraldehyde-3-phosphate dehydrogenase, and the streptococcal pyrogenic exotoxin B (SPEB) together with its more immunogenic zymogen precursor (zSPEB).

Evidence for nephritogenicity includes demonstration of NAPlr and SPEB in kidney biopsies with acute PSGN, and elevation of antibody titers to both antigens in most convalescent sera.5 In a Japanese study, 92% of PSGN convalescent sera and 60% of sera from patients with uncomplicated streptococcal infections contained anti-NAPlr antibodies.7 Nephritis-associated plasmin receptor has been localized to glomerular areas with plasmin-like activity but not with complement or immunoglobulin, suggesting local binding to plasmin produces glomerular inflammation and enhances immune complex deposition.3 7

Streptococcal pyrogenic exotoxin B also can bind plasmin, a possible common mechanism of action. However, unlike NAPlr, SPEB colocalizes with glomerular complement and immunoglobulin G (IgG), suggesting participation in immune-mediated glomerular damage.4

Streptococcal pyrogenic exotoxin B is the only streptococcal nephritogenic antigen demonstrated in subepithelial “hump” deposits characteristic of PSGN, possibly because of its cationic charge. Studies from Latin America and Central Europe demonstrated only SPEB in PSGN kidney biopsy tissue. In contrast, the S. zooepidemicus strain responsible for a Brazilian epidemic lacked the SPEB-related gene, suggesting that different streptococcal antigens induce PSGN in different ethnic groups.8

Thus, there likely are multiple nephritogenic antigens depending on the streptococcal species and genetic and other host factors.

Poststreptococcal GN is thought to occur when glomerular immune complexes or deposition of plasmin-activating nephritogenic bacterial antigens initiate an inflammatory cascade with local complement activation and recruitment of neutrophils and monocytemacrophages. Subepithelial immune deposits develop associated with cationic antigens (e.g., SPEB) resulting from subendothelial immune complex dissociation, transit through, and reformation on the outer glomerular basement membrane, or in situ immune complex formation. Complement activation in PSGN has garnered renewed interest.

In most patients with PSGN, serum C1q is normal while C3 is reduced, indicating predominantly alternative complement pathway activation. Because streptococcal antigens induce a robust antibody response, the classic complement pathway likely fails to be activated due to streptococcal produced “evasins” that bind C1q (endopeptidase O) and degrade IgG (IdeS/Mac-1, Mac-2, and endopeptidase S). Lectin complement pathway activation, characterized by early C4 level reduction, has been demonstrated in a significant number of patients with PSGN. One study identified mesangial deposits of mannose-binding lectin (MBL) and other lectin pathway components in 7 of 18 patients with PSGN.9 However, lectin pathway activation is not required, as PSGN can develop in patients with MBL deficiency.

The demonstration of pathogenic autoantibodies in PSGN has renewed interest in other autoimmune aspects of this disease.10 Rheumatoid factors (especially IgG) and cryoglobulins have been found in 35% of patient sera in the first week of disease. Rheumatoid factors were demonstrated in PSGN kidney tissue and kidney eluates from a fatal case. Loss of sialic acid from autologous IgG, due to streptococcal neuraminidase or from IgG Fc fragment binding to type II Fc receptors in the streptococcal wall, may induce anti-IgG reactivity. This anti-IgG antibody may play a role in deposition of IgG-containing complexes. Additional autoimmune manifestations include anti-C1q antibodies, particularly in severe cases, and rarely anti-DNA reactivity, antineutrophil cytoplasmic autoantibodies (ANCAs), and autoimmune hemolytic anemia.10

TABLE 57.1

Pathogenetic Mechanisms of Infection-Related Glomerular Injury

Mechanism	Representative Microorganism	Supportive Evidence
Circulating immune complexes	Streptococcus	Circulating antibodies against SPEB and NAPlr antigens
In situ immune complex formation	Streptococcus	Identification of SPEB in subepithelial deposits in PSGN
Nephritogenic antigen deposition with complement activation	Streptococcus	Glomerular deposition of NAPlr with plasmin activity
Superantigen binding to APCs activates T cells and polyclonal B cells, inducing immunoglobulin production	Staphylococcus	Selective peripheral blood activation of TCR Vβ repertoire
Direct kidney cell infection	HIV, parvovirus	Virus identification in glomerular epithelial cells
Direct kidney cell injury	HBV	HBV induces mesangial cell proliferation and type IV collagen production in vitro
Cryoglobulin production	HCV	IgM rheumatoid factor against the HCV E2 envelope protein
Complement activation	Streptococcus	Low C3 levels, lectin deposits, serum antifactor B autoantibodies

APC, Antigen-presenting cell; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgM, immunoglobulin M; NAPlr, nephritis-associated plasmin receptor; PSGN, poststreptococcal glomerulonephritis; SPEB, streptococcal pyrogenic exotoxin B.

TABLE 57.2

Infectious Organisms Causing Glomerular Injury

Microorganism	Associated Glomerular Lesions[a]
Bacteria	
Gram Positive	
Streptococci	DPGN, MPGN, DDD, IgA-dominant IRGN
Staphylococci	IgA-dominant IRGN, EPGN, DPGN, MesPGN, ICMGN, crescentic GN
Pneumococcus	
Propionibacterium	
Corynebacterium	

EPGN, MPGN
MPGN, ICMGN (shunt nephritis)
MPGN, ICMGN (shunt nephritis)

Gram Negative
Brucella
Campylobacter
Escherichia coli
Haemophilus
Klebsiella
Legionella
Meningococci
Pseudomonas
Rickettsia
Salmonella
Serratia
Yersinia

ICMGN
DPGN, MesPGN
IgA-dominant IRGN
IgAN
DPGN, IgA-dominant IRGN
Crescentic GN, EPGN, MesPGN
MesPGN, DPGN
MPGN, ICMGN (shunt nephritis)
Crescentic GN
MesPGN, IgAN
MPGN, ICMGN (shunt nephritis)
IgAN, EPGN

Other
Bartonella
Coxiella
Leptospira
Mycobacteria
Mycoplasma
Treponema

Crescentic GN (endocarditis)
Crescentic GN (endocarditis)
Segmental glomerular necrosis
MPGN, ICMGN, DPGN, amyloidosis
ICMGN
MN, MPGN, DPGN, MesPGN

Viruses
Hepatitis A
Hepatitis B
Hepatitis C
HIV
Parvovirus B19
Adenovirus
Coxsackie B virus
Cytomegalovirus
Dengue
Epstein-Barr
Hantavirus

MPGN, IgAN, MesPGN
MN, MPGN + cryoglobins, DPGN with cryoglobulins, EPGN, MesPGN, IgAN, FSGS, amyloidosis
MPGN ± cryoglobulins, MN, fibrillary GN, immunotactoid GN, MesPGN, collapsing GP
Collapsing GP, FSGS, IgAN, ICMGN (including lupus-like), MCD

Collapsing GP, ICMGN, EPGN, IgAN, FSGS
EPGN, MesPGN
Proliferative GN
MPGN, MesPGN, collapsing GP, MN, crescentic GN
MesPGN
Collapsing GP, MN, crescentic GN, MPGN, EPGN, MesPGN
MCD, MesPGN

TABLE 57.2

Infectious Organisms Causing Glomerular Injury—cont’d

Microorganism	Associated Glomerular Lesions[a]
Influenza	MesPGN, DPGN
Measles	DPGN
Mumps	MesPGN, DPGN
Rotavirus	MesPGN
Varicella	MesPGN, DPGN
Parasites and Protozoa (see Table 57.3 for more detail)	
Echinococcus	MN, MPGN
Filaria	MesPGN, MPGN, DPGN ± eosinophils, EPGN, MN, MCD, FSGS, collapsing GP, amyloidosis
Malaria	MPGN, MesPGN, MN, IgAN, MCD, FSGS, collapsing GP
Leishmania	MesPGN, MPGN, amyloidosis
Schistosoma	MPGN, FSGS, MesPGN, MN, amyloidosis
With Salmonella	PIGN
Toxoplasma	MPGN, FSGS, MesPGN
Trichinella	MesPGN, MPGN
Trypanosoma	MesPGN, MPGN

[a] These are glomerular lesions described in humans. More infection-associated glomerulopathies have been identified in animal models.

DDD, Dense deposit disease; DPGN, diffuse proliferative glomerulonephritis; EPGN, endocapillary proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GP, glomerulopathy; ICMGN, immune complex–mediated glomerulonephritis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IRGN, infection-related glomerulonephritis; MCD, minimal change disease; MesPGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis pattern; PIGN, immune complex-–mediated postinfectious glomerulonephritis.

Epidemiology

The incidence of PSGN is decreasing worldwide; however, it remains high in low-income countries, with an incidence of 9.3 to 28.5 per 100,000 inhabitants.[2,11] Over the past several decades, likely because of early antibiotic administration, the incidence of PSGN has decreased to 0.2 to 0.6 cases per 100,000 person-years in wealthy countries.12 Poststreptococcal GN now is more common in older adults with comorbid conditions such as diabetes, alcoholism, and malignancy.2 6 The higher incidence in low-income countries and in alcoholics likely is associated with poor socioeconomic conditions, limited health care access, delayed antibiotic administration, and a tropical climate. Poststreptococcal GN is the most common finding in children with acute nephritis in low-income countries occurring sporadically or in epidemics. It typically affects those 2 to 14 years old, with a 2:1 male predominance, and represents a major problem in indigenous populations as in Australia, where more than 95% of cases occur in aboriginal people residing in remote locations.13 The risk for PSGN varies with infection site and nephritogenic bacterial strain, ranging from 5% in throat infections to 25% in skin infection with the M type 49 streptococcus, and is diminished with early antibiotic therapy. Epidemics have been associated with both skin and throat infection, as well as consumption of unpasteurized milk from cows with mastitis caused by S. zooepidemicus. There is also a genetic predisposition: PSGN is associated with human leukocyte antigen (HLA)-DR4 and HLA-DR1 expression, and siblings of sporadically affected patients have a 38% risk for developing clinical or subclinical glomerular disease.6

Clinical Manifestations

Poststreptococcal GN presents differently in children and older debilitated adults. Symptomatic children typically present with acute nephritic syndrome, microhematuria in 100%, macroscopic hematuria in 30%, hypertension in 80%, edema in 80% to 90% (chief complaint in 60%), and oliguria in 25% to 40%. Nephrotic syndrome occurs in 2%, and ascites is uncommon. In contrast, 20% of adults with PSGN have nephrotic syndrome, 80% to 86% have hypertension, 83% have kidney impairment,

and 43% have congestive heart failure. Rapidly progressive kidney failure with glomerular crescents occurs in less than 1% of children and adults. Asymptomatic subclinical cases have microscopic hematuria, and transient hypocomplementemia is 4 times more frequent compared with symptomatic cases where hypocomplementemia typically is sustained. Serum CH50 is low and reduced C3 levels occur in more than 90% of patients in the first week of disease; these normalize within 2 months of disease resolution. Serum C1 levels are normal and C4 may be depressed early in disease. Eighty percent have elevated IgG and IgM with normal IgA in contrast to rheumatic fever, which has increased IgA levels in 80% of the patients. Cryoglobulins, rheumatoid factor, and anti-C1q antibodies occur in up to one-third of patients in the acute phase. Families may have various manifestations of PSGN; therefore, eliciting a family history for streptococcal infection and signs of glomerular disease is recommended. Most patients give a history of streptococcal infection, although it often has resolved at presentation. Streptococcus cultures are positive in 10% to 70% of epidemic and in 20% to 25% of sporadic cases. The latent period between infection and nephritis symptoms is 2 to 4 weeks after skin infections and 7 to 10 days after throat infections. As cultures are often negative, antistreptococcal antibody levels are used to ascertain prior infection. The most widely used are antistreptolysin O (ASO) titers, increased in more than 65% of patients with PSGN following throat infections, and anti-DNAse B titers, elevated in 73% of postimpetigo cases. The more sensitive streptozyme panel measures anti-DNAse B, antihyaluronidase, antistreptolysin O, and antistreptokinase antibodies, and is positive in more than 80% of patients. Antibody titers to NAPlr and SPEB/zymogen are more sensitive and specific, but not available clinically.5 11

Pathology

Kidney biopsy is not routinely indicated in PSGN but may be required for confirmation when clinical features are atypical, such as nephrotic proteinuria, decreased C3 levels for more than a month (suggesting transformation to C3 glomerulopathy), worsening kidney dysfunction, or adult age. The most common appearance is diffuse endocapillary

C

B

A

D

E

Fig. 57.1 Poststreptococcal Glomerulonephritis. (A) Light microscopic appearance of diffuse proliferative and exudative glomerulonephritis. (B–D) Immunofluorescence for C3 showing the mesangial (B), starry sky (C), and garland (D) patterns. (E) Immune electron microscopy showing the characteristic subepithelial electron dense deposit (hump) with intramembranous extension (arrowheads), inside which streptococcal pyrogenic exotoxin B (SPE B) is demonstrated (arrows) (immunogold staining). BM, Basement membrane; P, podocyte. (From Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007;71[11]:1094–1104.)

GN characterized by endocapillary neutrophils with fewer monocytes and variable mesangial hypercellularity (Fig. 57.1). Less often or during resolution, there may be diffuse proliferative GN with more mesangial and variable endocapillary hypercellularity, focal endocapillary GN, or mesangial proliferative GN (mesPGN). A membranoproliferative GN (MPGN) pattern is infrequent; however, NAPlr antigen has been identified in biopsy samples with an MPGN pattern, suggesting PSGN may have varied histology. Small numbers of necrotizing and crescentic lesions occur in up to 50% of cases, whereas extensive crescent formation is unusual.14

Immunofluorescence shows dominant C3 staining, and the pattern varies with the phase of disease.15 In acute and subacute disease the immune deposits are in glomerular capillary walls and mesangial regions in a “starry sky” pattern containing strong C3 with less frequent and intense IgG, and IgM in up to 50% of cases; IgA and C1q are minimal or absent. The “garland” pattern is associated with numerous subepithelial hump deposits and heavy proteinuria corresponding to active disease, although also has been described in later disease. As deposits are cleared in subacute to chronic injury, mesangial deposits may persist resulting in a mesangial pattern with predominant C3, loss of immunoglobulins, and fewer infiltrating leukocytes (see Fig. 57.1). Although not routinely assessed, properdin and the terminal membrane attack complex C5b-C9 have been identified in capillary wall and mesangial deposits.16

Electron microscopy (EM) demonstrates subepithelial individual hump-shaped deposits, which are typical, although not pathognomonic, of PSGN. These deposits may be infrequent or abundant and are preferentially located where the capillary basement membrane reflects over the mesangium. Glomerulonephritis resolves with deposit clearing and cell apoptosis. However, deposit fragments may remain for years, appearing as weak, irregular, granular glomerular C3 staining with electron-lucent areas or an appearance of striated membranous structures indicative of remote immune complex deposition.17

Differential Diagnosis

In a patient with typical symptoms and serologic findings, the diagnosis is straightforward. However, when oliguria lasts more than a week, acute decrease in kidney function lasts 2 weeks, hypocomplementemia lasts more than 1 month, or without a preceding infection history, kidney biopsy is indicated. The differential diagnosis encompasses the spectrum of C3 glomerulopathies and crescentic GN (see Chapter 23). C3 GN may appear morphologically indistinct from PSGN, including subepithelial humps, diffuse endocapillary GN, and weak immunoglobulin deposition. Dense deposit disease demonstrates diagnostic electron-dense transformation of glomerular and tubular basement membranes. Correlating clinical findings, the patient course and C3 levels may be required for a correct diagnosis. Recently, Chauvet and colleagues[18] found that transient antifactor B antibodies, which activate C3 convertase activity, were present in 31 of 34 patients with PSGN and correlated with serum C3 levels. These antifactor B autoantibodies differed from C3 nephritic factor and permitted discrimination between PSGN and C3 glomerulopathy with a sensitivity of 95% and a specificity of 82%. When glomerular crescents on light microscopy occur together with a positive ANCA assay, the differential diagnosis is pauci-immune (ANCA-associated) crescentic GN; the diagnosis of PSGN depends on identifying C3-containing electron-dense deposits in a subepithelial pattern.

A

C

B

D

Fig. 57.2 Immunoglobulin A (IgA)-Dominant Glomerulonephritis (GN) in a Diabetic Patient With Methicillin-Sensitive Staphylococcus aureus Infection. (A) A diffuse exudative GN is present with neutrophil infiltration. (B) Immunofluorescence shows IgA irregular granular mesangial and capillary wall deposits. (C) Immunofluorescence shows C3 in a pattern similar to that of IgA. (D) Electron microscopy shows domeshaped subepithelial deposit (white arrow) and mesangial deposit (yellow arrow).

Natural History

Most children with PSGN recover with increased urine output and clinical symptom resolution in 7 to 10 days, and normalization of serologic tests within 1 month. End-stage kidney disease (ESKD) occurs in less than 1% of children observed for one to two decades after the acute attack.11 Following recovery, mild proteinuria (<500 mg/day) and microscopic hematuria may persist for up to 1 year without affecting the long-term prognosis. However, older patients with comorbidities are more likely to experience acute complications, including kidney impairment in 30% to 77%, congestive heart failure in 40%, nephrotic proteinuria in 20%, and mortality in up to 30%.11 19 A nephrotic presentation and persisting proteinuria are associated with worse long-term prognosis. Underlying alternative complement pathway dysregulation may increase risk for progressive kidney disease leading to C3 GN, which is now thought to encompass most cases of “atypical” postinfectious GN. Certain epidemics also have reported a high incidence of chronicity, perhaps related to more affected adults, who tend to have worse outcomes.20 Studies in Australian aboriginal communities have shown that PSGN in infancy increases risk for subsequent albuminuria, hematuria, and chronic kidney disease (CKD).19 The latter is attributed to a two-hit injury resulting from imposition of diabetes, metabolic syndrome, or low birth weight on early PSGN.

Treatment

Management includes culture and treatment of any persistent streptococcal infection. Early antibiotic treatment likely prevents PSGN, and

prophylactic treatment of family members in high-risk communities or epidemic circumstances may be indicated. Treatment is with oral penicillin, intramuscular penicillin (a single intramuscular injection of 1.2 million units of benzathine penicillin in adults, or half this dose in small children), erythromycin (in patients allergic to penicillin), or cephalosporins. Oral treatments are given in doses every 6 hours for 7 to 10 days.21 Treatment of acute nephritic syndrome includes fluid and sodium intake restriction and loop diuretic administration. An oral long-acting calcium antagonist is usually sufficient to control hypertension. Intravenous medications may be indicated in exceptional cases with hypertensive emergency. Dialysis (hemodialysis or peritoneal dialysis) is required in 25% to 30% of adults but seldom in children. Poststreptococcal GN complicated with crescents may benefit from pulse methylprednisolone. The prognosis of crescentic PSGN is significantly better than for crescentic GN from other causes, but residual impairment of kidney function occurs in more than half the cases.

Immunoglobulin A–Dominant Infection-Related Glomerulonephritis

Etiology and Pathogenesis

Immunoglobulin A–dominant infection-related GN (IRGN) is an immune complex–mediated lesion typically associated with Staphylococcus aureus infections in adult patients with underlying comorbidities.22 Koyama and colleagues23 suggested that the pathogenesis involves staphylococcal enterotoxins functioning as superantigens that bind directly to the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. This enterotoxin–MHC class II complex engages the Vβ T cell–receptor region, resulting in T cell activation and a cytokine burst, initiating a B cell polyclonal IgG and IgA response putatively against a S. aureus cell envelope antigen.23 This antigen colocalizes with glomerular IgA deposits and induces mesangial deposits in an experimental model.

Epidemiology

Immunoglobulin A–dominant IRGN usually occurs in the setting of ongoing (rather than resolved) infection in adults, with an average age of 58 and up to 41% over 65 years.24,25 There is a male predominance, and most patients have comorbidities, including diabetes in up to 65% of patients, malignancy, heart disease, or alcohol or substance abuse.6 The incidence is unknown, but IgA-dominant IRGN occurred in 1.6% of kidney biopsies in adults in one institution and appears to be increasing.26,27 In developed countries, it has a 300% increased prevalence compared with PSGN, and many cases of IgA-dominant IRGN likely are asymptomatic and undiagnosed. Approximately 65% of patients are infected with methicillinresistant S. aureus (MRSA), and 25% have methicillin-sensitive S. aureus (MSSA).24 The most frequent sites of infection are the skin and viscera, including pneumonia, endocarditis, and osteomyelitis. Although less common, other pathogens such as S. epidermidis, Streptococcus, Klebsiella, and Escherichia coli have been associated with IgA-dominant IRGN.6,22,25

Clinical Manifestations and Pathology

Active disease often presents with acute or rapidly progressive kidney failure or nephrotic range proteinuria in 50%. Hematuria is universal with gross hematuria in 25%.24 However, a mild clinical course is not uncommon, with subacute or chronic disease and delayed diagnosis due to underlying chronic disease in elderly patients. Low C3 levels are found in 55% to 70% of patients, and serum IgA levels may be mildly increased. Kidney biopsy reveals diffuse endocapillary or proliferative GN in 40% to 80% of cases, MesPGN in 20% to 60%, and crescentic GN (≥ 50% crescents) in less than 5%.24-26 A smaller number of crescents occurs in up to 35% and positive ANCA in 22%.27 The deposits contain weak to intense IgA with codominant C3 staining in the same pattern and kappa light chain similar to or greater than lambda.22,27 Electron microscopy shows mesangial deposits in most cases, with up to 83% having variable numbers of subepithelial hump deposits and half with small and less frequent subendothelial deposits2 (Fig. 57.2). A subset of patients with cirrhosis and staphylococcus, or few other bacterial infections, develop large confluent mesangial and subendothelial (wire loop-like) deposits with fewer subepithelial and intramembranous deposits, typically IgA dominant or codominant.28

Differential Diagnosis, Natural History, and Treatment

Differentiation from IgA nephropathy is important for treatment and outcome. Immunoglobulin A–dominant IRGN is favored in the presence of staphylococcal infection, hypocomplementemia, severe proteinuria, and kidney biopsy demonstrating immune staining and electron-dense deposits as detailed earlier and absent IgA in globally sclerotic glomeruli. Recently, differences in kidney tissue protein abundance in IgA nephropathy versus IgA-dominant IRGN were identified by mass spectrometry and confirmed by immunohistochemistry.29 There is a worse outcome compared with IgA nephropathy, likely because of underlying comorbid conditions. Mesangial IgA deposits may persist despite recovery from infection, possibly related to an underlying risk for IgA immune complex disease.

Active infection should be treated with appropriate antibiotics, and recovery of kidney function may result despite ongoing infection. Corticosteroid treatment is contraindicated, at least during active

infection, highlighting the importance of differentiation from IgA nephropathy, in which corticosteroids may be indicated in severe cases (see Chapter 24).

Staphylococcus-Associated Glomerulonephritis

Etiology, Pathogenesis, and Epidemiology

Infection with MRSA, MSSA, and methicillin-resistant and methicillin-sensitive Staphylococcus epidermidis can cause GN, usually IgAdominant IRGN, endocarditis-associated GN, or shunt nephritis.
However, a minority of patients with staphylococcal infection will develop GN that does not fit into these categories.12,24 As described earlier, the infection results in immune complex deposition in most cases. In addition, an S. aureus plasmid-encoded peptide homologous to the myeloperoxidase (MPO) T cell epitope has been shown to induce MPO-ANCA, possibly inducing crescents and vasculitis in some patients.12 Staphylococcal infection–related GN has increased over the past three to four decades, although the incidence and prevalence are unknown. Most patients with staphylococcal-associated GN are adults and have comorbidities.

Clinical Manifestations and Pathology

There is no latent infection-free period, although the presence or source of infection may not be obvious. Low C3 is found in 30% to 50%, C4 levels are normal, and ANCA may be positive.
Hematuria, proteinuria, often in the nephrotic range, and acute kidney injury (AKI) variably occur. Glomerular lesions other than those previously indicated include MesPGN, diffuse endocapillary or proliferative GN, and necrosis and crescents. Immunofluorescence reveals moderate to strong glomerular C3 staining in most biopsies, weak IgA staining in 10%, no IgA or IgG in 15%, and a pauci-immune pattern in 13%.27 Electron microscopy shows mesangial and few subendothelial deposits, and subepithelial humps in less than one-third of cases.

Differential Diagnosis and Treatment

The differential diagnosis for the manifestations of staphylococcalassociated GNs includes PSGN, IgA nephropathy, IgA vasculitis, C3 GN, ANCA-associated crescentic GN, and rarely cryoglobulinemia. Clinical pathologic correlation and a search for infection, including endocarditis, are necessary. Treatment involves eliminating the infection and supportive care. Immunosuppression is contraindicated during active infection and has not been shown to improve outcome in this setting.

Endocarditis-Associated Glomerulonephritis

Etiology and Pathogenesis

Endocarditis may be an acute or subacute infection. Approximately onethird of patients with endocarditis develop AKI secondary to GN, kidney emboli (infarcts and cortical necrosis), or treatment (drug-induced interstitial nephritis). The pathogenesis of endocarditis-associated GN involves deposition of immune complexes containing bacterial antigens similar to that proposed for PSGN. Less virulent organisms with longer undiagnosed endocarditis may predispose to immune complex formation and development of GN.30 Polyclonal type III cryoglobulins occur in 50% of patients but rarely deposit in glomeruli. Some bacteria, classically MRSA, express superantigens that can activate T cells directly leading to a polyclonal gammopathy and immune complex GN.

Epidemiology

Historically, infective endocarditis (IE) affected young adults with rheumatic heart disease; however, it now occurs in older and at-risk patients, including drug users, prosthetic valve and implantable device recipients, and those with human immunodeficiency virus (HIV) and hepatitis C infection, diabetes, and health care–associated bacteremia.[30,31] S. aureus and S. epidermidis cause more than half of the endocarditis-associated

GN31 and are the most common pathogens in hospital-acquired IE. Streptococcus infections are more frequent in community-acquired and native valve endocarditis, although MRSA-associated communityacquired IE is increasing.32 Gram-negative bacteria (Enterococcus faecalis, E. coli, Brucella, and Proteus) and HACEK microorganisms (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella) less frequently cause IE. Culture-negative IE is usually caused by Coxiella burnetii, Bartonella spp., and Tropheryma whipplei in untreated patients and by streptococcal species in those with prior antibiotic administration.33 The HACEK organisms require special laboratory procedures; if these are not used, infected patients will be culture negative. Bartonella henselae endocarditis is frequently associated with congenital valvular disease and exposure to cats. Polybacterial infections are usually associated with drug abuse.

Clinical Manifestations

Patients often have fever, arthralgias, anemia, and purpura. Rarely, IE may present as primary kidney disease without systemic symptoms. Classic findings such as Osler nodes, Janeway lesions, and splinter hemorrhages are rare, and the diagnosis may be missed until autopsy in 38% of patients.30 The most common kidney presentation is AKI, and microhematuria and proteinuria are almost universally present, whereas nephrotic syndrome and rapidly progressive glomerulonephritis (RPGN) are infrequent. Risk factors include intravenous drug in 29% of patients and cardiac valvular disease in 30%.31 Decreased C3 and C4 levels, elevated rheumatoid factor, circulating immune complexes, and type III cryoglobulins are found in 50%, whereas ANCAs occur in 22% of patients. In those who develop GN, hypocomplementemia, particularly C3, is more frequent, suggesting alternative complement pathway activation. However, complement levels may be normal in superantigen-mediated GN.31

Pathology

Autopsy studies have demonstrated glomerular lesions in 7% to 17% of those with IE, including crescentic GN, MPGN, and focal and diffuse proliferative GN patterns, although morphologic details are not uniformly provided.30 Kidney biopsy findings also are variable, with up to 45% of biopsies demonstrating GN, including 55% crescentic GN, 35% diffuse or focal endocapillary GN, 10% MesPGN, and infrequently MPGN31 (Fig. 57.3). Immunofluorescence discloses pauciimmune GN in 44%. All proliferative GN cases have C3 staining with IgG or IgA in mesangial regions in more than half and less often in capillary walls. Electron-dense deposits occur in 90% of all GNs, mesangial in 85%, subepithelial humps in 49%, and subendothelial in 45% of the cases.31,34

Differential Diagnosis, Natural History, and Treatment

In crescentic GN with or without positive ANCA titers, hypocomplementemia should raise suspicion for underlying IE. Antibiotic treatment usually eradicates the endocarditis and corrects the serologic abnormalities. However, microhematuria, proteinuria, and decreased kidney function may persist for months after successful therapy. The overall mortality of IE is 20% and increases to 36% in patients who develop kidney failure; only 32% of the surviving patients have complete recovery of kidney function.31 Early diagnosis, risk stratification, and prompt antibiotic therapy are critical for successful resolution, with diminution of circulating immune complex levels correlating with better outcomes.35 In patients with crescentic GN, pulse plasma exchange with and without steroids has been used in addition to appropriate antibiotic therapy, but the value is unconfirmed. Immunosuppression currently is considered contraindicated in IE-associated crescentic GN.12

Shunt Nephritis

Etiology, Pathogenesis, and Epidemiology

Shunt nephritis is an immune complex GN that may develop in association with central nervous system shunt infections. It is rare in ventriculoperitoneal or ventriculovascular shunts presently used, but approximately 6% of previously used ventriculoatrial shunts became infected. Glomerulonephritis develops in 0.7% to 2% with infected shunts 2 months to many years after insertion, and is decreasing due to improved shunt infection rates. The microorganisms are usually S. epidermidis, S. aureus, or Propionibacterium acnes, and less often diphtheroids, Pseudomonas, Serratia, or Corynebacterium.

Clinical Manifestations and Pathology

Children are most frequently affected, typically within 6 months of surgery, with recurrent low-grade fever, arthralgias, weight loss, anemia, rash, hepatosplenomegaly, hypertension, and signs of increased intracranial pressure.12 There may be no signs of systemic infection. Microscopic hematuria occurs in 90%, often with nephrotic range proteinuria. Serologic findings include elevated rheumatoid factor, cryoglobulinemia, decreased serum C3, less often reduced C4, and occasionally positive PR3ANCA titers. Cerebrospinal fluid may demonstrate eosinophils. Kidney histology shows an MPGN pattern or MesPGN with variable crescent formation, and IgM, IgG, and C3 containing electron-dense deposits in subendothelial and mesangial regions. Cerebrospinal fluid cultures obtained by tapping the shunt are positive for the pathogen, but repeated cultures may be required due to the low numbers of bacteria.

Natural History and Treatment

Treatment requires antibiotic therapy and prompt removal of the infected shunt, usually replaced by a ventriculoperitoneal shunt. Delay in diagnosis and shunt removal worsens the kidney prognosis. If dialysis is required, hemodialysis is preferred because peritonitis carries the risk for meningitis in patients with a ventriculoperitoneal shunt. Complete recovery occurs in more than half of the patients, whereas 22% have persistent urinary abnormalities and 6% develop ESKD.

Glomerulonephritis Associated With Other Bacterial Infections

Osteomyelitis and intraabdominal, pelvic, pleural, and dental abscesses can be associated with GN, typically when infection persists for several months. Kidney disease encompasses mild urinary abnormalities to RPGN, with nephrotic syndrome the most frequent presentation, usually with normal complement levels. Kidney biopsy reveals an MPGN pattern, diffuse endocapillary or proliferative GN, MesPGN, or IgAdominant IRGN, with or without crescents. If started early, antibiotic treatment may result in recovery of kidney function.

Congenital, secondary, or early latent syphilis may be associated with GN. In congenital syphilis, nephrotic syndrome may be the primary clinical manifestation, with anasarca occurring 4 to 12 weeks after birth. Kidney involvement is uncommon in acquired syphilis, and usually occurs with secondary syphilis. The presentation is nephrotic syndrome or occasionally acute nephritis. Membranous nephropathy (MN) is the most common glomerular finding, but diffuse proliferative GN with or without crescents, an MPGN pattern, MesPGN, and rarely minimal change disease (MCD) have been observed. Treponemal antigens may be identified in the immune deposits. Syphilitic GN responds to antibiotic treatment, often with rapid resolution of nephrotic syndrome in MN, although remission may not occur for 4 to 18 months, particularly with other glomerular manifestations.

Acute typhoid fever from Salmonella typhi is characterized by fever, splenomegaly, and gastrointestinal symptoms. In severe cases, disseminated intravascular coagulation or thrombotic microangiopathy

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Fig. 57.3 Crescentic Glomerulonephritis Associated With Infective Endocarditis. (A) Glomerulus with a necrotizing and cellular crescent. Note the uninvolved tufts have no inflammation or hypercellularity (arrow). (B) Immunofluorescence for C3 with mesangial staining pattern. (C) Small electron dense deposits (arrows) are in mesangial regions without subepithelial hump deposits.

occur rarely. Microhematuria and mild proteinuria appear in 25% of patients with MesPGN.36

Leprosy (Mycobacterium leprae infection) affects 10 to 15 million patients worldwide, with up to 45% having glomerular disease. Glomerulonephritis is immune complex mediated with frequent hypocomplementemia. Nonnephrotic to nephrotic range proteinuria occurs in 2% to 68%, and kidney dysfunction occurs in 4% of patients.37 38 Nephrotic syndrome is rare and is usually associated with amyloidosis, often with erythema nodosum.38 Prospective studies demonstrate increased serum creatinine in 35% of patients at some time during their course, and hypertension is common. Kidney biopsy shows proliferative GN and MN with similar frequencies, whereas in autopsy studies, 4% to 31% have amyloidosis, and 5% to 14% demonstrate MPGN or diffuse proliferative GN with IgG, C3, and less frequently IgM, IgA, and fibrin deposition.36 The incidence of reduced kidney function decreases to 9% after 8 months of multidrug therapy.

Pneumococcal pneumonia is rarely associated with microhematuria and proteinuria, seen with delayed treatment. Diffuse endocapillary GN with crescents and MPGN have been reported, with pneumococcal antigen in the immune deposits. Streptococcus pneumoniae is rarely associated with hemolytic uremic syndrome due to unmasking of the glomerular and erythrocyte Thomsen-Friedenreich antigen by pneumococcal neuraminidase A, allowing preformed antibodies to bind and elicit an immune response.

Gastroenteritis caused by Campylobacter jejuni may be associated with MesPGN or diffuse proliferative GN. Other bacteria, including E. coli, Yersinia, meningococcus, and Mycoplasma pneumonia, may induce GN in this setting (see Table 57.2).

CHAPTER 57 Glomerular Diseases Associated With Infection

VIRAL INFECTIONS

Glomerular injury can occur in several viral infections, primarily hepatitis B virus (HBV), hepatitis C virus (HCV) (see Chapter 22), and HIV (see Chapter 58). These may coincide with acute or chronic infection, depending on the virus and host response, including genetic risk factors such as APOL1. The advent of better antiviral therapeutic agents has modified associated glomerulopathies and improved prognoses for patients with virus-associated GN.

Hepatitis A–Associated Glomerulonephritis

Hepatitis A virus (HAV) infection has increased in the last few years in the United States with an epidemiologic shift from contaminated foods to drug abuse and person-to-person transmission leading to updates in vaccination strategies; associated kidney involvement is uncommon.39 Immunoglobulin A nephropathy has been temporally associated with HAV, with simultaneous resolution of the viral infection and GN suggesting a causal relationship. There are case reports of MesPGN and MPGN, including with dominant IgA. There is experimental evidence for HAV-associated mesangial proliferation and immune complex GN, further supporting causation in humans. Patients present with microscopic hematuria and nonnephrotic proteinuria or may be nephrotic, particularly in association with MPGN. Glomerulonephritis resolution usually coincides with recovery from the viral infection.

Hepatitis B–Associated Glomerular Lesions

Etiology and Pathogenesis

Hepatitis B virus is a DNA virus of the Hepadnaviridae family and contains the hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg), which is a splice variant of the core antigen. The virus causes immune complex–mediated glomerular injury predominantly through deposition of circulating immune complexes that have been identified in the serum of infected patients with GN. Immune complexes contain the three major hepatitis B antigens, which differ in specific glomerular locations likely related to their size and charge.1 Hepatitis B e antigen is in smaller cationic subepithelial immune complexes in MN. The larger HBcAg and HBsAg typically deposit in subendothelial and mesangial regions.1,40 In situ immune complex formation may occur associated with locally expressed HBcAg, evidenced by identification of glomerular HBcAg and its corresponding RNA. Hepatitis B virus may directly injure glomerular cells, as it induces mesangial cell proliferation and increased type IV collagen production in vitro. There likely are contributing host factors, including MHC class II risk alleles.

Epidemiology

Chronic HBV infection is defined as persistence of HBsAg-positive serology without IgM antibodies to HBcAg. Persistent infection occurs in 0.1% to 15% of those with HBV infection and afflicts approximately 350 million people worldwide, who often are asymptomatic.
Infection with HBV becomes chronic in more than 90% of infants, 25% to 50% of children infected between 1 and 5 years of age, and 6% to 10% of older children and adults. Vertical transmission (maternalinfant) often occurs in endemic areas, such as China and Southeast Asia. Horizontal transmission follows blood contamination or direct mucous membrane contact. The prevalence of HBV infection is lower in Europe and the United States, with most carriers becoming infected as adolescents or adults by horizontal transmission because of drug abuse, blood transfusions, or sexual relations.

Clinical Manifestations and Pathology

Acute HBV infection may cause nausea, vomiting, fever, hepatomegaly, and a short-lived serum sickness–like syndrome with urticaria,

maculopapular rash, neuropathy, arthralgias, arthritis, microscopic hematuria, and nonnephrotic proteinuria. There are no published kidney biopsy studies in acute infection, and kidney disease associated with acute infection resolves in 1 to 2 months associated with viral illness recovery. In chronic HBV infection, 3% to 5% of patients develop kidney disease; additionally, 10% to 30% of patients with chronic HBV are coinfected with HCV and 5% to 10% with HIV.1,40

Hepatitis B Virus–Associated Membranous Nephropathy

Membranous nephropathy is the most common glomerular disease in chronic HBV carriers. Children usually present between 6 and 12 years of age and show a strong male predominance, asymptomatic proteinuria or nephrotic syndrome, microhematuria, normal kidney function, and minimal liver disease.40 The prognosis is usually good with frequent spontaneous remission associated with anti-HBeAg antibody production. Adults develop proteinuria or nephrotic syndrome, often with impaired kidney function and liver disease; approximately 30% will progress to CKD and 10% to ESKD. Hypocomplementemia occurs in less than half the patients.

Kidney biopsy shows MN with active to clearing deposits depending on lesion chronicity. In contrast to primary MN, there often is mesangial hypercellularity with mesangial and/or subendothelial deposits indicative of a form of secondary MN. Endocapillary hypercellularity and endothelial cell tubuloreticular inclusions may occur. Circulating antiphospholipase A2 receptor (PLA2R) antibodies and PLA2R in subepithelial deposits typically are associated with primary MN. However, in HBV-endemic areas in Asia, PLA2R has been reported to colocalize with HBV antigens in glomerular deposits in HBV-associated MN; the significance of this is uncertain.1 Immunoglobulin G subclass staining of deposits may be helpful, as IgG4 usually dominates in primary MN but is nondominant in secondary MN.40 Both HBeAg and HBsAg may be identified in glomerular deposits, and HBeAg has been found in eluted proteins (Fig. 57.4).

Hepatitis B Virus–Associated Glomerulonephritis With a Membranoproliferative Pattern

An MPGN pattern is the second most frequent HBV-associated glomerular lesion, typically found in adults. Patients present with nephrotic or less frequently nonnephrotic proteinuria and microhematuria; half are hypertensive, and 20% have reduced kidney function.1 This pattern is associated with serum HBsAg and HBcAg and reduced serum C3 and C4 levels. Cryoglobulinemia, type II or more often type III, occasionally occurs in HBV-infected patients, whereas type II is more prevalent with concurrent HCV infection.1,40 Kidney biopsy shows an MPGN pattern with additional subepithelial deposits if there is concomitant MN, and HBsAg may be identified in mesangial and subendothelial deposits (see Fig. 57.5).

Other Hepatitis B Virus–Associated Glomerular Lesions

There are several reports of IgA nephropathy associated with HBV infection, including some that have entered a sustained remission of kidney disease following successful HBV treatment with pegylated interferon. Other studies have shown similar outcomes for patients with IgA nephropathy with and without HBV infection, possibly due to a coincidental association rather than a causal relationship. Immunoglobulin A nephropathy is highly prevalent in HBV-endemic areas in Asia, and mesangial IgA deposits occur in chronic liver disease secondary to impaired clearance of IgA circulating immune complexes (see Chapter 24). There is a report of 10 patients with chronic HBV infection and all three HBV antigens in the serum, showing diffuse endocapillary GN with uncommon subepithelial humps and glomerular HBsAg and HBV

DNA.41 Amyloid A amyloidosis is associated with chronic inflammatory diseases, has been identified in adults and children with chronic HBV infection, and presents with proteinuria

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A

C

Fig. 57.4 Hepatitis B–associated membranous nephropathy. (A) Irregular glomerular capillary due to small subepithelial spikes with segmental mesangial hypercellularity (arrow). (B) Immunofluorescence shows granular immunoglobulin G along capillary walls and segmentally in mesangial regions. (C) Electron microscopy shows subepithelial (white arrows) and mesangial (yellow arrows) electron-dense deposits.

or nephrotic syndrome. There are rare reports of MCD and collapsing glomerulopathy associated with HBV infection, with HBV DNA in shed urinary podocytes in the latter, suggesting direct HBV infection. Clinical remission occurred after successful HBV infection treatment.40

Polyarteritis Nodosa

This vasculitis has been associated with HBV infection and is discussed in Chapter 26

Treatment

This section addresses only the treatment of patients with GN related to HBV infection (positive HBe antigen or HBV DNA more than 2000 units in HBeAg negative patients). Antiviral treatment is indicated in this setting, as there is consistent evidence that treatment response is associated with reduction in proteinuria. Interferon or nucleoside/nucleotide monotherapy induces seroconversion of positive HBeAg to anti-HBe, and the decrease in HBV DNA levels is associated with significant reduction of proteinuria in 30% to 80% of patients.42 43

Interferon therapy has a high rate of seroconversion and sustained remission, although side effects can be frequent and severe.44 Pegylated interferon may be used in young patients with mild hepatitis and low viral load if not contraindicated (advanced liver disease, leukopenia, thrombocytopenia, depression, pregnancy) but should not be used to treat patients with replicative HBV infection and glomerulonephritis.

In most patients, nucleoside/nucleotide therapy may be chosen, including lamivudine, adefovir, telbivudine, entecavir, or tenofovir, which are all given orally. Nucleoside/nucleotide analog administration should be maintained until HBe antigenemia disappears, usually 4 to 5 years or longer. Early therapy discontinuation increases the risk of virus-related liver failure. All nucleoside/nucleotide drugs are excreted by the kidney in unchanged form, and some have dose-related nephrotoxicity,44 which is increased with comorbidities including diabetes, hypertension, and CKD.45

Entecavir and tenofovir are preferred initial therapies due to higher antiviral activity and lower resistance rates compared with other nucleoside/nucleotide agents. Entecavir is generally safe and is used for treatment and prophylaxis of HBV infection in kidney transplant patients. The dose of entecavir is 0.5 mg/day when CrCl is 50 mL/min or more, 0.25 mg/day or 0.5 mg every 48 hours if CrCl is 30 to 50 mL/min, 0.15 mg/day or 0.5 mg every 72 hours if CrCl is 10 to 29 mL/min, and 0.5 mg weekly if CrCl is less than 10 mL/min or the patient is on hemodialysis. Entecavir treatment can be complicated by lactic

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Fig. 57.5 Hepatitis B–Associated Membranoproliferative Glomerulonephritis (MPGN). (A) MPGN pattern of injury with a lobular hypercellular glomerulus. (B) Predominantly mesangial staining for C3 by immunofluorescence. (C) Capillary wall and lesser mesangial staining by immunofluorescence for immunoglobulin M. (D) Hepatitis B surface antigen staining most prominent in mesangial regions. (E) Subendothelial and mesangial electron dense deposits.

acidosis in patients with impaired liver function. Tenofovir is used as initial therapy or in patients with resistance to other drugs. The main adverse effects are reduced bone density (osteomalacia) and nephrotoxicity with proximal tubular mitochondriopathy and Fanconi syndrome. Formulations include tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), the latter a newer formulation with better stability and more hepatic uptake, requiring substantially lower doses for comparable antiviral activity. A dose of 25 mg of TAF induces similar reduction of HBV DNA levels as low as 300 mg of TDF without adverse effects.46 Patients switched from TDF to TAF demonstrate improvements in bone density and urinary biomarkers. The dose of TDF is 300 mg/day if CrCl is 50 mL/min or higher, 300 mg every 48 hours if CrCl is 30 to 49 mL/min, 300 mg every 72 to 96 hours if CrCl is 10 to 39 mL/min, and 300 mg once a week if the patient is on hemodialysis. The dose of TAF is 25 mg/day if CrCl is 15 mL/min or more, and in those with CrCl less than 15 mL/min and on hemodialysis, the dose is 25 mg after dialysis on hemodialysis days. Insufficient data are available to recommend doses of TDF or TAF in patients with CrCl less than 10 to 15 mL/min who are not receiving hemodialysis or who are receiving peritoneal dialysis.

Other nucleoside/nucleotide drugs are less effective with a higher incidence of resistance. Lamivudine is a second-line therapy with a 20% annual rate of resistance. Lamivudine dosage (100 mg/day) is reduced to 50 mg/day after the first dose if CrCl is 30 to 49 mL/min, to 25 mg/day if CrCl is 15 to 29 mL/min, to 15 mg/day if CrCl is 5 to 14 mL/min, and to 10 mg/day in those on hemodialysis or peritoneal dialysis. Serious adverse effects are rare and include liver failure and rhabdomyolysis. Telbivudine has a 25% annual resistance rate, and serious adverse effects include myopathy (cumulative incidence of creatine kinase elevation is 84%), peripheral neuropathy (particularly combined with peg-interferon), hepatoxicity, and lactic acidosis. Adefovir is rarely used today due to high resistance rate and dose-dependent nephrotoxicity and Fanconi syndrome that may persist for months after drug withdrawal.

Antiviral drug combinations have been used with variable success, but there is no convincing evidence that initial combination therapy with two nucleoside analogs is better than monotherapy.

Patients with concomitant HBV and HCV infections and GN should have HBV DNA and HCV RNA assessed to determine which virus is more likely responsible for the kidney disease. Direct-acting antivirals used to treat HCV infections may activate HBsAg without affecting HBV-associated GN; therefore, patients with combined infections should be treated with interferon that is active against both viruses or have concurrent administration of direct-acting antivirals and nucleoside/nucleotide drugs.

Treatment of HBV-related GN should be limited to antiviral therapy in most patients because seroconversion from HBeAg positive to antiHBe and reduced HBV DNA levels usually induce proteinuria remission, whereas immunosuppression may stimulate viral replication.

To be noted, a retrospective analysis of 317 patients with HBVrelated GN (12 clinical trials) who received combined antiviral and immunosuppressive therapy showed the majority of patients had reduced proteinuria without increase in HBV-DNA viral replication or alterations in liver function.47 However, immunosuppressive agents are best avoided in patients with replicative HBV infection. In patients with simultaneous HBV infection and anti-PLA2R antibody-mediated MN, treatment with rituximab and cyclophosphamide should be postponed until a sustained virologic remission has been obtained by nucleoside or nucleotide analog therapy.

In specific settings, such as RPGN or severe polyarteritis nodosa (PAN), combination therapy appears to be useful (see Chapter 26). Whenever combined antiviral and immunosuppressive therapy is used, it is important to monitor HBV DNA levels for at least 6 months after immunosuppressive therapy is discontinued.

Other Virus-Associated Kidney Disease

Cytomegalovirus (CMV) infection rarely causes diffuse proliferative GN with immune deposits containing CMV antigens in native kidneys. Cytomegalovirus also has been linked to collapsing glomerulopathy and ESKD in patients without HIV infection. In kidney allograft patients with CMV infection, immunosuppression is reduced (see Chapter 110). Depending on infection severity, oral valganciclovir 900 mg twice daily or ganciclovir 5 mg/kg intravenously every 12 hours is administered until clinical recovery and two blood samples negative for CMV by polymerase chain reaction are obtained, followed by 3 months of oral valganciclovir 900 mg/day or oral ganciclovir 1 g three times daily. Toxic effects of these drugs include neutropenia, central nervous system dysfunction, and carcinogenicity and teratogenicity in experimental studies.

Parvovirus B19 is a single-stranded DNA virus with marked tropism for erythroid precursor cells. Its receptors include the erythrocyte P antigen and glycosphingolipid globoside (Gb4). Infection with a viral prodrome may be followed by nephritic or nephrotic syndrome; nephrotic syndrome may precede an aplastic crisis in patients with sickle cell disease. In transplanted patients, parvovirus infection should be suspected when there is severe anemia resistant to erythropoietin treatment with inappropriate reticulocyte response. Diffuse endocapillary and proliferative GN and MPGN have been reported with subendothelial and fewer mesangial IgG and C3 deposits.48 Collapsing glomerulopathy has been attributed to parvovirus B19 infection; some, but not all, studies have detected viral DNA in kidney biopsy tissue, and there appears to be an association with APOL1 risk alleles. There is no specific antiviral therapy, and treatment is intravenous immunoglobulin administration 2 g/kg given over a period of 5 days.

Dengue hemorrhagic fever is currently the most prevalent mosquito-borne urban viral infection worldwide, and is caused by four serotypes of the Flaviviridae virus family. The most common kidney complication is AKI (see Chapter 71). Glomerular involvement may be secondary to direct glomerular cell injury or immune complex deposition. Infected patients may present with hematuria, proteinuria, and kidney failure associated with diffuse endocapillary or proliferative GN with IgG, IgM, and C3, transient IgA deposits, or MPGN.49 There are no specific treatments, and management is supportive.

Mild kidney abnormalities occur in acute Epstein-Barr virus (EBV) infection, with microhematuria and proteinuria in 10% to 15% of cases associated with diffuse endocapillary GN, MesPGN, MPGN pattern, and collapsing glomerulopathy. Many viral infections, including varicella, mumps, adenovirus, coxsackievirus, and influenza, can be associated with transient microscopic hematuria, nonnephrotic proteinuria, and a mesangial or diffuse proliferative GN in which viral antigens can be identified in the mesangium. Measles may cause diffuse proliferative GN but is better known for its unique ability to induce remission

in patients with MCD and nephrotic syndrome as infection abates, due to increased production of Treg cells.

PARASITIC INFECTIONS

Kidney involvement is common in various parasitic infections and includes a range of kidney lesions (Table 57.3). With the exception of malaria, leishmaniasis, filariasis, and schistosomiasis, glomerular involvement is usually mild and transient.50,51

Malaria

Etiology and Pathogenesis

There are four major species of Plasmodium, two of which typically are associated with GNs in humans: Plasmodium falciparum and Plasmodium malariae.52 Malarial antigens activate the immune system by interaction with monocytes, secretion of chemokines and cytokines, polyclonal B cell activation, and circulating immune complex formation. Infected erythrocytes may participate in immune activation through preferential expression of surface antigens and endothelial activation. Malarial antigens have been identified in 25% of glomerular immune complexes and in glomeruli without immune complex deposition, suggesting in situ immune complex formation. Additionally, the alternative complement pathway may be directly activated.36,52 Concomitant infection with other parasites (schistosomiasis) or viruses (EBV, HIV), or genetic factors such as APOL1 risk alleles may participate in the pathogenesis of kidney injury and influence geographic disease variations.

Epidemiology, Clinical Manifestations, and Pathology

Malaria is the most prevalent endemic global infectious disease, with 200 million cases predominantly occurring in Africa, India, Southeast Asia, and Latin America causing 600,000 deaths each year (Fig. 57.6).53 It is acquired by the bite of infected Anopheles mosquitoes or infected vectors from blood transfusion or infected organ transplants. P. falciparum invades erythrocytes of any age and may cause AKI and multiple organ failure (see Chapter 71). Transient mild proteinuria and microhematuria occur in 25% to 50% of patients, more often children, with infrequent nephritic syndrome and impaired kidney function. Patients develop MesPGN with deposits of IgG, IgM, and C3 and rarely IgAN (Fig. 57.7). Patients present with nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS), infrequently MCD, and most often collapsing glomerulopathy with and without concomitant HIV infection, and associated with African descent and APOL1 risk alleles.54 In contrast, P. malariae (quartan malaria) infects aging erythrocytes and is less severe. Patients present with steroid-resistant nephrotic syndrome (tropical nephritis or nephrotic syndrome) primarily in children 4 to 8 years old. Adult GN often manifests with hypertension and reduced kidney function. Kidney biopsy shows an MPGN pattern with granular IgG, IgM, and C3 deposition and subendothelial and mesangial electron-dense deposits, and infrequently MN or MCD52,55 (Fig. 57.8). Despite treating the infection, with or without corticosteroids, there is progression to ESKD, which is attributed to continuing autoimmune mechanisms. Plasmodium vivax causes AKI and rarely thrombotic microangiopathy (see Chapter 71), but GN has not been reported. For severe malaria the treatment is artesunate intravenously 2.4 mg/kg per dose at hours 0, 12, and 24, then artemisinin-based combination therapy orally for 3 days. In uncomplicated malaria, recommended treatment options include Artemether-lumefantrine (1.4–4.4/10–16 mg/kg) by mouth twice daily for 3 days or artesunate (4 mg/kg) plus amodiaquine (10 mg/kg) orally daily for 3 days or artesunate (2 mg/kg) orally daily plus tetracycline (4 mg/kg) orally every 6 hours for 7 days. Immunosuppressive treatment is not indicated for malarial nephropathy.

TABLE 57.3
Parasite

Kidney Lesions in Parasitic Infections
Glomerular Lesions

Schistosomiasis
S. haematobiuma
MesPGN DPGN with Salmonella
MesPGN, MPGN, FSGS, MN,
S. mansonia
DPGN with Salmonella
S. japonicum
MesPGN, MPGN (primates,
rabbits)
S. mekongi
Malaria
Plasmodium
malariaea
Plasmodium
falciparuma
Filariasis
Onchocerciasisa
Loiasis
Bancroftiasis

Dirofilariasis
Other
Brugia malayi
Visceral leishmania
Kala-azara
Trichinosis
Strongyloidiasis
Echinococcosis
Opisthorchiasisa
Chagas diseasea
Babesiosis
Trypanosomiasis
Toxoplasmosisa

MPGN, MesPGN, MCD (rare),
FSGS (rare), MN (rare)
MesPGN, DPGN, collapsing
GP, FSGS, MCD (rare), MPGN
(rare), IgAN (rare)

Tubulointerstitial
Lesions
Amyloidosis

Tissue Reaction, Acute Kidney Posttransplant
Symptoms
Injury
Disease

+++
+

Granulomas
Granulomas

++
++

+
+

+
+++

+

MesPGN, MPGN, MCD
MN, MesPGN, MPGN, FSGS (rare)
MesPGN, MPGN, EPGN,
collapsing GP

++

River blindness
+

+

+

Chyluria
Pneumonia
Elephantiasis

MPGN (dogs), MN (dogs, cats)
MesPGN, MPGN, DPGN
DPGN, MesPGN, MPGN
MesPGN, MPGN
MesPGN
MPGN, MN (rare)
MesPGN
MesPGN (mice)
MesPGN (rat)
MesPGN, MPGN (monkey, rat)
MesPGN, MPGN, FSGS (rare)

+ (rare)
++

+ (rare)
++

+

+

+
Hydatid cysts
++

+

++
++

+

+

aParasitic

antigens or specific antibodies detected in the glomeruli.

All conditions documented in humans unless otherwise indicated.

DPGN, Diffuse proliferative glomerulonephritis; EPGN, endocapillary proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; GP, glomerulopathy; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; MesPGN, mesangial proliferative glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis pattern.

Malaria-associated kidney disease in low-income countries has declined due to malarial control and overall improved health care.

Filariasis

Filariae are nematodes, of which only eight of the hundreds of species affect humans and only three are associated with kidney disease.

Wuchereria bancrofti is responsible for several clinical syndromes, including tropical eosinophilic pneumonia, elephantiasis, and chyluria, and induces proteinuria, hypoproteinemia, and hematuria in infected patients. The dominant glomerular lesion is MesPGN; less frequently an MPGN pattern or acute endocapillary GN with eosinophilic predominance can be seen; and rarely amyloidosis or collapsing glomerulopathy are found. Immune complex deposits containing worm antigens have been demonstrated in glomeruli.52 56

Bancroftiasis is often associated with bacterial infection, usually staphylococci and certain streptococci; it is uncertain if this contributes to the development of GN. Even less understood is a potential

role of the rickettsia-like bacteria Wolbachia, discovered within filarial nematodes and blamed for activation of innate immune pathways.

Ivermectin, diethylcarbamazine, and albendazole are approved treatments for filariasis.

Onchocerca volvulus is less common and causes scrotal lymph node obstruction (“hanging scrotum”). Onchocercosis is associated with immune-mediated manifestations, including keratitis, anterior uveitis, and optic atrophy leading to “river blindness.” GN induces proteinuria, including steroid-resistant nephrotic syndrome with progressive kidney impairment, usually an MPGN pattern with IgM, IgG, and C3 in subendothelial and mesangial deposits, with less frequent MCD and sclerosing glomerular lesions.52 56 Glomeruli may contain onchocercal antigens, and GN recurs in transplanted kidneys. When W. bancrofti or O. volvulus is treated, the proteinuria and hematuria may worsen due to parasitic disintegration and increase in circulating immune complex formation. After successful parasite eradication, the kidney disease typically resolves.

Geographic Distribution of Malaria-Associated Glomerular Disease

P. malariae

P. falciparum

P. malariae
P. falciparum

Fig. 57.6 Geographic Distribution of Malaria-Associated Glomerular Disease. Although malaria is endogenous to many areas of the world (shaded orange), the major areas where malaria-associated glomerular disease has been reported (ringed) and their respective species are shown.

B

A

C

Fig. 57.7 Glomerulonephritis Associated With Plasmodium falciparum Malaria. (A) Light microscopy shows mesangial proliferative glomerulonephritis. (B) Immunofluorescence may reveal P. falciparum antigens in a mesangial pattern. (C) Peripheral blood smear confirms acute P. falciparum infection, with bananashaped gametocytes and multiple ring forms in erythrocytes. (A, From Barsoum RS. Malarial nephropathies. Nephrol Dial Transplant. 1998;13[6]:1588–1597. B and C, Courtesy V. Boonpucknavig.)

A

B

C

Fig. 57.8 Quartan Malarial Nephropathy. (A) Light microscopy shows sclerosing membranoproliferative glomerulonephritis. (B) Silver stain shows a double contour (arrows) of the basement membrane. (C) Malarial antigens are present on immunofluorescence. (From Barsoum RS. Malarial nephropathies. Nephrol Dial Transplant. 1998;13[6]:1588–1597.)

Loa is the least prevalent of the nephritogenic filariae. Associated glomerular disease includes MN and less commonly MPGN and FSGS.52 57 Unlike the other forms of filariasis, treatment for Loa loa generally does not result in GN resolution. All three filaria parasites often occur with HBV and/or malaria coinfection, which independently can cause GN; it is unknown whether this affects the incidence or types of GN associated with filariasis.

Leishmaniasis

Leishmania are obligatory intracellular protozoa that infect 12 million humans and many animals. Of 30 known leishmanial spp., only visceral leishmaniasis (kala-azar) induced by Leishmania donovani or by the closely related Leishmania infantum (Leishmania chagasi) involves the kidney. Sixty percent of those infected with L. donovani have mild proteinuria and microscopic hematuria. There is glomerular immune complex deposition with MesPGN or an MPGN pattern; the latter may occur with cryoglobulinemia.58 59 Amyloidosis may occur, usually associated with coincident HIV infection. Treatments for leishmaniasis (pentavalent antimony compounds, liposomal amphotericin B, miltefosine) have substantial adverse effects and high rates of resistance.

Schistosomiasis

Schistosomiasis is a common cause worldwide of glomerular disease and is discussed in Chapter 56

SELF-ASSESSMENT QUESTIONS

1. At the present time, infection-related GN in wealthy countries is associated with debilitating conditions (neoplasia, diabetes, AIDS, alcoholism) and IgA deposits.
A. True
B. False
2. Patients with acute poststreptococcal GN usually have:
A. low serum CH50 and C3 levels.
B. low serum C4 levels.
C. high serum C3 levels.
D. high serum CH50 and high serum C4 levels.

3. Patients with infective endocarditis may have crescentic GN without immune deposits.
A. True
B. False
4. Combined antiviral therapy and immunosuppression (cyclophosphamide and steroids) is:
A. contraindicated in patients with active HBV infection and associated GN.
B. usually indicated in patients with active HBV infection and associated GN.

REFERENCES

1. Kupin WL. Viral-associated GN: hepatitis B and other viral infections. Clin J Am Soc Nephrol. 2017;12(9):1529–1533.
2. Nast CC. Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis. 2012;19(2):68–75.
3. Oda T, Yoshizawa N, Yamakami K, et al. Localization of nephritisassociated plasmin receptor in acute poststreptococcal glomerulonephritis. Hum Pathol. 2010;41(9):1276–1285.
4. Batsford SR, Mezzano S, Mihatsch M, Schiltz E, Rodreguez-iturbe B. Is the nephritogenic antigen in post-streptococcal glomerulonephritis pyrogenic exotoxin B (SPE B) or GAPDH? Kidney Int. 2005;68(3):1120–1129.
5. Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007;71(11):1094–1104.
6. Nasr SH, Radhakrishnan J, D D’Agati V. Bacterial infection–related glomerulonephritis in adults. Kidney Int. 2013;83(5):792–803.
7. Yoshizawa N, Yamakami K, Fujino M, et al. Nephritis-associated plasmin receptor and acute poststreptococcal glomerulonephritis: characterization of the antigen and associated immune response. J Am Soc Nephrol. 2004;15(7):1785–1793.
8. Beres SB, Sesso R, Pinto SWL, et al. Genome sequence of a Lancefield group C Streptococcus zooepidemicus strain causing epidemic nephritis: new information about an old disease. PLoS One. 2008;3(8):e3026.
9. Hisano S, Matsushita M, Fujita T, Takeshita M, Iwasaki H. Activation of the lectin complement pathway in post-streptococcal acute glomerulonephritis. Pathol Int. 2007;57(6):351–357.
10. Rodriguez-Iturbe B. Autoimmunity in acute poststreptococcal GN: a neglected aspect of the disease. J Am Soc Nephrol. 2021;32(3):534–542.
11. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol. 2008;19(10):1855–1864.
12. Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. Nat Rev Nephrol. 2020;16(1):32–50.
13. Marshall CS, Cheng AC, Markey PG, et al. Acute post-streptococcal glomerulonephritis in the Northern Territory of Australia: a review of 16 years data and comparison with the literature. Am j tropical med hygiene. 2011;85(4):703–710.
14. Nasr SH, Markowitz GS, Stokes MB, Said SM, Valeri AM, D’Agati VD. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine. 2008;87(1):21–32.
15. Sorger K, Gessler M, Hübner F, et al. Follow-up studies of three subtypes of acute postinfectious glomerulonephritis ascertained by renal biopsy. Clin Nephrol. 1987;27(3):111–124.
16. Parra G, Platt JL, Falk RJ, Rodriguez-Iturbe B, Michael AF. Cell populations and membrane attack complex in glomeruli of patients with post-streptococcal glomerulonephritis: identification using monoclonal antibodies by indirect immunofluorescence. Clin Immunol Immunopathol. 1984;33(3):324–332.
17. Haas M. Incidental healed postinfectious glomerulonephritis: a study of 1012 renal biopsy specimens examined by electron microscopy. Hum Pathol. 2003;34(1):3–10.
18. Chauvet S, Berthaud R, Devriese M, et al. Anti-Factor B antibodies and acute postinfectious GN in children. J Am Soc Nephrol. 2020;31(4):829–840.
19. Hoy WE, White AV, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. Kidney Int. 2012;81(10):1026–1032.
20. Sesso R, Pinto SWL. Five-year follow-up of patients with epidemic glomerulonephritis due to Streptococcus zooepidemicus. Nephrol Dialysis Transplant. 2005;20(9):1808–1812.
21. Johnston F, Carapetis J, Patel MS, Wallace T, Spillane P. Evaluating the use of penicillin to control outbreaks of acute poststreptococcal glomerulonephritis. Pediatr Infect Dis J. 1999;18(4):327–332.
22. Nasr SH, D’Agati VD. IgA-dominant postinfectious glomerulonephritis: a

new twist on an old disease. Nephron Clin Pract. 2011;119(1):c18-c26.

23. Koyama A, Kobayashi M, Yamaguchi N, et al. Glomerulonephritis associated with MRSA infection: a possible role of bacterial superantigen. Kidney Int. 1995;47(1):207–216.
24. Wang S-Y, Bu R, Zhang Q, et al. Clinical, pathological, and prognostic characteristics of glomerulonephritis related to staphylococcal infection. Medicine. 2016;95(15).
25. Bu R, Li Q, Duan Z-y, et al. Clinicopathologic features of IgA-dominant infection-associated glomerulonephritis: a pooled analysis of 78 cases. Am J Nephrol. 2015;41(2):98–106.
26. Meehan SM, Lee JS. Increasing frequency of IgA GN related to infection. Nefrologia. 2019;39(4):438–439.
27. Satoskar AA, Nadasdy G, Plaza JA, et al. Staphylococcus infectionassociated glomerulonephritis mimicking IgA nephropathy. Clin J Am Soc Nephrol. 2006;1(6):1179–1186.
28. Hemminger J, Arole V, Ayoub I, Brodsky SV, Nadasdy T, Satoskar AA. Acute glomerulonephritis with large confluent IgA-dominant deposits associated with liver cirrhosis. PLoS One. 2018;13(4):e0193274.
29. Satoskar AA, Shapiro JP, Jones M, et al. Differentiating Staphylococcus infection-associated glomerulonephritis and primary IgA nephropathy: a mass spectrometry-based exploratory study. Sci Rep. 2020;10(1):1–14.
30. Guerrero MLF, Alvarez B, Manzarbeitia F, Renedo G. Infective endocarditis at autopsy: a review of pathologic manifestations and clinical correlates. Medicine. 2012;91(3):152–164.
31. Boils CL, Nasr SH, Walker PD, Couser WG, Larsen CP. Update on endocarditis-associated glomerulonephritis. Kidney Int. 2015;87(6):1241–1249.
32. David MZ, Daum RS. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev. 2010;23(3):616–687.
33. Lamas CC, Fournier P-E, Zappa M, et al. Diagnosis of blood culturenegative endocarditis and clinical comparison between blood culturenegative and blood culture-positive cases. Infection. 2016;44(4):459–466.
34. Majumdar A, Chowdhary S, Ferreira MA, et al. Renal pathological findings in infective endocarditis. Nephrol Dial Transplant. 2000;15(11):1782–1787.
35. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: challenges and perspectives. Lancet. 2012;379(9819):965–975.
36. Boonpucknavig V, Soontornniyomkij V. Pathology of renal diseases in the tropics. Paper presented at Semin Nephrol. 2003.
37. Daher EF, Júnior GBS, Cezar LC, et al. Renal dysfunction in leprosy: a historical cohort of 923 patients in Brazil. Trop Doct. 2011;41(3):148–150.
38. Silva Junior GB, Daher EDF, Pires Neto RdJ, et al. Leprosy nephropathy: a review of clinical and histopathological features. Rev Inst Med Trop Sao Paulo. 2015;57(1):15–20.
39. Desai AN, Kim AY. Management of Hepatitis A in 2020-2021. JAMA; 2020.
40. Gupta A, Quigg RJ. Glomerular diseases associated with hepatitis B and C. Adv Chronic Kidney Dis. 2015;22(5):343–351.
41. Zhang Y, Li J, Peng W, et al. HBV-Associated postinfectious acute glomerulonephritis: a report of 10 cases. PLoS One. 2016;11(8):e0160626.
42. Wang W-N, Wu M-Y, Ma F-Z, Sun T, Xu Z-G. Meta-analysis of the efficacy and safety of nucleotide/nucleoside analog monotherapy for hepatitis B virus-associated glomerulonephritis. Clin Nephrol. 2016;85(1):21–29.
43. Fabrizi F, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. Aliment Pharmacol Ther. 2006;24(5):781–788.
44. Liu Y, Shi C, Fan J, Wang B, Li G. Hepatitis B-related glomerulonephritis and optimization of treatment. Expert Rev Gastroenterol Hepatol. 2020;14(2):113–125.
45. Mauss S, Berger F, Filmann N, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. J Hepatol.

2011;55(6):1235–1240.
46. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol. 2015;62(3):533–540.

References

47. Zheng X-Y, Wei R-B, Tang L, Li P, Zheng X-D. Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis. World J Gastroenterol: WJG. 2012;18(8):821.
48. Prasad N, Novak JE, Patel MR. Kidney diseases associated with parvovirus B19, hanta, Ebola, and dengue virus infection: a brief review. Adv Chronic Kidney Dis. 2019;26(3):207–219.
49. Gurugama P, Jayarajah U, Wanigasuriya K, Wijewickrama A, Perera J, Seneviratne SL. Renal manifestations of dengue virus infections. J Clin Virol. 2018;101:1–6.
50. Barsoum RS. Parasitic kidney disease: milestones in the evolution of our knowledge. Am J Kidney Dis. 2013;61(3):501–513.
51. Chapter 9: infection-related glomerulonephritis. Kidney Int Suppl (2011). 2012;2(2):200–208.
52. Van Velthuysen M-L, Florquin S. Glomerulopathy associated with parasitic infections. Clin Microbiol Rev. 2000;13(1):55–66.
53. Silva Junior GB, Pinto JR, Barros EJG, Farias GMN, Daher EDF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017;59.

54. Amoura A, Moktefi A, Halfon M, et al. Malaria, Collapsing Glomerulopathy, and Focal and Segmental Glomerulosclerosis. Clin J Am Soc Nephrol. 2020.
55. Barsoum RS. Malarial nephropathies. Nephrol Dial Transplant. 1998;13(6):1588–1597.
56. Ngu J, Chatelanat F, Leke R, Ndumbe P, Youmbissi J. Nephropathy in Cameroon: evidence for filarial derived immune-complex pathogenesis in some cases. Clin Nephrol. 1985;24(3):128–134.
57. Pillay VK, Kirch E, Kurtzman NA. Glomerulopathy associated with filarial loiasis. JAMA. 1973;225(2):179.
58. Ortiz M, Mon C, Herrero JC, et al. Glomerulonephritis and cryoglobulinemia: first manifestation of visceral leishmaniasis. Clin Nephrol. 2015;83(6):370–377.
59. Clementi A, Battaglia G, Floris M, Castellino P, Ronco C, Cruz DN. Renal involvement in leishmaniasis: a review of the literature. Nephrol Dial Transplant. 2011;4(3):147–152.

58

Human Immunodeficiency Virus Infection and the Kidney

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INTRODUCTION

According to the United Nations acquired immunodeficiency syndrome (AIDS) program, an estimated 38 million individuals had human immunodeficiency virus (HIV)-1 in 2021, including 1.7 million with newly acquired infections. In 2019 an estimated 0.69 million deaths were attributed to HIV-related illness. In 2019 an estimated 25 million individuals were receiving antiretroviral therapy, representing 67% of all HIV-positive (HIV+) individuals. In 2019 around 150,000 children aged 0 to 9 years were newly infected with HIV. This brings the total number of children aged 0 to 9 years with HIV to 1.1 million (https://data.unicef.org/topic/hivaids). In the United States, an estimated 1.2 million individuals were HIV+ in 2019 and approximately 2000 patients were receiving renal replacement therapy (RRT; dialysis or kidney transplant) for HIVassociated kidney disease.

HIV-1 infection is associated with glomerular and tubulointerstitial disease, and patients with HIV infection are at risk for nephrotoxicity from antiretroviral therapy[1] and from other medications such as antibiotics and nonsteroidal antiinflammatory agents (NSAIDs).

Acute kidney injury (AKI), interstitial nephritis from medication and opportunistic infections, and coinfections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are relatively common. Advances in treatment are to be celebrated but also mean that people with HIV are more likely to experience complications such as atherosclerosis, metabolic syndrome, type 2 diabetes, and end-stage kidney disease (ESKD). HIV-2 can cause immunodeficiency but rarely causes kidney disease. In this chapter, we use HIV to refer to HIV-1.

EPIDEMIOLOGY OF HIV CHRONIC KIDNEY DISEASE

High-Income Countries

There are relatively few data on the worldwide prevalence of chronic kidney disease (CKD) associated with HIV infection. In the European EUROSIDA observational study, only 3% had estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 and only 0.3% had eGFR less than 30 mL/min/1.73 m^2 [2] In the United States, the incidence (absolute counts) of ESKD attributed to HIV continues to decline (from 893 individuals in 2006 to 525 in 2011).[3]

The United States Renal Data System (USRDS) reports that for the period from 2006 to 2010, there were 3834 cases of AIDS nephropathy (0.7% of total ESKD); 86% of the patients were Black and 15% were White. The unadjusted relative risk for ESKD was 4.7 for Black patients compared with Whites. This relative risk is less than previously estimated for HIV-associated nephropathy (HIVAN) and supports the idea that the distribution of kidney diseases associated with HIV infection is shifting. Patients reaching ESKD are also living longer.

Among those who started dialysis in 2009 to 2011, mortality declined by 64% compared with 1988 to 1992 but remained nearly threefold higher than other dialysis patients.[3]

Lower- and Middle-Income Countries

Sub-Saharan Africa is home to approximately 70% of the global infections, with 26 million HIV+ people. In 2018, 470,000 people died with HIV in Africa. Globally, 91% of HIV+ children live in Africa. Of HIV+ individuals in sub-Saharan Africa, an estimated 54% have access to combination antiretroviral therapy (cART).

Prevention of mother-to-child transmission programs have resulted in a dramatically decreased number of childhood HIV cases. This condition may cease to exist in time with this preventive strategy.4 In cases where there has been perinatal transmission, the use of highly active retroviral therapy (HAART) has also largely prevented HIV-associated kidney disease and thus decreased the mortality rate. Adolescents may still acquire HIV infection, and thus it is important to focus on HIV prevention in this age group. Females aged 15 to 24 are the group with the highest rate of new HIV infection in subSaharan Africa.5

Compared with high-income countries, access to RRT is frequently limited in low- and middle-income countries. The prevalence of CKD, as assessed by the presence of proteinuria or eGFR, ranges widely in Africa, from 6% to 48.5%.6 This wide variation may be partly ascribed to differences in study design, study population, and the definitions used for CKD. Based on single-center studies that used proteinuria as a marker of CKD in HIV+ subjects, the prevalence of CKD in HIV+ subjects ranges from 1% to 6% in Brazil to 20% in Iran and 27% in India.

In South Africa, HIVAN is the dominant kidney disease among HIV+ individuals and is documented in up to 80% of kidney biopsy specimens, which is consistent with findings in the United States in the pre-cART era. As in high-income countries, other kidney causes are also observed, including HIV-associated immune complex kidney disease (HIVICK) from postinfectious and other causes, membranous nephropathy, and interstitial nephritis. Some kidney biopsies show nonspecific changes (e.g., mesangial hyperplasia and chronic active interstitial nephritis) that do not fulfill the diagnostic criteria for HIVAN but do show regression on cART. The latter finding suggests that the diagnostic criteria for HIV-associated CKD may need to be broadened.

HIV-ASSOCIATED NEPHROPATHY

HIV infection is associated with various glomerular disorders (Table 58.1). The classic glomerulopathy of HIV infection is collapsing

Kidney Diseases Associated With Human Immunodeficiency Virus (HIV) Infection or Its Treatment

TABLE 58.1

Glomerular

Tubular

Interstitial

Entity

Frequency

Associations

HIV-associated nephropathy
HIV-associated immune complex kidney disease
Thrombotic microangiopathy
Membranoproliferative glomerulonephritis ± cryoglobulin-associated vasculitis
Membranous nephropathy
Fibrillary and immunotactoid glomerulopathies
Amyloid nephropathy (AA type)
Minimal change nephropathy
Acute kidney injury
Proximal tubule injury (Fanconi syndrome)
Diabetes insipidus
Chronic tubular injury
Crystal nephropathy
Interstitial nephritis

Common
Common
Uncommon
Rare

African descent; often advanced HIV disease
All ethnic backgrounds
Hepatitis C; enfuvirtide

Uncommon
Rare
Rare
Rare
Moderately common
Moderately common
Uncommon
Moderately common
Uncommon
Uncommon

glomerulopathy (CG), also known as collapsing focal segmental glomerulosclerosis (FSGS) and as HIVAN.

Etiology and Pathogenesis

HIVAN occurs during both the acute and chronic phases of HIV infection; in the latter case, it is associated with higher viral RNA levels and lower CD4 T-lymphocyte counts. Studies from human kidney biopsies have shown that HIV can infect glomerular and tubular cells, setting up a chronic and possibly latent infection.7 Specific HIV accessory proteins such as Vpr and Nef can damage kidney cells independent of direct infection. In transgenic mice, the expression of HIV accessory proteins Vpr or Nef in podocytes is associated with progressive CKD, loss of podocyte differentiation markers, and features suggestive of human CG and FSGS.8 These transgenic mouse experiments also suggest that HIV gene products are toxic to tubular epithelial cells, resulting in both apoptosis and inhibition of cell proliferation.

Host factors also determine susceptibility to HIVAN, especially in individuals of African descent compared with those of European or Asian descent. Apolipoprotein L1, encoded by APOL1 on chromosome 22, is a component of high-density lipoprotein particles.

APOL1 variants have been identified as a major cause of the predilection for chronic glomerular disease that characterizes populations of sub-Saharan African descent.9 10 The presence of two APOL1 codonchanging variants confer an odds ratio of 29 for HIVAN in the United States11 and 89 in South Africa,12 a strikingly large effect for a complex disease. Homozygosity, or dual heterozygosity for two risk alleles (termed G1 and G2; G1 is actually a haplotype, but the term allele is used here for simplicity), is observed in 72% of African Americans and South Africans with HIVAN, compared with only 12% of African American controls and 3% of South African controls. Among South Africans, a single copy of the APOL1-G1 variant confers an odds ratio [OR] of 21 for HIVAN. These variants appear to protect individuals from African sleeping sickness caused by Trypanosoma brucei rhodesiense, and this may explain the rapid rise in allele frequency in Africa, particularly West African populations, that has occurred in the past 40,000 years.9

Hepatitis B

Nonsteroidal antiinflammatory medication
Aminoglycosides, cidofovir, foscarnet
Tenofovir disoproxil, adefovir, cidofovir, didanosine
Amphotericin, tenofovir disoproxil, didanosine, abacavir
Amphotericin, cidofovir, adefovir, tenofovir disoproxil
Indinavir, atazanavir; sulfadiazine, ciprofloxacin, intravenous acyclovir
Allergy to β-lactam, sulfonamides, ciprofloxacin, rifampin, proton pump inhibitor, allopurinol, phenytoin; also causes of crystal nephropathy listed previously
BK virus
Immune reconstitution inflammatory syndrome; generally advanced disease; after initiation of antiretroviral therapy

In a U.S. study, among HIV+ individuals with proteinuria and two APOL1 risk variants, 76% had FSGS or CG and had a nearly threefold increased risk of progression to ESKD compared with those with other biopsy findings. APOL1 high-risk genotype individuals manifested more CG and greater extent of glomerulosclerosis, tubular atrophy, and interstitial fibrosis.13 HIV+ women with CKD with two APOL1 risk alleles had more severe proteinuria, more rapid decline in eGFR, and a 1.7- to 3.4-fold greater risk for incident CKD.14

The particular association between HIV infection and APOL1 kidney disease is likely a consequence of HIV infection promoting systemic interferon production, which, in turn, promotes expression of the APOL1 gene.

At least seven mechanisms have been identified to explain the toxic effect of the APOL1 variants on kidney cells. Evidence for these seven mechanisms have been shown in molecular studies, cell culture, or animal models. Most mechanisms are envisioned to be acting chiefly on podocytes to produce glomerular disease.

1. Increased flux through plasma membrane cation channels, either Na+ and Ca2+ or K+, the latter activating stress kinases and leading

to cell swelling.15

2. Increased generation of interleukin (IL)-1β, leading to pyroptosis and podocyte loss.16
3. Disruption of an APOL1-mir193 axis, leading to dysfunction of the endoplasmic reticulum and protein production.17
4. Mitochondrial stress, leading to podocyte energy deficits.18
5. Activation of protein kinase R, leading to reduced protein synthesis.19
6. Formation of a tripartite complex of APOL1, soluble urokinasetype plasminogen activator receptor (suPAR), and αvβ3 integrin, resulting in integrin activation, altering podocyte-matrix interactions, and impairing podocyte function.20
7. Alterations in APOL1/APOL3 interactions.21

Some of these mechanisms have shown only or largely in cell culture studies or animal model, and their clinical relevance remains to be established. Novel therapies for APOL1 kidney disease are currently in clinical trials.

Clinical Manifestations of HIVAN

Diagnosis and Differential Diagnosis

Patients with HIVAN typically present with proteinuria and reduced eGFR. Some patients present with edema, although edema is less common than with other conditions associated with nephrotic range proteinuria, suggesting a defect in tubular sodium handing. Imaging studies may reveal increased kidney size despite reduced eGFR and, in some cases, increased echogenicity; this unusual feature is shared with diabetic nephropathy and amyloid nephropathy. However, no ultrasound features predict the kidney histology, and kidney biopsy is required for diagnosis.

Indications for kidney biopsy include AKI without clear associated cause, especially with a nephritic sediment; nephrotic proteinuria; laboratory evidence of thrombotic microangiopathy (TMA); and unexplained CKD. In the past, some clinicians argued that nephrotic proteinuria in an individual of African descent is likely to be HIVAN, which is a form of collapsing FSGS or CG, and that a biopsy is not necessary. The widespread use of antiretroviral therapy (ART) in the current era makes this decision less tenable, and kidney biopsy is often indicated to guide prognosis and therapy, particularly when substantial proteinuria is present.

With the advent of ART, a wider range of HIV-associated kidney diseases is now seen. Rather than the initial pattern of HIVAN in individuals of African descent and HIVICK among all ethnic backgrounds, HIV-associated kidney diseases now includes FSGS, diabetic nephropathy, and arterionephrosclerosis (the term is used for the histopathology that is seen in some APOL1-associated kidney disease but also with aging). In patients with HIV and hepatitis, membranoproliferative glomerulonephritis associated with HCV should be considered.

Other diagnoses include membranous nephropathy (associated with HBV infection, or presumably idiopathic, but possibly related to the polyclonal B cell expansion typical of HIV disease) and amyloidosis.

Chronic tubular injury is usually associated with tenofovir disoproxil fumarate (TDF) therapy but may occur with other ART; when early diagnosis leads to cessation of the offending medication, CKD is

Pathology of HIVAN

HIVAN is indistinguishable from idiopathic collapsing FSGS (CG), with pathologic changes in glomeruli (proliferation and dysregulation of podocytes or podocyte stem cells, together with glomerular collapse), tubular injury (both acute and chronic injury, sometimes with microcystic tubular changes), and interstitial changes (chronic inflammation, fibrosis; Fig. 58.1). On electron microscopy (EM), both HIVAN and idiopathic collapsing FSGS may manifest tubuloreticular inclusions within dilated endosomal compartments within glomerular endothelial cells, which are believed to be markers for interferonmediated injury. Some patients with progressive loss of kidney function (e.g., from HIVICK or interstitial nephritis) may develop postadaptive FSGS from the consequences of glomerular hyperperfusion and hyperfiltration.

A

B

C

Fig. 58.1 Human Immunodeficiency Virus–Associated Nephropathy. (A) A globally

collapsed glomerulus shows marked podocyte hypertrophy and hyperplasia (Jones methenamine silver). (B) At low power, the kidney parenchyma contains abundant tubular microcysts with proteinaceous casts. The glomerulus is collapsed with dilated urinary space (periodic acid–Schiff stain). (C) The glomerular endothelial cell pictured here contains a large intracytoplasmic tubuloreticular inclusion (“interferon footprint”; arrow) composed of interanastomosing tubular structures within a dilated cisterna of endoplasmic reticulum (electron micrograph).

usually averted. Despite the plethora of diagnoses, HIVAN remains the leading cause of ESKD in patients with HIV in the United States.

The diagnoses of HIVAN and HIVICK, and other diagnoses previously listed, are made by kidney biopsy. In some cases, nephrotic proteinuria and low CD4 T-lymphocyte count in individuals of African descent is sufficiently suggestive of HIVAN that some clinicians may opt not to biopsy the kidney. Plasma HIV RNA of less than 400 copies/mL at the time of presentation suggests another kidney disease. Among individuals of African descent, other possible diagnoses include primary or secondary FSGS (although a pathogenic role for HIV cannot be excluded in conferring susceptibility) and arterionephrosclerosis (see later discussion). In all individuals, diabetic nephropathy and HIVICK should be considered (see later discussion and Table 58.1).

Treatment of HIVAN

The HIV Medicine Association of the Infectious Diseases Society of America provides clinical practice guidelines for the management of HIV disease, with the most recent update published in 2020.[22] All HIV+ individuals should receive cART[1] beginning at the time of diagnosis. This may include a three-drug combination or two-drug combination that includes an integrase strand transfer inhibitor. The presence of kidney disease does not affect this recommendation.[23] In the era before cART was available, HIVAN progressed rapidly, with patients reaching ESKD in months to a few years. The marked decline in HIV-associated ESKD in the United States after the introduction of cART in the mid-1990s suggests that effective control of viral replication, achievable with cART, prevents HIVAN. Retrospective studies also suggest that cART treatment of HIVAN may prolong kidney survival.[24]

A growing number of prospective and retrospective studies have demonstrated rapid resolution or reduction in proteinuria within 6 months of commencing ART. The Development of Anti-Retroviral Therapy in Africa (DART) study, conducted in Uganda and Zimbabwe, demonstrated improvement of kidney function of 2 to 6 mL/min/1.73 m^2 after 4 to 5 years of ART.[25] [26] Other studies suggest that ART is most effective when it is initiated before the onset of severe kidney disease.[27–31] In a few cases, regression of histologic lesions with cART has been demonstrated.[32] [33] According to a French study, the pattern of kidney disease has changed since the introduction of ART, with a relative decrease in HIVAN and emergence of classic FSGS as the commonest cause of glomerular disease.[34] In this study, HIVAN occurred more frequently in Black patients with severe immunodeficiency and severe kidney failure, whereas FSGS patients were older, more likely to have received cART, more frequently had cardiovascular risk, and had more severe interstitial fibrosis on kidney biopsy.

Treatment of HIV-associated kidney disease also includes standard therapies for CKD, including control of BP and the use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), combined with a thiazide diuretic, low sodium diet, and weight loss if obese. An aldosterone antagonist such as spironolactone or eplerenone, used in low doses, may potentiate the antiproteinuric effect of this regimen but requires monitoring to avoid hyperkalemia. A prospective and controlled, but nonrandomized, trial of HIVAN demonstrated improved kidney survival with ACE inhibitor therapy.[35] Glucocorticoids have shown benefit for HIVAN in a prospective and several retrospective studies, as reviewed recently.[36] Nevertheless, although there is no consensus, these medications should only be considered in HIVAN and HIVICK when viral replication is suppressed with cART and proteinuria or progressive kidney function decline continues. BP targets should be treated to achieve a systolic BP of less than 120 mm Hg consistent with the 2020 Kidney Disease Improving Global Outcomes (KDIGO).[1]

Natural History of HIVAN

Progression of CKD is more rapid in HIV+ individuals of African descent, probably reflecting the effect of the APOL1 variants. Patients with HIVAN may progress to ESKD despite cART, but the use of these antiretroviral therapies may slow or even halt progression. Predictors of progression are a high degree of chronic damage on histology. as well as severe kidney dysfunction at baseline, high-grade proteinuria, and presence of many sclerotic glomeruli.37,38

OTHER GLOMERULAR DISORDERS

HIV-Associated Immune Complex Disease

In populations of European and Asian ancestry, the most common glomerular disease associated with HIV disease is immune complex disease (reviewed in Cohen and Kimmel39; case series have been reported from high-income countries, including the United States,40,41 the United Kingdom,42 and France,34 and from low-income countries, including Thailand43 and India44). HIVICK is also seen in populations of African descent, although much less frequently than HIVAN, and most lack two APOL1 risk alleles. Compared with those with HIVAN, HIVICK subjects tend to have lower HIV viral copy number and are more likely to have diabetes and hypertension.45

HIVICK can take various forms, including postinfectious glomerulonephritis, membranous nephropathy, and a lupus-like histologic pattern.46 Patients with HCV coinfection may manifest a membranoproliferative glomerulonephritis (MPGN) pattern (see Chapter 22).

Some patients may have only mesangial immunoglobulin A (IgA) deposits (especially those with microhematuria and nonnephrotic proteinuria), resembling idiopathic IgA nephropathy. Hence, the diagnosis of HIVICK may be fraught with challenges for the pathologist, who must exclude other immune complex disease.

HIVICK may be clinically indistinguishable from HIVAN, although hematuria may be more marked, and some patients present with lower levels of proteinuria. Kidney biopsy findings may vary from MPGN to focal or diffuse proliferative glomerulonephritis with endocapillary proliferation (Fig. 58.2). In some cases, changes consistent with HIVAN may also be present, including tubuloreticular inclusions within glomerular capillary endothelial cells. Immune deposits may be in mesangial, subendothelial, or subepithelial locations and may include IgG and IgM or IgG, IgM, and IgA (so-called “full house deposits”), often with C3. These forms resemble lupus nephritis, although lupus serologic test results are typically negative. If lupus serologies are positive, then in most cases the individual has lupus and HIV-1 infection, although early case reports suggest that some patients with HIV-1 infection may have false-positive lupus serology tests.47

The pathogenesis of HIVICK is not well understood and may involve various mechanisms. It is not known whether complexes form locally within the glomeruli or are passively trapped as from the glomerular microcirculation. In some cases, immune complexes include HIV antigens. Other cases may represent generalized polyclonal B-cell expansion that accompanies HIV disease.

An important issue is whether some or perhaps many HIVICK cases are not because of HIV-1 infection per se but instead are examples of idiopathic glomerular immune disease, in some cases possibly arising as a consequence of the immune reconstitution syndrome after institution of ART. Membranous nephropathy may appear after immune reconstitution, and such patients often have antibodies against the phospholipase-A2 receptor (PLA2R), the most common antigen associated with idiopathic membranous nephropathy.

HIVICK is often associated with progressive loss of eGFR. Foy and colleagues in the United States found that at 2 years after diagnosis, 70% of HIVAN cases and 32% of HIVICK cases had reached

A

B

Fig. 58.2 Human Immunodeficiency Virus (HIV)-Associated Glomerulonephritis. This HIV-positive individual presented with microhematuria and nonnephrotic proteinuria with normal kidney function. Kidney biopsy shows mild mesangial expansion with mesangial and paramesangial deposits, together with varying numbers of subepithelial-based deposits (arrows), resulting in the "ball-and-cup" appearance. (Courtesy Professor Stewart Goetsch, University of the Witwatersrand, Johannesburg, South Africa.)

ESKD. Further, the use of cART or the attainment of viral suppression was not associated with lower risk of ESKD in HIVICK, whereas use of cART was associated with reduced likelihood of progression with HIVAN.[45] In contrast, a UK study reported a slower rate of progression of HIVICK to ESKD, but these authors considered HIV-associated IgA nephropathy to be a distinct entity and with a risk for progression that is intermediate between HIVAN and HIVICK.[42]

OTHER GLOMERULAR DISORDERS

Thrombotic microangiopathy may occur with HIV infection and is associated with low CD4 cell counts, high viral burden, and AIDS.[48] Fibrillary glomerulonephritis, immunotactoid glomerulopathy, and amyloidosis have also been reported in HIV infection, but a causal role for HIV infection has not been established.

SYSTEMIC INFLAMMATION AND ARTERIONEPHROSCLEROSIS

A paradigm shift has emerged over the past two decades, with the recognition that long-term suppression of HIV replication dramatically improves survival but at the cost of chronic inflammation and premature aging.[49] Peripheral inflammatory markers correlate with Framingham risk scores and Veteran Aging Cohort Scores,[50] and hypertension is common.[51] The causes of chronic inflammation in HIV disease are complex. Chronic immune activation is associated with lymphocyte depletion, manifesting as reduced numbers of CD4+ and CD8+ naïve T cells. Alterations in the intestinal microbiome and microbial translocation may contribute.[52]

Inflammation promotes disease processes that resemble premature aging (including atherosclerosis) and manifests in the kidney as arterionephrosclerosis. This disease involves systemic arterial intimal thickening, medial hypertrophy, duplication of the internal elastic lamina, and global glomerulosclerosis. These afferent arteriolar lesions predispose to glomerulosclerosis and hypertension by altering kidney autoregulation. Arterionephrosclerosis was traditionally ascribed to hypertension, but it is now apparent that other mechanisms often contribute. Arterionephrosclerosis is associated with genetic mutations (e.g., APOL1), metabolic disorders (e.g., diabetes, obesity, hyperlipidemia, metabolic syndrome, and HIV infection), and chronic inflammation (smoking, oxidative stress, hemodynamic shear stress, and renin-angiotensin system activation).[53] A U.S. study of HIV-1 patients reported that isolated arterionephrosclerosis was the most common single pathology,[54] and this trend has become stronger as more HIV+ individuals have achieved viral suppression and are living longer while taking ART for longer durations.

TUBULAR DISORDERS

HIV infection is associated with tubular disorders, often because of medications (see Table 58.1), the most common being tenofovir disoproxil fumarate (TDF). AKI most commonly occurs in outpatient settings, with prekidney causes (extracellular volume contraction, or reduced kidney blood flow because of nonsteroidal anti-inflammatory agents [NSAIDs]) and postrenal causes (including obstruction as a result of prostate disease, kidney stone, or crystalluria). Kidney causes of AKI include tubular injury from medication, particularly TDF; interstitial nephritis because of NSAIDs or antibiotics; and less commonly, acute presentations of glomerular disease. Risk factors for HIV-associated AKI include male sex, sub-Saharan African ancestry, low CD4 count, high viral load, diabetes, CKD, and hepatic disease.55 Chronic proximal tubular injury manifests as various components of Fanconi syndrome: glycosuria, phosphaturia (sometimes associated with clinically significant hypophosphatemia), uricosuria, tubular proteinuria (predominantly low-molecular-weight proteins), and aminoaciduria. Diabetes insipidus may also be present, indicating that the distal nephron is also involved.

NEPHROTOXICITY AND DOSING OF ART AND ASSOCIATED DRUGS

Current Antiretroviral Drug Regimens and Kidney Toxicity

As of 2021, there are 25 antiretroviral medications and 24 antiretroviral medication combination formulations approved for use in the treatment of HIV disease in the United States. Recommendations for first-line therapy of HIV in adults include a combination of three medications. These are TDF, a nucleotide reverse transcriptase inhibitor (NRTI); either lamivudine or emtricitabine, nucleoside reverse transcriptase inhibitors, also abbreviated NRTI; and efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI). The difference between a nucleotide and a nucleoside is that the latter must be phosphorylated to become active. To underscore its ubiquity, TDF is a component of four of the six regimens currently recommended for treatment-naïve patients and hence widely used globally. TDF nephrotoxicity is discussed later. By contrast, NNRTIs have an excellent kidney safety profile.

In addition to these two drug classes (NRTI, NNRTI), there are six other classes of antiretroviral medications currently in clinical use

TABLE 58.2

Adjustments in Drug Dosing for Selected Antiretroviral Medications

Medication Class

Medication

Adjustment for GFR

Dosing in Dialysis

NRTI

Abacavir
Didanosinea
Emtricitabine
Lamivudine
Stavudinea
TDF
Tenofovir alafenamide

No change
Reduce for eGFR < 60
Reduce for eGFR < 50
Reduce for eGFR < 30
Reduce for eGFR < 50
Reduce for eGFR < 50
Not recommended if eGFR < 15 and not on hemodialysis
Reduce for eGFR < 15
No change
No change
No change
No change eGFR ≥ 20, not recommended eGFR< 20

No change
No dose after dialysis
No change; dose after dialysis
Reduce dose; dose after dialysis
Reduce dose
Reduce dose; dose after dialysis
No change

NNRTI

Protease inhibitor

Fusion inhibitor
Entry inhibitor (gp41)
INSTI

Zidovudine
Doravirine
Efavirenz
Etravirine
Nevirapine
Rilpivirine
Atazanavir
Darunavir
Fosamprenavir
Indinavira

Lopinavir
Nelfinavir
Saquinavira
Tipranavir
Enfuvirtide
Maraviroc^
Cabotegravira
Dolutegravir
Raltegravir
Bictegravir

Pharmacokinetic
enhancer
CD4 postattachment
inhibitor
gp120 attachment
inhibitor

Cobicistat

Use with caution in severe CKD
No change
No change
No data
No change
No data
No data
Not recommended for severe CKD
Probably no change
No change
eGFR < 30: dosing depends on concomitant
medications
eGFR < 15: no data
No change; use caution in INSTI-experienced
patients with severe renal impairment
No change
Not recommended

Ritonavir
Ibalizumab

No change
For eGFR < 70, avoid combination with TDF
No change
No data

Fostemsavir

No change

Reduce dose; dose after dialysis
Not studied
No change
No change
Additional 200 mg dose of immediate
release formulation recommended after dialysis
No data
Depends on antiretroviral treatment status
No data
No data
No change
Avoid once-daily dosing regimen

No data
No data
No data
No change
Dosing depends on concomitant medications
No data
No data
Dose after dialysis
eGFR < 30 acceptable in dialysis if benefits outweigh risks
No data
No data
No data
No change

As of 2021, there are 30 antiretroviral medications and 24 antiretroviral medication combination formulations approved for use in the treatment of HIV disease in the United States.

aNo longer available in the United States.

CCR5, C-C chemokine receptor 5; CKD, chronic kidney disease; CrCl, creatine clearance; eGFR, estimated glomerular filtration rate; gp, glycoprotein; HIV, human immunodeficiency virus; INSTI, integrase strand-transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

(Table 58.2). These include protease inhibitors, fusion inhibitors (GP41 antagonist), an entry inhibitor (CCR5 antagonist), integrase inhibitor, integrase strand inhibitor (cabotegravir), and postattachment inhibitors, as well as a pharmacokinetic enhancer. Two long-acting injectable agents are available, cabotegravir and rilpirivine (NNRTI). Of these six classes, only protease inhibitors exhibit kidney toxicity. Indinavir was a formerly common cause of tubular injury but is rarely used at present and has been discontinued in the United States. Case series show that in individuals taking ritonavir-boosted atazanavir, urinary crystals composed of atazanavir affect 10% of subjects56 and kidney stones occur at a rate of 2.4 cases per 100 patient-years of therapy.57 Risk factors for nephrolithiasis include alkaline urine and kidney impairment; serum levels of atazanavir were not associated with stones.58 Atazanavir has

been also associated with interstitial nephritis.59 Atazanavir is no longer commonly used.

Tenofovir Disoproxil Fumarate

TDF is the most common cause of tubular injury in HIV+ individuals and manifests primarily as proximal tubular dysfunction with Fanconi syndrome. TDF is taken up by proximal tubular cells by one or more organic anion transporters and converted to the active drug that inhibits DNA repair and DNA replication in host cells and in HIV. TDF also causes mitochondrial enlargement and dysmorphic changes and is associated with cellular adenosine triphosphate (ATP) depletion.60 A mild decrease in GFR has also been associated with TDF use, but usually it is not severe enough to require discontinuation of treatment.

TABLE 58.3

Kidney Toxicity of Antiretroviral Therapy

Antiretroviral Class	Antiretroviral Therapy	Kidney Effect	Clinical Recommendations
Protease inhibitors	Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute kidney injury, interstitial nephritis Ritonavir may increase toxicity of indinavir	Daily fluid intake of >2 L/day
	Atazanavir	Crystalluria, stones, interstitial nephritis	Daily fluid intake of >2 L/day
	Ritonavir	Increases levels of TDF	
Reverse transcriptase inhibitors	TDF	Kidney tubular damage: proximal tubular dysfunction, Fanconi syndrome, nephrogenic diabetes insipidus, acute tubular necrosis, acute kidney injury	Patients taking TDF should be monitored for signs of tubular dysfunction, including elevated serum creatinine, hypophosphatemia, low serum uric acid, acidosis, glycosuria, and proteinuria

TDF, Tenofovir disoproxil, fumarate.

Nonetheless, full recovery of kidney function may take months to years after stopping TDF.61 In some cases, recovery is partial or progresses to CKD.62 Risk factors for TDF-induced kidney toxicity include low CD4 cell count, prior kidney impairment, longer duration of therapy, and combined therapy with didanosine and protease inhibitors (lopinavir and ritonavir); the latter agents elevate TDF plasma levels, which, in turn, are associated with a higher risk of nephrotoxicity.63

TDF is taken up into the kidney tubular epithelial cell from basolateral space by the organic anion transporter (OAT) 1 and OAT3 and is secreted into the tubular lumen by the multidrug resistance protein (MRP) 4. Mutations in ABCC4, encoding MRP4, are associated with increased plasma TDF concentrations and nephrotoxicity risk64 and mutations in ABCC10, encoding MRP10, are associated with increased risk of phosphate wasting.65 On the other hand, the use of MRP inhibitors such as NSAIDs, salicylates, and dipyridamole does not increase toxicity.66

Tenofovir-alafenamide (TAF) has proven effective and welltolerated. Like TDF, TAF is a prodrug but, unlike TDF, it is not a substrate for the OAT1 and OAT2 transporters and thus is not taken up by tubular cells. Currently available data suggest lower levels of kidney toxicity compared with TDF but longer trials will be required to confirm this.67 TAF is also associated with less phosphaturia and better preserved bone mineralization in adults older than 60 years.

ANTIRETROVIRAL THERAPY DOSING IN CHRONIC KIDNEY DISEASE

Many antiretroviral medications are partially or completely eliminated by the kidney and require dosage adjustment in CKD. Certain drug classes, such as the protease inhibitors and the NNRTIs, are extensively metabolized by the liver and do not require dosage adjustment. Most of the NRTIs are excreted unchanged in the urine and require dosage adjustment, except for abacavir, which has substantial extrarenal biotransformation that requires little if any dosage adjustment. In uremia, drug dosages may be affected by altered gastric pH and altered volumes of distribution. Factors that influence dialyzability of antiretroviral medications relate to the properties of the particular dialysis membrane and molecular weight, degree of protein binding, molecular charge, and water solubility of the drug. Drugs that are substantially removed by hemodialysis should be taken after dialysis sessions. If the drug is removed in peritoneal dialysis effluent, the dose may have to be adjusted. Dosage recommendations (Table 58.3) in both hemodialysis and peritoneal dialysis are limited; there is a recommendation for NRTI dosing in patients undergoing venovenous hemofiltration.68

END-STAGE KIDNEY DISEASE

With the increasing survival of HIV+ individuals with treatment and the declining cost of cART, the incidence of HIV-associated ESKD will likely increase worldwide, as it has in high-income countries. Currently, survival among dialysis-dependent HIV+ patients who are stable on cART is comparable to that among dialysis patients without HIV infection, and choice of dialysis modality (hemodialysis versus peritoneal dialysis) does not have an impact on survival. Immunization schedules are the same as for non–HIV-negative dialysis patients.69 In both CKD and HIV infection, anemia is independently associated with shorter survival. The response to recombinant erythropoietin (EPO) in HIV+ patients with ESKD is similar to that in HIV-negative patients.70 Measurements of iron indices are complicated in HIV+ patients because levels of ferritin (an acute phase reactant) are often elevated in patients with HIV infection. Elevated soluble transferrin receptor concentrations are more reliable than serum ferritin to distinguish iron deficiency in inflammatory disease states.71

Hemodialysis

Strict adherence to universal precautions is the best form of prevention of HIV transmission in dialysis units, and there is no reason for these patients to be isolated. Even reprocessing of dialyzers from HIV+ patients does not place staff members at increased risk for infection, if necessary sterile precautions are undertaken. The risk of viral seroconversion after a needle-stick injury has been estimated as 6 in 1000 for HCV, 4 in 1000 for HBV, and 2 in 1000 for HIV.72 ART may reduce the risk of transmission after a needle stick injury, and postexposure prophylaxis for 28 days with a combination of two reverse transcriptase inhibitors and one protease inhibitor is recommended. Native arteriovenous fistulas are the preferred types of access for all patients with ESKD because of better patency rates and lower complication rates, compared with other access options. A recent study from South Africa showed similar patient survival outcomes for HIV+ and HIV-negative hemodialysis patients, except for increased incidence of tuberculosis in the HIV+ group.73

Peritoneal Dialysis

HIV-1 remains infectious at room temperature in peritoneal dialysis (PD) exchange tubing for up to 48 hours and for up to 7 days in peritoneal effluent.74 Dialysate should therefore be handled as a contaminated body fluid.74 Sodium hypochlorite (50% solution) and household bleach (10% solution), each further diluted 1 to 512, are effective at inactivating HIV in dialysate. PD patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home garbage.

Kidney Transplantation

The past few years have seen a surge of interest in kidney transplantation for HIV+ patients with ESKD. In a report of 150 kidney transplants from HIV-negative donors (both living and deceased) to HIV+ recipients,75 acute rejection rates were higher than in other subjects, but HIV replication remained controlled. Similar outcomes were reported subsequently from other centers, including 25 HIV+ recipients who received 43 kidneys from HIV+ deceased donors in South Africa76 77 and 92 subjects in the United States.78 With longer-term follow-up, compared with HIV-negative recipients, HIV+ recipients had a marginally increased risk of graft loss and no increased risk of death.79 HIV+ pediatric recipients have also received kidneys from HIV-negative donors with good outcomes.80

Interestingly, Canaud et al. reported that kidneys from HIVnegative donors became infected after transplantation into HIV+ recipients, with HIV RNA detected in podocytes and tubular cells.81

In 2013 the HOPE (HIV Organ Policy Equity) Act was passed by the U.S. Congress, which legalized research involving HIV+ living donors providing kidneys to HIV+ recipients, and studies with this population are being developed.82

EVALUATION FOR KIDNEY DISEASE

HIV+ individuals should undergo regular evaluation for kidney disease, probably at least every 6 months and more frequently if kidney disease is suspected (Fig. 58.3). Early identification of kidney injury

disease offers the prospect of discovering kidney injury when it first appears, defining the nature of the process, removing provocative factors when possible (particularly medications), and initiating therapy to slow, halt, or possibly reverse the disease process.

Periodic testing should include a history of nephrotoxic medications and measurement of BP, serum creatinine, blood urea nitrogen, and urine protein/creatinine ratio. Three studies in HIV+ patients have compared the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations against the gold standard iothalamate GFR: All three concluded that the CKD-EPI equation correlated well with measured GFR. When doses prescribed were compared with those recommended by the CKD-EPI eGFR, 6% to 19% of patients received an inappropriate dose; these subjects tended to be older and were more likely to have diabetes.

Most proteinuria in HIV+ patients is tubular in origin. In a study from London, 10% of subjects had proteinuria (defined as protein/creatinine ratio > 200 mg/g), most of which was not albumin; 17% had microalbuminuria, and 67% had increased excretion of the low molecular protein neutrophil gelatinase–associated lipocalin (NGAL).83

Microalbuminuria, defined as 20 to 200 mg/g of creatinine, may indicate early glomerular disease (including in diabetic nephropathy, arterionephrosclerosis, HIV-associated glomerular disease), tubular disease, metabolic syndrome, or systemic inflammation. In six of seven South African patients with persistent microalbuminuria, HIVAN was present on kidney biopsy,84 documenting that this disease may have an insidious presentation. Modestly elevated albuminuria may be persistent or intermittent and may reflect other processes, such as diabetes and hypertension. Indeed, in HIV+ individuals, microalbuminuria is associated with Framingham risk score,85 endothelial dysfunction,86 and intimal medial thickness and with all-cause mortality.87

SELF-ASSESSMENT QUESTIONS

1. In individuals of African descent with HIV infection, genetic variants in the APOL1 gene are associated with which of the following kidney biopsy diagnoses?

A. HIV-associated nephropathy (collapsing glomerulopathy) or focal segmental glomerulosclerosis
B. Membranous nephropathy
C. Immune complex glomerulonephritis
D. IgA nephropathy

2. An HIV-positive individual is receiving antiviral therapy and has suppressed viral replication. At a routine clinic visit, reduced serum phosphate and uric acid along with glycosuria are noted. Which of the following is the most likely explanation for these abnormalities?

A. Efavirenz

B. Allopurinol
C. Tenofovir disoproxil
D. Ritonavir

3. The clinician of the patient in question 2 was not provided with the laboratory results, and no changes were made in the clinical management of the patient. At the next visit 6 months later, the serum creatinine has risen and a kidney biopsy is performed. Which of the following findings would be most specific in clarifying the cause of the injury?

A. Arterionephrosclerosis
B. Focal global glomerulosclerosis
C. Tubular atrophy and interstitial nephritis
D. Giant mitochondria within the tubular cells

Screening HIV-Positive Individuals for Acute and Chronic Kidney Disease

All HIV-positive individuals should be offered antiretroviral therapy at the time of HIV diagnosis
and if they decline, should be offered at each clinic visit

Assessment for kidney disease in all HIV-infected individuals
Risk factors for CKD: Sub-Saharan African descent, family history of CKD, use of nephrotoxic therapies
including traditional medicines, hepatitis C, HIV viral load >400 copies/mL, CD4 cell count <200 cells/mm3
Assessment: Urine dipstick and serum creatinine, then calculate eGFR (see Chapter 3)

1. Urine dipstick for leukocytes
If negative, repeat annually
If positive, perform urine microscopy and culture for bacteria
UTI symptoms: Culture or treat empirically, adjust therapy when sensitivities are known
Sterile pyuria: Test for sexually transmitted infections, including syphilis, and tuberculosis
Repeat urine dipstick at follow-up visit

2. Urine dipstick for proteinuria
If negative, measure urine albumin-to-creatinine ratio and repeat in 1 year
If positive, measure urine albumin/creatinine and urine protein/creatinine ratio
Moderately increased albuminuria (albumin/creatinine ratio 20−200 mg/g); see Chapter 31
- Acute causes: Fever, pregnancy, uncontrolled hypertension, uncontrolled diabetes, congestive heart failure
- Chronic causes: Metabolic syndrome, diabetes

Severely increased albuminuria (albumin/creatinine ratio >200 mg/g)
Acute causes: Fever, systemic infection, hypertensive emergency
Chronic causes:
Nephrotic or subnephrotic proteinuria: HIVAN, FSGS, arterionephrosclerosis, diabetes, hepatitis B, syphilis
Nephritic syndrome: HIVICK, lupus, hepatitis C, postinfectious glomerulonephritis
Consider kidney biopsy
Tubular proteinuria (urinary albumin/total protein <40%)
- Tenofovir toxicity
- Interstitial nephritis (NSAIDs , antibiotics, tenofovir)

3. Serum creatinine and eGFR
Acute kidney injury: If eGFR has recently fallen by >25% (risk) or >50% (injury)
- Prerenal conditions: Look for signs of extracellular volume contraction
- Renal conditions

Review nephrotoxic medications including nonprescription medications (particularly NSAIDs), prescription
medications (particular tenofovir, disoproxil, fumarate, atazanavir), and intravenous contrast
Consider rhabdomyolysis if heme pigment is present without erythrocytes
- Postrenal conditions: Bladder retention (including prostatism), stone, cancer; consider renal ultrasound

Chronic kidney disease: If eGFR is stable or slowly declining and <60 mL/min/1.73m ^{2}
- Renal ultrasound for kidney size and echogenicity
- Review nephrotoxic medications
- Serologic testing for hepatitis B and C

- Evaluation for Plasmodium malariae in endemic areas
- Serum K <5 mmol/L: Start RAAS antagonist
- Manage blood pressure and CKD stage appropriately (Chapter 82)

Fig. 58.3 Management Algorithm for Screening of Human Immunodeficiency Virus (HIV)-Positive Antiretroviral Therapy–Naive Patients for Chronic Kidney Disease. Tuberculosis may be pulmonary or extrapulmonary. Antiproteinuric agents may be used in normotensive individuals with gradual uptitration of dose, depending on tolerance and severity of proteinuria. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate, calculated by the Cockcroft-Gault formula or the modified Modification of Diet in Renal Disease (MDRD) formula; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; HIVICK, HIV-associated immune complex kidney disease; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; STI, sexually transmitted infection; UTI, urinary tract infection.

REFERENCES

1. Cheung AK, et al. Blood pressure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int. 2019;95:1027–1036.
2. Mocroft A, et al. Deteriorating renal function and clinical outcomes in HIV-positive persons. Aids. 2014;28:727–737.
3. Razzak Chaudhary S, et al. Trends in the outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. Nephrol Dial Transplant. 2015;30:1734–1740.
4. Hurst SA, Appelgren KE, Kourtis AP. Prevention of mother-to-child transmission of HIV type 1: the role of neonatal and infant prophylaxis. Expert Rev Anti Infect Ther. 2015;13(2):169–181.
5. Davidson B., Okpechi I., McCulloch M., Wearne N., Adolescent nephrology: an emerging frontier for kidney care in sub-Saharan Africa. Nephrology (Carlton). 2017;22(12):933–939. PMID: 28782147
6. Naicker S, Fabian J. Risk factors for the development of chronic kidney disease with HIV/AIDS. Clin Nephrol. 2010;74(suppl 1):S51–S56.
7. Bruggeman LA, et al. Renal epithelium is a previously unrecognized site of HIV-1 infection. J Am Soc Nephrol. 2000;11:2079–2087.
8. Zuo Y, et al. HIV-1 genes vpr and nef synergistically damage podocytes, leading to glomerulosclerosis. J Am Soc Nephrol. 2006;17:2832–2843.
9. Genovese G, et al. Association of trypanolytic apol1 variants with kidney disease in African Americans. Science. 2010;329:841–845.
10. Tzur S, Rosset S, Skorecki K, Wasser WG. APOL1 allelic variants are associated with lower age of dialysis initiation and thereby increased dialysis vintage in African and Hispanic Americans with non-diabetic endstage kidney disease. Nephrol Dial Transplant. 2012;27:1498–1505.
11. Kopp JB, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 2011;22:2129–2137.
12. Kasembeli AN, et al. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. J Am Soc Nephrol. 2015.
13. Fine DM, et al. APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. J Am Soc Nephrol. 2012;23:343–350.
14. Jotwani V, et al. APOL1 genotype and glomerular and tubular kidney injury in women with HIV. Am J Kidney Dis. 2015;65:889–898.
15. Olabisi OA, Zhang JY, VerPlank L, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. Proc Natl Acad Sci U S A. 2016;113(4):830–837.
16. Wakashin H, Heymann J, Roshanravan H, et al. APOL1 renal risk variants exacerbate podocyte injury by increasing inflammatory stress. BMC Nephrol. 2020;21(1):371.
17. Kumar V, Ayasolla K, Jha A, et al. Disrupted apolipoprotein L1-miR193a axis dedifferentiates podocytes through autophagy blockade in an APOL1 risk milieu. Am J Physiol Cell Physiol. 2019;317(2):C209–C225.
18. Ma L, Chou JW, Snipes JA, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. J Am Soc Nephrol. 2017;28(4):1093–1105.
19. Okamoto K, Rausch JW, Wakashin H, et al. APOL1 risk allele RNA contributes to renal toxicity by activating protein kinase R. Commun Biol. 2018;1:188.
20. Hayek SS, Koh KH, Grams ME, et al. A tripartite complex of supar, APOL1 risk variants and αvβ3 integrin on podocytes mediates chronic kidney disease. Nat Med. 2017;23(8):945–953.
21. Uzureau S, Lecordier L, Uzureau P, et al. APOL1 C-terminal variants may trigger kidney disease through interference with APOL3 control of actomyosin. Cell Rep. 2020;30(11):3821–3836. e13.
22. Saag MS, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the international antiviral society-USA panel. JAMA. 2020;324:1651–1669.
23. Lucas GM, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV

Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e96–e138.

24. Atta MG, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. Nephrol Dial Transplant. 2006;21:2809–2813.
25. Peters PJ, et al. Antiretroviral therapy improves renal function among HIV-infected Ugandans. Kidney Int. 2008;74:925–929.
26. Stohr W, et al. Glomerular dysfunction and associated risk factors over 4-5 years following antiretroviral therapy initiation in Africa. Anti ther. 2011;16:1011–1020.
27. Wearne N, Swanepoel CR, Boulle A, Duffield MS, Rayner BL. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. Nephrol Dial Transplant. 2012;27:4109–4118.
28. Mulenga LB, et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. AIDS. 2008;22:1821–1827.
29. Ifudu O, et al. Zidovudine is beneficial in human immunodeficiency virus associated nephropathy. Am J Nephrol. 1995;15:217–221.
30. Lucas GM, et al. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. J Infect Dis. 2008;197:1548–1557.
31. Michel C, et al. Nephropathy associated with infection by human immunodeficiency virus: a report on 11 cases including 6 treated with zidovudine. Nephron. 1992;62:434–440.
32. Pope SD, Johnson MD, May DB. Pharmacotherapy for human immunodeficiency virus-associated nephropathy. Pharmacotherapy. 2005;25:1761–1772.
33. Winston JA, Burns GC, Klotman PE. Treatment of HIV-associated nephropathy. Semin Nephrol. 2000;20:293–298.
34. Lescure FX, et al. HIV-associated kidney glomerular diseases: changes with time and HAART. Nephrol Dial Transplant. 2012;27:2349–2355.
35. Wei A, et al. Long-term renal survival in HIV-associated nephropathy with angiotensin-converting enzyme inhibition. Kidney Int. 2003;64:1462–1471.
36. Kalayjian RC. The treatment of HIV-associated nephropathy. Adv chronic kidney dis. 2010;17:59–71.
37. Bige N, et al. Presentation of HIV-associated nephropathy and outcome in HAART-treated patients. Nephrol Dial Transplant. 2012;27:1114–1121.
38. Post FA, et al. Predictors of renal outcome in HIV-associated nephropathy. Clin Infect Dis. 2008;46:1282–1289.
39. Cohen SD, Kimmel PL. Immune complex renal disease and human immunodeficiency virus infection. Semin Nephrol. 2008;28:535–544.
40. Murakami CA, et al. The clinical characteristics and pathological patterns of postinfectious glomerulonephritis in HIV-infected patients. PLoS One. 2014;9. e108398.
41. Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with “lupus-like” features: a clinicopathologic study of 14 cases. Kidney Int. 2005;67:1381–1390.
42. Booth JW, et al. Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. Nephrol Dial Transplant. 2016;31:2099–2107.
43. Praditpornsilpa K, et al. Renal pathology and HIV infection in Thailand. Am J Kidney Dis. 1999;33:282–286.
44. Gupta V, et al. HIV associated renal disease: a pilot study from north India. Indian J Med Res. 2013;137:950–956.
45. Foy MC, et al. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. Clin J Am Soc Nephrol. 2013;8:1524–1532.
46. Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD atlas of renal pathology: HIV-Associated Immune Complex Kidney Disease (HIVICK). Am J Kidney Dis. 2016;68:e9–e10.
47. González CM, López-Longo FJ, Samson J, et al. Antiribonucleoprotein antibodies in children with HIV infection: a comparative study with

childhood-onset systemic lupus erythematosus. AIDS Patient Care STDS. 1998;12(1):21–28.
48. Coppo P, Veyradier A. Current management and therapeutical perspectives in thrombotic thrombocytopenic purpura. Presse Med. 2012;41:e163–e176.
49. Appay V, Kelleher AD. Immune activation and immune aging in HIV infection. Curr Opin HIV AIDS. 2016;11:242–249.

References

50. Mooney S, Tracy R, Osler T, Grace C. Elevated biomarkers of inflammation and coagulation in patients with HIV are associated with higher Framingham and VACS risk index scores. PLoS One. 2015;10. e0144312.
51. Martin-Iguacel R, Negredo E, Peck R, Friis-Moller N. Hypertension is a key feature of the metabolic syndrome in subjects aging with HIV. Curr Hypertens Rep. 2016;18:46.
52. Gootenberg DB, Paer JM, Luevano JM, Kwon DS. HIV-associated changes in the enteric microbial community: potential role in loss of homeostasis and development of systemic inflammation. Curr Opin Infect Dis. 2017;30:31–43.
53. Kopp JB. Rethinking hypertensive kidney disease: arterionephrosclerosis as a genetic, metabolic, and inflammatory disorder. Curr Opinion Nephrol Hypertens. 2013;22:266–272.
54. Mallipattu SK, Wyatt CM, He JC. The new epidemiology of HIV-related kidney disease. J AIDS Clin Res. 2012;(suppl 4). 001.
55. Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. Curr Opin Crit Care. 2008;14:647–653.
56. de Lastours V, et al. High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients. J Antimicrob Chemother. 2013;68:1850–1856.
57. Hamada Y, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis. 2012;55:1262–1269.
58. Marinescu CI, et al. Relationships between serum levels of atazanavir and renal toxicity or lithiasis. AIDS Res Treat. 2015;2015:106954.
59. Kanzaki G, et al. Diffuse tubulointerstitial nephritis accompanied by renal crystal formation in an HIV-infected patient undergoing highly active antiretroviral therapy. Intern Med. 2012;51:1543–1548.
60. Herlitz LC, et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. Kidney Int. 2010;78:1171–1177.
61. Szczech LA. Renal dysfunction and tenofovir toxicity in HIV-infected patients. Top HIV Med. 2008;16:122–126.
62. Scherzer R, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. Aids. 2012;26:867–875.
63. Baxi SM, et al. Higher tenofovir exposure is associated with longitudinal declines in kidney function in women living with HIV. Aids. 2016;30:609–618.
64. Izzedine H, et al. Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy. J Infect Dis. 2006;194:1481–1491.
65. Pushpakom SP, et al. Genetic variants of ABCC10, a novel tenofovir transporter, are associated with kidney tubular dysfunction. J Infect Dis. 2011;204:145–153.
66. Rokx C, et al. Renal toxicity of concomitant exposure to tenofovir and inhibitors of tenofovir’s renal efflux transporters in patients infected with HIV type 1. J Infect Dis. 2016;213:561–568.
67. Gibson AK, Shah BM, Nambiar PH, Schafer JJ. Tenofovir alafenamide: a review of its use in the treatment of HIV-1 infection. Ann Pharmacother. 2016.
68. McLaughlin MM, Ammar AT, Gerzenshtein L, Scarsi KK. Dosing nucleoside reverse transcriptase inhibitors in adults receiving continuous veno-venous hemofiltration. Clin Drug Investig. 2015;35:275–280.

69. Gupta SK, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis.

2005;40:1559–1585.
70. Shrivastava D, et al. The efficacy of erythropoietin in human immunodeficiency virus-infected end-stage renal disease patients treated by maintenance hemodialysis. Am J Kidney Dis. 1995;25:904–909.
71. Eley BS, Sive AA, Shuttleworth M, Hussey GD. A prospective, crosssectional study of anaemia and peripheral iron status in antiretroviral naive, HIV-1 infected children in Cape Town, South Africa. BMC Infect Dis. 2002;2:3.
72. Elseviers MM, Arias-Guillen M, Gorke A, Arens HJ. Sharps injuries amongst healthcare workers: review of incidence, transmissions and costs. J Ren Care. 2014;40:150–156.
73. Fabian J, et al. Morbidity and mortality of black HIV-positive patients with end-stage kidney disease receiving chronic haemodialysis in South Africa. S Afr Med J. 2015;105:110–114.
74. Farzadegan H, Ford D, Malan M, Masters B, Scheel Jr PJ. HIV-1 survival kinetics in peritoneal dialysis effluent. Kidney Int. 1996;50:1659–1662.
75. Stock PG, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. 2010;363:2004–2014.
76. Muller E, Barday Z. HIV-positive kidney donor selection for HIV-positive transplant recipients. J Am Soc Nephrol. 2018;29(4):1090–1095.
77. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive-to-HIV-positive kidney transplantation-results at 3 to 5 years. N Engl J Med. 2015;372:613–620.
78. Malat GE, et al. High frequency of rejections in HIV-positive recipients of kidney transplantation: a single center prospective trial. Transplantation. 2012;94:1020–1024.
79. Roland ME, et al. Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls. AIDS. 2016;30:435–444.
80. Shroff RC, McCulloch M, Novelli V, et al. Successful outcome of renal transplantation in a child with HIV-associated nephropathy. Arch Dis Child. 2014;99(11):1026–1028.
81. Canaud G, et al. The kidney as a reservoir for HIV-1 after renal transplantation. J Am Soc Nephrol. 2014;25:407–419.
82. Mehta S, Locke JE. Human immunodeficiency virus from life taking to life giving: expanding the donor pool by using HIV-positive donors. Curr Opin Organ Transplant. 2020;25(6):626–630.
83. Campbell LJ, et al. Total protein, albumin and low-molecular-weight protein excretion in HIV-positive patients. BMC Nephrol. 2012;13:85.
84. Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006;69:2243–2250.
85. Tongma C, et al. Albuminuria as a marker of cardiovascular risk in HIVinfected individuals receiving stable antiretroviral therapy. Hawaii J Med Public Health. 2013;72:34–38.
86. Pirro M, et al. Urinary albumin-to-creatinine ratio is associated with endothelial dysfunction in HIV-infected patients receiving antiretroviral therapy. Sci Rep. 2016;6:28741.
87. Wyatt CM, et al. Microalbuminuria is associated with all-cause and AIDS mortality in women with HIV infection. J Acquir Immune Defic Syndr. 2010;55:73–77.

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Kidney Diseases Associated With Coronaviruses

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The first cases of COVID-19 were reported in Wuhan, China, in late 2019, and by mid-March 2020, the World Health Organization officially declared a pandemic.1 COVID-19 has since caused millions of deaths worldwide, and acute kidney injury (AKI) and other kidney syndromes are important complications COVID-19.2 Moreover, COVID-19 has disproportionately impacted persons with kidney failure who receive chronic dialysis and are kidney transplant recipients (KTRs).

micrographs of intracellular structures that appeared to be consistent with SARS-CoV-2 virions.8 Subsequent studies suggested that technical limitations of the assays used for SARS-CoV-2 antigen and nucleic acid detection as well as difficulty in differentiating intracellular organelles from virions may have led to some false positive results.9 More recently, viral RNA and protein have been detected in kidney tubular cells, where the nucleocapsid and spike proteins colocalized with ACE2.10 Therefore, it is likely that kidney tubular cells become infected by SARS-CoV-2, but it is unknown if this causes clinically apparent kidney injury.

SARS-COV-2 AND VIRAL PATHOGENESIS

COVID-19 ACUTE KIDNEY INJURY

INTRODUCTION

The virus that causes COVID-19 is SARS-CoV-2. Coronaviruses are enveloped, single-stranded RNA viruses that infect humans, other mammals, and nonmammalian species.1 The first coronavirus found to induce severe disease in humans was severe acute respiratory syndrome coronavirus (SARS-CoV), which caused the first reported SARS outbreak in China in 2002 and subsequent sporadic outbreaks. In 2012, the Middle Eastern respiratory syndrome (MERS), caused by MERS-CoV, was reported on the Arabian Peninsula. SARS-CoV and MERS-CoV use the same receptor (ACE2) as SARS-CoV-2 to infect host cells.3 Kidney injury is a common complication of MERS but probably occurs less often in patients with SARS.4 5

Cellular entry of SARS-CoV-2 is mediated by binding of the viral spike (S) protein to ACE2 on the surface of target cells and subsequent cleavage/activation of S by the type 2 transmembrane serine protease (TMPRSS2), thereby enabling the S protein to mediate entry of the virus into the host cell (Fig. 59.1), leading to cellular injury and activation of inflammatory responses.1

Robust innate immune responses, including interferon production early after SARS-CoV-2 infection, are important for limiting the severity of COVID-19.6 However, in hospitalized patients with established COVID-19, high levels of inflammatory mediators predict increased risk of AKI, mechanical ventilation, and mortality, whereas immunosuppression with high-dose corticosteroids reduces mortality.1 7

Similarly, dysregulated activation of coagulation in COVID-19 causes microvascular and, less often, macrovascular occlusion, which is an important contributor to lung injury,1 but the role of dysregulated coagulation in COVID-19–associated kidney injury is less clear.

DOES SARS-COV-2 INFECT THE KIDNEY?

The receptor ACE2 is strongly expressed in proximal tubular cells, whereas other kidney cells, including podocytes, express ACE2 at lower levels.8 Studies have reported the presence of viral antigens and nucleic acids in kidney autopsy and biopsy specimens, and electron

Epidemiology

The incidence of COVID-19–associated AKI (COVID-19 AKI) is high, ranging from 17% to 46% in large cohorts of hospitalized patients with COVID-19.11-13 This variability likely reflects differences in disease severity, age, and comorbidities, and it is not clear whether the incidence and severity of AKI is higher in patients with COVID-19 than otherwise similar patients without COVID-19.

There is significant heterogeneity in the severity of COVID-19 AKI with the proportion of stage 3 AKI, ranging from 11% to 42% with as many as 19% requiring kidney replacement therapy (KRT).12-14 In a multicenter cohort study of intensive care unit (ICU) patients from 67 US hospitals, 21% developed AKI requiring KRT within 14 days of ICU admission.7

Risk Factors for COVID-19 AKI

Although many factors contribute to AKI in patients with COVID-19 (Fig. 59.1), hypovolemia and sepsis are the most common causes reported.13 Risk factors associated with the incidence and severity of COVID-19 AKI include older age, male sex, Black race, obesity, hypertension, and diabetes mellitus. The presence of chronic kidney disease (CKD) and CKD stage are strongly associated with increased risk of COVID-19 AKI and the need for KRT.7,11-13

Increased severity of illness, including hypotension, hypoxia, and the need for mechanical ventilation are associated with increased risk of COVID-19 AKI.7,13 Hypovolemia is a major contributor to COVID-19 AKI. COVID-19 illness leads to hypovolemia by increasing insensible losses (fever and tachypnea), reducing oral intake (sore throat, nausea, and anorexia), and increasing gastrointestinal losses (diarrhea).15

Some groups have reported partial Fanconi syndrome with wasting of low-molecular-weight proteins, amino acids, uric acid, and phosphate but not glucose.15 It is unknown whether primary tubular wasting contributes to hypovolemia in COVID-19.

Elevated serum biomarkers of inflammation (C-reactive protein and ferritin) and/or coagulation (D-dimer) are associated with

Pathogenesis of Acute Kidney Injury in COVID-19
SARS-CoV-2

Myocarditis
Cytokine storm

Insensible losses
Endothelial
dysfunction

Medication
nephrotoxicity

Rhabdomyolysis

High-risk APOL1
genotype

Hypercoagulable

Myoglobin cast
nephropathy
Glomerular diseases
Prerenal

Thrombotic
microangiopathy

Hypotension
Sepsis

Cardiorenal syndrome
Acute
tubular
necrosis

Acute kidney injury

Fig. 59.1 Pathogenesis of acute kidney injury in patients with COVID-19.

increased risk of COVID-19 AKI in retrospective analyses[7]; however, the value of biomarkers as independent predictors of COVID-19 AKI remains to be demonstrated.

Histopathology of COVID-19 AKI

Small case series have reported pathologic findings in autopsy and kidney biopsy specimens from patients with COVID-19 AKI. Acute tubular injury (ATI) or tubular necrosis were identified in up to 90%, and glomerular and peritubular capillary congestion were common findings without additional glomerular lesions or fibrin thrombi[16-20] (Fig. 59.2). Myoglobin casts indicative of rhabdomyolysis have been found in up to 10% of biopsies showing ATI.

Treatment of COVID-19 AKI

There are no specific treatments to prevent or reduce the severity or duration of COVID-19 AKI. Treatment is supportive and includes optimization of kidney perfusion and minimizing exposures that may exacerbate kidney injury. Though studies have not demonstrated that a specific KRT modality results in superior clinical outcomes in patients with COVID-19, continuous kidney replacement therapy (CKRT) is preferred in hemodynamically unstable patients. Because patients with

COVID-19 often require prone positioning to improve oxygenation, placement of dialysis catheters in the internal jugular rather than the femoral vein allows for easier access during proning. Anticoagulation is often required during KRT because patients with COVID-19 are at increased risk of thrombotic complications, including vascular access and dialysis circuit clotting. Small retrospective studies have reported increased CKRT filter life span with anticoagulation, but the optimal approach to anticoagulation for CKRT in patients with COVID-19 remains undetermined.21

In regions where the incidence of COVID-19 AKI has overwhelmed KRT capacity, several strategies have been used to increase KRT availability. Increased blood and dialysate flow rates and shortened

Fig. 59.2 Acute Tubular Injury in a Patient With COVID-19 and Acute Kidney Injury. Proximal tubular cells show loss of brush border staining, flattening, and degenerative change (arrows) with cellular debris in a tubular lumen (arrowhead).

treatments for intermittent HD can allow for a greater number of treatments. Similarly, flows on CKRT machines can be increased to provide prolonged intermittent kidney replacement therapy, allowing CKRT machines to be used for multiple patients each day.21 Finally, several centers have reported using acute peritoneal dialysis in patients with COVID-19 AKI.21 Important advantages of peritoneal dialysis include scalability due to lack of requirement for a dialysis machine or high volumes of dialysate-quality water, and elimination of issues with dialysis circuit and vascular access clotting. Though studies reported

A

B

Fig. 59.3 Collapsing Glomerulopathy in an African American Patient With Moderately Symptomatic COVID-19 and Nephrotic Syndrome. (A) Global epithelial cell hypertrophy and hyperplasia with wrinkling and retraction of glomerular capillaries. (B) Microcystic tubules with proteinaceous casts.

clinical outcomes that appear to be acceptable with acute peritoneal dialysis in patients with COVID-19 AKI, peritoneal dialysis was sometimes difficult to perform in the most acutely ill patients, especially those who required prone positioning.

Prognosis of COVID-19 AKI

COVID-19 AKI often has a prolonged course and 35% to 40% of hospitalized patients with COVID-19 AKI meet criteria for acute kidney disease (i.e., AKI persisting for >7 days).12 13 Of those with acute kidney disease, 36% had resolution to baseline kidney function during follow-up. However, 14% of patients with complete AKI resolution at discharge subsequently developed acute kidney disease, and 30% of survivors with AKI requiring KRT remained dialysis-dependent at the time of hospital discharge.12

Mortality among patients with COVID-19 AKI is high, ranging from 19% in those with stage 1 AKI to more than 60% in those with stage 3D AKI and/or highest severity of illness.7 11-13 Among ICU patients with COVID-19 AKI, older age, receipt of two or more vasopressors at time of KRT initiation, and daily urine output less than 100 mL are associated with higher 28-day mortality.7

COVID-19–ASSOCIATED GLOMERULAR DISEASES

Clinical Presentation and Histopathology

Collapsing glomerulopathy (CG), minimal change disease (MCD), membranous nephropathy, and pauci-immune crescentic glomerulonephritis are the predominant glomerular lesions observed in patients with COVID-19.22-24a Clinical features of COVID-19–associated CG and MCD are new onset nephrotic syndrome or nephrotic range proteinuria with AKI. Collapsing glomerulopathy (Fig. 59.3) has been reported predominantly in persons of African ancestry, and high-risk APOL1 genotypes have been identified in the great majority of patients with CG who underwent testing, suggesting that genetic susceptibility likely contributes to risk of CG in patients with COVID-19.22-24a Severe COVID-19 is associated with coagulopathy and microvascular thromboses which can resemble immune-triggered, complement-mediated thrombotic microangiopathy (TMA). COVID-19–associated TMA (Fig. 59.4) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and severe AKI requiring KRT. Those with a predisposing risk factor for endothelial injury, such as hypertension, drug exposure, or a genetic or acquired defect in the alternative complement pathway, may be at increased risk.19 22 25 COVID-19 also has been associated with immune-mediated glomerular disease. Cases of anti–glomerular basement membrane (anti-GBM) disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, immunoglobulin A (IgA) nephropathy, and membranous nephropathy (MN) have been reported in patients with COVID-19.22 26 27 These glomerular diseases may manifest concurrently or several weeks after resolution of the acute infection, and it is unknown if this is chance occurrence or is pathogenetically linked. Interestingly, IgA nephropathy may occur de novo or be exacerbated after SARS-CoV-2 infection, and gross hematuria and/or transient worsening of kidney function have occurred after COVID-19 vaccination in patients with IgA nephropathy, possibly due to augmented immune injury.28-31

Treatment and Prognosis

Despite a 50% or higher incidence of severe AKI requiring KRT in patients with COVID-19–associated CG, kidney function and proteinuria improve in many patients up to 90 days after resolution of infection. Therefore, those who are discharged on KRT should be monitored closely for recovery of kidney function.19 22 23 25 All patients should receive supportive care directed at blood pressure control and maintaining euvolemia. Treatment with immunosuppression can be considered in those with severe nephrotic syndrome or persistent nephrotic range proteinuria that fails to improve despite resolution of infection, though potential risks of immunosuppression in patients with active or recent infection must be considered.

COVID-19–associated TMA is associated with a poor prognosis including dialysis dependence and high mortality. In the absence of controlled clinical studies to guide treatment, clinicians may consider interventions used for non–COVID-19–related TMA including plasma exchange and terminal complement inhibitors.

A

B

Fig. 59.4 Thrombotic Microangiopathy in a Patient With COVID-19 Presenting With Hypertension, Anemia, Thrombocytopenia, Hematuria, and Proteinuria. (A) Glomerulus with global capillary thrombosis. (B) Immunofluorescence showing extensive glomerular fibrin deposition.

COVID-19 IN PATIENTS WITH KIDNEY FAILURE REQUIRING CHRONIC DIALYSIS

COVID-19 incidence and mortality are significantly increased in patients with end-stage kidney disease (ESKD). Male sex, older age, and residence in a congregate setting have been consistently identified as risk factors for contracting COVID-19, whereas home dialysis has been associated with a reduced risk of infection compared with incenter dialysis.[32]

Hospitalization rates approach 60% or higher among chronic dialysis patients with COVID-19 compared with 15% to 20% observed in the general population.[33,34] Moreover, ESKD patients hospitalized with COVID-19 have 1.4-fold higher odds of in-hospital death after adjusting for demographics and comorbidities, suggesting ESKD is an independent risk factor for mortality due to COVID-19.[35] National and international registries estimate short-term mortality of 20% or greater among all dialysis patients with COVID-19 and 40% mortality in those who require hospitalization, underscoring the importance of prevention in this vulnerable population.[36]

Patients receiving in-center dialysis are at increased risk for contracting COVID-19 due to the requirement of transportation to and from dialysis and frequent contact with caregivers, health care providers, nonmedical staff, and other patients.[37] Thus, prevention of infection at the dialysis unit is critical. Screening for signs and symptoms of COVID-19 should be performed prior to each dialysis session. Additionally, some centers perform weekly point-of-care testing of all dialysis patients, which may lead to early detection of COVID-19 prior to symptom onset and may help prevent disease spread. For patients with suspected or confirmed COVID-19, dialysis must be provided in a location and manner that minimizes risk to staff and patients.[37]

COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

Epidemiology and Risk Factors

Compared to the general population, kidney transplant recipients are at increased risk of hospitalization and death from COVID-19 due to treatment with immunosuppressive medications and excess burden of comorbidities. The incidence of AKI may exceed 50%, and allograft loss has been reported in 4% to 11% of patients.[38] Large registries of KTRs with symptomatic COVID-19 report hospitalization rates of 87% to 100% and mortality of 19% to 32%.[38,39] However, routine testing for SARS-CoV-2 IgG antibodies in asymptomatic patients suggests that a significant proportion of KTRs have a mild disease course. One transplant center that performed routine testing for SARS-CoV-2 antibodies found that 42% of KTRs who tested positive were asymptomatic or had mild symptoms not requiring medical attention.[40]

Treatment and Management of Immunosuppression

Decisions regarding reduction in immunosuppression in KTRs should be based on severity of illness and weighed against the risks of allograft loss. Factors to consider when reducing immunosuppressive medications include allograft function, history of rejection, and presence of donor-specific antibodies. Most centers recommend a 50% dose reduction or complete cessation of the antimetabolite in KTRs with COVID-19.41 42 In patients with worsening symptoms or evidence of COVID-19 pneumonia, the calcineurin inhibitor (CNI) should be reduced to target the lower limit of the therapeutic range, and an increase in corticosteroid dosing can be considered. In those requiring ventilatory support, CNI withdrawal should be considered, and corticosteroid dosing should be increased to prevent acute rejection.

Recipient and Donor Screening and Selection

Both donor and prospective KTRs should have negative SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) testing prior to transplantation. Screening with chest computed tomography may reveal signs of COVID-19–related disease preceding a positive test and may be considered.38 Donors with active or recent COVID-19 should be declined or deferred. T cell–depleting induction therapy may reduce viral clearance and decrease the ability to mount an immune response to SARS-CoV-2. In highly sensitized patients who require potent immunosuppression, it may be reasonable to delay transplantation until vaccination. Though it is unknown how long transplantation should be deferred in prospective KTRs who test positive, the American Society of Transplantation suggests waiting for resolution of symptoms and at least 2 negative SARS-CoV-2 RT-PCR tests.43

RENIN-ANGIOTENSIN SYSTEM INHIBITORS IN COVID-19

The ACE2 receptor, the entry receptor for SARS-CoV-2, is upregulated by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers (ARB), leading to theoretical concerns that these medications may increase susceptibility to COVID-19. However, ACE2 is a carboxypeptidase that reduces Ang II levels by cleaving Ang II to Ang (1–7) and by cleaving Ang I to Ang (1–9), which is converted by ACE to Ang (1–7), which binds the MAS receptor.44 These effects of ACE2 are cytoprotective, and increased lung expression of ACE2 is associated with improved outcomes in lung injury,3 leading investigators to study whether ACE inhibitors and/or ARB are protective or harmful in patients with or at risk for COVID-19. At this time, there is no compelling evidence that ACE inhibitors/ARBs affect susceptibility to or severity of COVID-19, and major medical societies, including the American Society of Nephrology and the American Heart Association, have issued statements urging clinicians to continue prescribing these medications for patients who are likely to otherwise benefit from them.

ANTI–SARS-COV-2 THERAPIES AND VACCINES IN PATIENTS WITH KIDNEY DISEASE

At this time, no evidence-based recommendations can be made regarding the use of antiviral therapies in patients with kidney disease and COVID-19. Most clinical trials evaluating the use of these medications

have excluded patients with severe kidney disease and/or KTRs. Monoclonal anti-SARS-CoV-2 therapies do not require dose adjustment for kidney function. Remdesivir is not currently recommended in those with eGFR less than 30 mL/min/1.73 m2, though small series have reported its use in patients with ESKD or AKI requiring dialysis.45 The carrier molecule of remdesivir is eliminated by the kidney and may accumulate in those with eGFR less than 30 mL/min/1.73 m2. One study using postmarketing data found that remdesivir was associated with sevenfold higher odds of AKI compared with other COVID-19 therapies.46 Therefore, caution should be used in patients with reduced eGFR and in those at high risk for development of AKI. The optimal timing of hemodialysis relative to remdesivir dosing remains to be determined.

Data on vaccine efficacy for prevention of COVID-19 in patients with severe CKD are currently lacking. Small preliminary studies suggest that patients with ESKD receiving dialysis mount vigorous antibody responses after vaccination47; however, KTRs may have weakened antibody responses.48 Given the increased risk of COVID-19–related complications in patients with kidney disease, it is important to prioritize these patients for vaccination and to optimize approaches to maximize the efficacy of vaccination in this vulnerable population.

CONCLUSIONS

Acute and chronic kidney injury are important complications of COVID-19 and determinants of clinical outcomes in patients with COVID-19. Further research is needed to identify novel strategies to prevent and treat COVID-19 induced kidney injury and to determine optimal approaches to improve outcomes in patients with COVID-19 who have kidney disease.

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782–793.
2. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020;16(12):747–764.
3. Zamorano Cuervo N, Grandvaux N. ACE2: evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. Elife. 2020;9.
4. Cha RH, Joh JS, Jeong I, et al. Renal complications and their prognosis in Korean patients with Middle East respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. J Korean Med Sci. 2015;30(12):1807–1814.
5. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67(2):698–705.
6. Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020;19(7):102567.
7. Gupta S, Coca SG, Chan L, et al. AKI treated with renal replacement therapy in Critically ill patients with COVID-19. J Am Soc Nephrol. 2021;32(1):161–176.
8. Khan S, Chen L, Yang CR, Raghuram V, Khundmiri SJ, Knepper MA. Does SARS-CoV-2 infect the kidney? J Am Soc Nephrol. 2020;31(12):2746–2748.
9. Roufosse C, Curtis E, Moran L, et al. Electron microscopic investigations in COVID-19: not all crowns are coronas. Kidney Int. 2020;98(2):505–506.
10. Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nat Commun. 2021;12(1):2506.
11. Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z. Acute kidney injury in a national cohort of hospitalized US veterans with COVID-19. Clin J Am Soc Nephrol. 2020;16(1):14–25.
12. Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol. 2021;32(1):151–160.
13. Procaccini FL, Alcázar Arroyo R, Albalate Ramón M, et al. Acute kidney injury in 3182 patients admitted with COVID-19: a single center retrospective case–control study. Clin Kidney J. 2021;14(6):1557–1569.
14. Fisher M, Neugarten J, Bellin E, et al. AKI in hospitalized patients with and without COVID-19: a comparison study. J Am Soc Nephrol. 2020;31(9):2145–2157.
15. Werion A, Belkhir L, Perrot M, et al. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. Kidney Int. 2020;98(5):1296–1307.
16. Sharma P, Uppal NN, Wanchoo R, et al. COVID-19-Associated kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol. 2020;31(9):1948–1958.
17. Santoriello D, Khairallah P, Bomback AS, et al. Postmortem kidney Pathology findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):2158–2167.
18. Ng JH, Bijol V, Sparks MA, Sise ME, Izzedine H, Jhaveri KD. Pathophysiology and Pathology of acute kidney injury in patients with COVID-19. Adv Chronic Kidney Dis. 2020;27(5):365–376.
19. Akilesh S, Nast CC, Yamashita M, et al. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. Am J Kidney Dis. 2021;77(1):82–93. e81.
20. Bouquegneau A, Erpicum P, Grosch S, et al. COVID-19-associated nephropathy includes tubular necrosis and capillary congestion, with evidence of SARS-CoV-2 in the nephron. Kidney360. 2021;2(4):639–652.
21. Stevens JS, Velez JCQ, Mohan S. Continuous renal replacement therapy and the COVID pandemic. Semin Dial. 2021;34(6):561–566.

22. Kudose S, Batal I, Santoriello D, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):1959–1968.

23. Shetty AA, Tawhari I, Safar-Boueri L, et al. COVID-19-Associated glomerular disease. J Am Soc Nephrol. 2021;32(1):33–40.
24. Ferlicot S, Jamme M, Gaillard F, et al. The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury, and/or proteinuria. Nephrol Dial Transplant. 2020;Feb 12:gfab042.
24a. May RM, Cassol C, Hannoudi A, et al. A multi-center retrospective cohort study defines the spectrum of kidney pathology in Coronavirus 2019 Disease (COVID-19). Kidney Int. 2021;100(6):1303–1315.
25. Sharma P, Ng JH, Bijol V, Jhaveri KD, Wanchoo R. Pathology of COVID-19-associated acute kidney injury. Clin Kidney J. 2021;14(suppl1):i30–i39.
26. Sacchi MC, Tamiazzo S, Stobbione P, et al. SARS-CoV-2 infection as a trigger of autoimmune response. Clin Transl Sci. 2021;14(3):898–907.
27. Uppal NN, Kello N, Shah HH, et al. De novo ANCA-associated vasculitis with glomerulonephritis in COVID-19. Kidney Int Rep. 2020;5(11):2079–2083.
28. Perrin P, Bassand X, Benotmane I, Bouvier N. Gross hematuria following SARS-CoV-2 vaccination in patients with IgA nephropathy. Kidney Int. 2021;100:466–468.
29. Negrea L, Rovin BH. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. Kidney Int. 2021;99(6):1487.
30. Li NL, Papini AB, Shao T, Girard L. Immunoglobulin-A vasculitis with renal involvement in a patient with COVID-19: a case report and Review of acute kidney injury related to SARS-CoV-2. Can J Kidney Health Dis. 2021;8. 2054358121991684.
31. Huang Y, Li XJ, Li YQ, et al. Clinical and pathological findings of SARSCoV-2 infection and concurrent IgA nephropathy: a case report. BMC Nephrol. 2020;21(1):504.
32. Hsu CM, Weiner DE, Aweh G, et al. COVID-19 infection among US dialysis patients: risk factors and outcomes from a national dialysis provider. Am J Kidney Dis. 2021;77(5):748–756.
33. Alberici F, Delbarba E, Manenti C, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. Kidney Int. 2020;98(1):20–26.
34. Corbett RW, Blakey S, Nitsch D, et al. Epidemiology of COVID-19 in an urban dialysis center. J Am Soc Nephrol. 2020;31(8):1815–1823.
35. Ng JH, Hirsch JS, Wanchoo R, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. Kidney Int. 2020;98(6):1530–1539.
36. Jager KJ, Kramer A, Chesnaye NC, et al. Results from the ERAEDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int. 2020;98(6):1540–1548.
37. Verma A, Patel AB, Tio MC, Waikar SS. Caring for dialysis patients in a time of COVID-19. Kidney Med. 2020. Epub ahead of print.
38. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and solid organ transplantation: a review article. Transplantation. 2021;105(1):37–55.
39. Cravedi P, Mothi SS, Azzi Y, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. Am J Transplant. 2020;20(11):3140–3148.
40. Azzi Y, Parides M, Alani O, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. Kidney Int. 2020;98(6):1559–1567.
41. Gleeson SE, Formica RN, Marin EP. Outpatient management of the kidney transplant recipient during the SARS-CoV-2 virus pandemic. Clin J Am Soc Nephrol. 2020;15(6):892–895.
42. Maggiore U, Abramowicz D, Crespo M, et al. How should I manage immunosuppression in a kidney transplant patient with COVID-19?

An ERA-EDTA descartes expert opinion. Nephrol Dial Transplant. 2020;35(6):899–904.
43. American Society for Transplantation. Information for transplant professionals and community members regarding 2019 novel coronavirus. https://www.myast.org/sites/default/files/1COVID19%20FAQ%20Tx%20Centers%2004.15.2020.pdf.

References

44. Ortiz-Melo DI, Gurley SB. Angiotensin converting enzyme 2 and the kidney. Curr Opin Nephrol Hypertens. 2016;25(1):59–66.
45. Sorgel F, Malin JJ, Hagmann H, et al. Pharmacokinetics of remdesivir in a COVID-19 patient with end-stage renal disease on intermittent haemodialysis. J Antimicrob Chemother. 2021;76(3):825–827.
46. Chouchana L, Preta LH, Tisseyre M, Terrier B, Treluyer JM, Montastruc F. Kidney disorders as serious adverse drug reactions of remdesivir in covid-19: a retrospective case-non case study. Kidney Int. 2021;99(5):1235–1236.

47. Grupper A, Sharon N, Finn T, et al. Humoral response to the pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol. 2021;16(7):1037–1042.
48. Benotmane I, Gautier-Vargas G, Cognard N, et al. Weak antiSARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int. 2021;99(6):1487–1489.

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Nephrolithiasis and Nephrocalcinosis

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NEPHROLITHIASIS

Epidemiology

Kidney stones are common in high-income countries, with an annual incidence of more than 1 in 1000 persons and a lifetime risk for forming stones of approximately 9% in women and 13% in men.1-4 In the United States the prevalence of nephrolithiasis increased from 3.2% in the late 1970s to 5.2% in the 1990s, to 8.8% in the first decade of the 2000s, and further to approximately 10% in the 2010s, in parallel with the rising incidence of obesity, insulin resistance, and type 2 diabetes mellitus.5-7 Factors that determine kidney stone prevalence include age, sex, race, and geographic distribution. Incidence peaks in the third and fourth decades, and prevalence increases with age until approximately 70 years in men and 60 years in women. Men are more prone to stone formation than women.5 In the United States, Whites are more likely to develop kidney stones than African Americans, Hispanics, or Asian Americans, but the prevalence is rising in non-Whites as well.5 The tendency in the United States for the development of stones also depends on geographic location, with an increasing prevalence from north to south and, to a lesser degree, from west to east. The increase in nephrolithiasis rates from north to south may be due to increased environmental temperatures, and greater sunlight exposure leading to an increase in insensible losses through sweating and more concentrated urine.1,8 The higher urine calcium excretion in a smaller urine volume will increase the risk for supersaturation for calcium-containing crystals, thereby promoting stone formation.

Stone type varies with worldwide geography and genetic predisposition. In the Mediterranean and Middle East, 75% of stones are composed of uric acid. In the United States, the majority of stones are calcium oxalate and/or calcium phosphate (>70%), with less than 10% being pure uric acid stones. Magnesium ammonium phosphate (struvite) stones account for 10% to 25% of stones formed (with a higher incidence in the United Kingdom), and cystine stones constitute 2% of all stones formed (Fig. 60.1).9

Kidney stones are associated with systemic conditions including chronic kidney disease (CKD), cardiovascular disease, and bone disease. In a Canadian cohort,10 having one or more episodes of kidney stones was associated with increased risk for end-stage kidney disease (ESKD; adjusted hazard ratio [HR], 2.16; 95% confidence interval [CI], 1.79–2.62) and development of CKD (HR, 1.74; 95% CI, 1.61–1.88). The risk for CKD development was greater in women than in men and in people younger than 50 years. However, the absolute increase in the rate of adverse kidney outcomes associated with kidney stones was small; the unadjusted rate of ESKD was 2.48 and 0.52 per million person-days in people who developed kidney stones and

in people without stones, respectively. Development of kidney stones was associated with increased risk for coronary heart disease in women but not in men, and with greater aortic calcification.11,12 Those with calcium-based stones were shown to have lower bone mineral density and higher risk of fracture than non–stone formers.12-14

Pathogenesis

Stones occur in urine that is supersaturated with respect to the ionic constituents of the specific type of stone. Supersaturation depends on the product of the free ion activities of stone components rather than on their molar concentrations. The free ion activities of stone components can be affected by the concentration of the crystal components, presence of inhibitors, and urine pH. An increasing concentration of the components of the crystal increases their free ion activity. When calcium and oxalate are dissolved in pure water, the solution becomes saturated when the addition of any more calcium or oxalate does not result in further dissolution. However, urine, unlike pure water, contains numerous calcification inhibitors that can form soluble complexes with the ionic components of the stone. The interactions with these inhibitors (e.g., citrate) may result in a decrease in free ion activity that allows the stone constituents to increase in total concentration to levels that would normally cause stone formation in pure water.

Urinary pH also influences free ion activity. The level of chemical free ion activity in which stones will neither grow nor dissolve is referred to as the equilibrium solubility product, or the upper limit of metastability. Above this level, the urine will be supersaturated, and any stone present will grow in size.

When the solution becomes supersaturated with respect to a solid phase, ions can join together to form the more stable, solid phase, a process termed nucleation. Homogeneous nucleation refers to the joining of similar ions into crystals. The more common and thermodynamically favored heterogeneous nucleation results when crystals grow adjacent to crystals or other substances in the urine, such as sloughed epithelial cells. Calcium oxalate crystals, for example, can nucleate with uric acid crystals. These small crystals may then aggregate to form larger stones, which would pass into the urine, causing crystalluria, if they did not anchor to the urothelium.

Calcium oxalate crystals anchor on areas of calcium phosphate deposits termed Randall plaques, which are located in the renal papillae. Randall plaques appear to originate around the thin loop of Henle.

In the outer medulla, the vascular bundles are surrounded by the thick ascending limb, which absorbs calcium independently of water. As the delivery of calcium to the thick ascending limb increases, the calcium concentration in the vascular bundles increases. This promotes supersaturation of crystals in the thin limb, which fosters plaque formation.

Distribution of Stone Types
Calcium oxalate
and calcium
phosphate 37%
Calcium
oxalate 26%
Cystine 2%
Calcium
phosphate 7%

Struvite 22%
Uric acid 5%

Fig. 60.1 Proportion of stone types in a typical U.S. population.

TABLE 60.1 Clinical Presentations of Nephrolithiasis

Presentation	Characteristics
Pain	Ureteral colic, loin pain, dysuria
Hematuria	–
Urinary tract infection	Recurrent, chronic infection, pyelonephritis
Asymptomatic urine abnormality	Microhematuria, proteinuria, sterile pyuria
Interruption of urinary stream	–
Calculus anuria	–

This theoretical mechanism is referred to as vas washdown and has yet to be proven experimentally.[15] Calcium oxalate crystals attach to Randall plaques, allowing significant stone growth.[16] Clinically apparent stone disease occurs when the calcium oxalate crystals break off from the Randall plaques and cause injury or obstruction.

Several genetic polymorphisms have been implicated in the pathogenesis of calcium stones in genome-wide association studies. They include genes coding for proteins regulating tubular calcium and phosphate reabsorption (e.g., calcium-sensing receptor, vitamin D receptor, and claudins), genes coding for proteins preventing calcium salt precipitation (e.g., matrix Gla protein), and genes coding for aquaporin in the proximal tubule.[3,17] Besides genetic polymorphisms, microbiome and exposure to antibiotics have also been implicated in the pathogenesis of nephrolithiasis. Exposure to sulfas, fluoroquinolones, cephalosporins, nitrofurantoin/methenamine, and broad-spectrum penicillin was associated with increased odds of nephrolithiasis.[18,19] Antibiotics may change the composition of the intestinal microbiome and alter the metabolism of macronutrients and ionic absorption, thus affecting the risk of nephrolithiasis.

Clinical Manifestations

The two most characteristic symptoms of nephrolithiasis are pain and hematuria. Other presentations include urinary tract infection (UTI) and acute kidney injury caused by obstructive uropathy if stones cause bilateral kidney outflow tract obstruction or unilateral obstruction in a single functioning kidney (Table 60.1).

Pain

The classic manifestation of pain in patients with nephrolithiasis is ureteral colic. Pain is of abrupt onset and intensifies over time into an excruciating, severe flank pain that resolves only with stone passage or removal. The pain may migrate anteriorly along the abdomen and inferiorly to the groin, testicles, or labia majora as the stone moves toward the ureterovesical junction. Gross hematuria, urinary urgency, frequency, nausea, and vomiting may occur. Stones smaller than 5 mm usually pass spontaneously with hydration, whereas progressively larger stones are increasingly likely to require urologic intervention (Fig. 60.2).16 Ureteral colic may occur with the passage of clots from hematuria of any cause ("clot colic") or with papillary necrosis. Nephrolithiasis also may provoke less-specific loin pain that poorly localizes to the kidney and therefore has a wide differential diagnosis, particularly if not associated with other urinary symptoms. The finding of a stone on radiologic examination does not preclude a coincidental cause of pain from another source.

Fig. 60.2 Ureteral Calculus. A 1-cm-wide calcium oxalate stone that provoked ureteral colic and required surgical removal.

BOX 60.1

Causes of Hematuria

- Nephrolithiasis
- Infection: cystitis, prostatitis, urethritis, acute pyelonephritis, tuberculosis, schistosomiasis
- Malignancy: renal cell carcinoma, transitional cell carcinoma, prostate cancer, Wilms tumor
- Trauma
- Glomerular disease
- Interstitial nephritis
- Polycystic kidney disease
- Papillary necrosis
- Medullary sponge kidney
- Miscellaneous: loin pain–hematuria syndrome, arteriovenous malformation, chemical cystitis, caruncle, factitious

Hematuria

Stone disease is a common cause of hematuria. Macrohematuria occurs more commonly with large calculi and during UTI and colic. Although typically associated with loin pain or ureteral colic, the hematuria of nephrolithiasis also may be painless. The clinical differential diagnosis of hematuria is wide (Box 60.1). Painless microhematuria in children may occur with hypercalciuria in the absence of demonstrable stones.

Loin Pain–Hematuria Syndrome

Loin pain–hematuria syndrome is a poorly understood condition that must be considered in the differential diagnosis of nephrolithiasis. It is diagnosed by exclusion when patients (most typically young and middle-aged women) present with loin pain and persistent microhematuria or intermittent macrohematuria.[20] Careful evaluation is required to exclude small stones, tumor, UTI, and glomerular disease.

Angiographic abnormalities implying intrarenal vasospasm or occlusion have been reported, as have kidney biopsy abnormalities typified by deposition of complement C3 in arteriolar walls. However, these findings are not consistent, nor do they provide a coherent framework to explain the pathogenesis of this condition.

In one study, 43 consecutive patients with clinical manifestations of loin pain–hematuria syndrome were evaluated by kidney biopsy after other causes of their symptoms had been excluded with at least two imaging studies.20 Thirty-four patients were considered to have idiopathic loin pain–hematuria syndrome after nine with histologic evidence of immunoglobulin A nephropathy were excluded. Of these, 66% had glomerular basement membranes that were either unusually thick or thin on electron microscopy and 47% had a history of kidney stones, though none had obstructing stones at the time of imaging assessment. Evidence of glomerular hematuria was more common in biopsy samples of patients with loin pain–hematuria syndrome compared with those of healthy living kidney donors who also underwent kidney biopsy. The investigators postulated that the structurally abnormal glomerular basement membranes in the majority of these patients may lead to rupture of the glomerular capillary walls, with consequent hemorrhage into the renal tubules and tubular obstruction by red blood cells, triggering kidney edema, stretching of the renal capsule, and severe flank pain.

Loin pain–hematuria syndrome is a chronic condition requiring reassurance, careful management of analgesia, and ongoing psychological support. The condition usually remits after several years. Denervation of the kidney by autotransplantation is rarely successful. The extreme measure of nephrectomy has been used, but pain often recurs promptly in the contralateral kidney. Bilateral nephrectomy and kidney replacement therapy have been reported as an approach of very last resort. Referral to a pain clinic can assist in providing psychiatric counseling, analgesia, and exclusion of other disorders. In one retrospective study, patients who eventually came to accept a nonsurgical approach along with pain-coping strategies that did not involve narcotic analgesics had the most successful outcomes.21

Asymptomatic Stone Disease

Even large staghorn calculi may be asymptomatic and discovered only during the investigation of unrelated abdominal or musculoskeletal symptoms. Obstructive uropathy caused by calculi also may be painless; therefore, nephrolithiasis always should be considered in the differential diagnosis of unexplained kidney failure. In an outbreak of melamine-associated nephrolithiasis in Chinese infants, the majority of patients brought to a screening clinic had no symptoms or signs of stones, and the diagnosis of nephrolithiasis was made only by ultrasound in at-risk infants and toddlers.22

Clinical Evaluation of Stone Formers

All patients with recurrent nephrolithiasis merit metabolic evaluation to determine the cause of their kidney stones.23 Patients with a single stone should at least undergo a basic evaluation. Those with metabolically active stones (stones growing in size or number within 1 year), all children, non–calcium stone formers, and patients in demographic groups not typically prone to stone formation warrant a complete evaluation, which includes a 24-hour urine collection made with the patient ingesting his or her typical diet.

Basic Evaluation

The evaluation of stone formers includes a careful history and physical examination and requires specific data gathering on stone formation, diet, and specific laboratory studies, as shown in Box 60.2

Basic Evaluation of Nephrolithiasis

BOX 60.2

- Stone history
- Number of stones formed
- Frequency of stone formation
- Age at first onset
- Size of stones passed or still present
- Kidney involved (left, right, or both)
- Stone type, if known
- Need for urologic intervention such as extracorporeal shock wave lithotripsy or percutaneous nephrolithotomy
- Response to surgical procedure
- Association of stones with urinary tract infections
- Medical history
- Medications
- Family history
- Occupation and lifestyle
- Fluid intake and diet
- Physical examination
- Evidence of systemic causes of stones (e.g., tophi)
- Laboratory data
- Urinalysis
- Urine culture
- Stone analysis
- Blood chemistry
- Sodium, potassium, chloride, bicarbonate
- Creatinine, calcium, phosphorus, uric acid
- Intact parathyroid hormone level if calcium elevated
- Radiologic evaluation
- Abdominal radiograph (no contrast)
- Noncontrast computed tomography
- Ultrasound (generally recommended)

History. The history may uncover a systemic cause for nephrolithiasis. Any disease that can lead to hypercalcemia (including malignancy, hyperparathyroidism, and sarcoidosis) can result in hypercalciuria and increase the risk for calcium stone formation. A number of malabsorptive gastrointestinal disorders (including Crohn disease and celiac disease) can result in calcium oxalate stone formation as a result of volume depletion and hyperoxaluria. Uric acid stones often occur in patients with a history of gout and insulin resistance.9

The stone history (see Box 60.2) includes the number and frequency of stones formed, patient age at incidence of first stone, size of stones, stone type (if known), and whether the patient required surgical removal of the calculi. This information indicates the severity of the stone disease and provides clues to the cause of the stone formation. For example, large staghorn calculi that do not pass spontaneously and recur despite frequent surgical intervention are more consistent with struvite than calcium oxalate stones. Stones that develop at a young age may be caused by cystinuria or primary hyperoxaluria. Stone response to intervention is also significant; cystine stones, for example, do not fragment well with lithotripsy. If stones recur frequently in a single kidney, a congenital abnormality in that kidney, such as megacalyx or medullary sponge kidney, should be explored.

Family history is important because a number of stone types have a genetic basis. Idiopathic hypercalciuria appears to be a polygenic disorder. Mutations in the claudins, which regulate calcium reabsorption in the thick ascending limb of the loop of Henle, cause familial hypercalciuria and nephrocalcinosis. A genome-wide association study in

Medications Associated With Nephrolithiasis and Nephrocalcinosis

BOX 60.3

Calcium Stone Formation

- Loop diuretics
- Vitamin D
- Corticosteroids
- Calcium supplements
- Antacids (calcium and noncalcium antacids)
- Theophylline
- Acetazolamide[a]
- Amphotericin[a]
- Topiramate

Uric Acid Stone Formation

- Salicylates
- Probenecid
- Melamine (in contaminated infant formula and milk products)

Medications That May Precipitate Into Stones

- Triamterene
- Acyclovir (if infused rapidly intravenously)
- Indinavir
- Nelfinavir

[a] Associated with nephrocalcinosis.

patients with kidney stones identified sequence variants in the gene encoding claudin 14 that were associated with hypercalciuria.[24]

Cystinuria is usually autosomal recessive, and hyperuricosuria has been associated with rare inherited metabolic disorders. Nephrolithiasis and nephrocalcinosis can result from a variety of monogenic disorders, such as Dent disease (X-linked recessive nephrolithiasis), McCuneAlbright syndrome, osteogenesis imperfecta type 1, and congenital lactate deficiency (see also Chapter 50). The various genetic disorders can lead to hypercalciuria by increasing bone resorption, affecting intestinal absorption, by decreasing renal tubular reabsorption transport, or by unknown mechanisms.[1,16,24]

Certain medications can potentiate calcium stone formation (e.g., loop diuretics are calciuric) or may predispose to uric acid lithiasis (salicylates, probenecid) (Box 60.3). Drugs can also precipitate into stones themselves, such as rapidly infused intravenous acyclovir, high-dose sulfadiazine, triamterene, and the antiretroviral agents indinavir and nelfinavir.[25] In addition, some medications (e.g., acetazolamide, topiramate) promote nephrolithiasis by inhibiting carbonic anhydrase activity. With these drugs, the metabolic acidosis that ensues, along with lower urine citrate, higher urine pH, and increased urinary calcium excretion, predisposes to calcium phosphate stone formation.

The social history should include details regarding occupation and lifestyle. Surgeons and real-estate agents, for example, may minimize fluid intake to avoid bathroom breaks during the workday. Those who engage in vigorous physical activities, such as running, may not rehydrate adequately to keep up with insensible losses, producing excessively concentrated urine and precipitation of stone crystals in those prone to nephrolithiasis.

A dietary history and review of fluid intake are essential in determining potential causes or contributors to stone formation. The patient should be asked about commonly consumed foods, with attention paid to sodium-containing foods, as well as quantities of calcium, animal protein, purine, and oxalate (Box 60.4). Dietary calcium intake should be reviewed, because many patients with nephrolithiasis are erroneously instructed to eliminate all calcium from their diet, a suggestion that can result not only in bone demineralization, particularly in women and children, but also in an increase in stone formation.2-4 26 Sugar-sweetened soda appears to be associated with a greater risk for stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice appears to be associated with a lower risk.27 The exact mechanism of nephrolithiasis from soda is not known but is likely related to the high fructose content of soda, which may trigger a vasopressin-dependent concentration of urine, lower urinary pH, and cause uricosuria.28 29

BOX 60.4

Foods High in Oxalate and Purine

High-Oxalate Foods (Avoid in Setting of Hyperoxaluria)
- Green beans
- Beets
- Celery
- Green onions
- Leeks
- Leafy greens: collard greens, dandelion greens, Swiss chard, spinach, escarole, mustard greens, sorrel, kale, rhubarb
- Cocoa
- Chocolate
- Black tea
- Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries
- Orange peel
- Lemon peel
- Dried figs
- Summer squash
- Nuts, peanut butter
- Tofu (bean curd)

High-Purine Foods (Avoid in Setting of Hyperuricosuria)
- Organ meats: sweetbreads, liver, kidney, brains, heart
- Shellfish
- Meat: beef, pork, lamb, poultry
- Fish: anchovies, sardines (canned), herring, mackerel, cod, halibut, tuna, carp
- Meat extracts: bouillon, broth, consommé, stock
- Gravies
- Certain vegetables: asparagus, cauliflower, peas, spinach, mushrooms, lima and kidney beans, lentils

Physical examination. Most patients with idiopathic hypercalciuria are healthy and have normal findings on physical examination. Patients with hyperuricosuria and uric acid stone formation may display tophi. Central obesity is associated with a predisposition to metabolic syndrome and uric acid stones. Paraplegic patients with a chronic indwelling bladder catheter may be predisposed to chronic UTI and struvite stones.

Laboratory findings. Urine pH is generally high in patients with struvite and calcium phosphate stones but low in patients with uric acid and calcium oxalate stones. Bacteriuria with urine pH greater than 7.0 suggests struvite stones. Urine should be cultured, and because many bacteria produce urease even when urine bacterial colony counts are low, the microbiology laboratory should be instructed to type the organism even if there are fewer than 105 colony-forming units/mL. The specific gravity, if high, will confirm inadequate fluid intake in many patients. Hematuria may imply active stone disease with crystal or stone passage. Examination of the urine may reveal red blood cells along with characteristic crystals (Fig. 60.3).

A

C

B

D

Fig. 60.3 Urine Crystals. (A) Oxalate crystals: a pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dihydrate. (B) Uric acid crystals: complex crystals suggestive of acute uric acid nephropathy or uric acid nephrolithiasis. (C) A typical hexagonal cystine crystal; a single crystal provides a definitive diagnosis of cystinuria. (D) Coffin lid crystals of magnesium ammonium phosphate (struvite). (Courtesy Dr. Patrick Fleet, University of Washington, Seattle.)

Blood tests required in the basic evaluation are serum electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, calcium, phosphorus, and uric acid. If the serum calcium is elevated or at the upper limit of normal, serum parathyroid hormone level should be measured, especially if the serum phosphorus is low. A low potassium or bicarbonate level may indicate a cause for hypocitraturia, such as distal renal tubular acidosis.

Stone analysis. Patients should be encouraged to retrieve any stone they excrete for chemical analysis, which may help define the underlying metabolic abnormality and guide therapy.

Imaging. Current imaging techniques used to evaluate stones include plain abdominal radiograph, unenhanced helical computed tomography (CT), and kidney ultrasound. Plain abdominal radiography performed with views of the kidneys, ureters, and bladder (KUB) may reveal opacifications in the areas of the kidneys and ureters that could be a result of calcium, cystine, or struvite stones (Fig. 60.4). Uric acid and xanthine calculi are radiolucent and will not be visible on plain films. Unenhanced helical CT scanning, also known as spiral CT, or CT urography, has replaced contrast intravenous urography (IVU) as a diagnostic test for acute ureteral colic because it is more sensitive and specific for ureteral stones and ureteral obstruction, and avoids the need for contrast (see Fig. 60.5A). Results from CT urography are available in minutes rather than hours, and this is an advantage in the emergency setting. There are several disadvantages of CT imaging: radiation dose from a CT urography is approximately three times that of a conventional IVU; CT urography is more expensive and is associated with a high rate of incidental findings that could lead to inappropriate referral and treatment. In addition, an experienced radiologist is required for optimal interpretation of the images, and may not be available at all times in urgent care facilities. CT urography should be avoided or limited in patients at risk for radiation exposure, such as children and pregnant women. Low-dose CT reduces radiation exposure and provides similar information to that provided by standard CT. However, low-dose CT is not recommended for patients with a body mass index greater than 30 kg/m^2[30]

Kidney ultrasound has a lower sensitivity and specificity than CT but does not expose patients to ionizing radiation and is less expensive. A recent study indicated that ultrasonography may be a better choice than CT, especially for those patients who must avoid radiation exposure (Fig. 60.5B). In a multicenter, comparative effectiveness trial, 2759 patients who presented to the emergency department (ED) with suspected nephrolithiasis were randomized to undergo either initial ultrasound or abdominal CT.31 Ultrasound was associated with lower cumulative radiation exposure than initial CT. There were no significant differences in high-risk diagnoses with complications (e.g., abdominal aortic aneurysm with rupture, pneumonia with sepsis), serious adverse events, pain scores, return visits to the emergency department, or hospitalizations between the ultrasound (whether assigned to either point of care in the emergency department or to the radiology department) and CT. Ultrasonography is the first-line imagining modality for pregnant women and patients younger than 14 years.30

A

B

Fig. 60.4 Radiopaque Kidney Calculi. (A) Radiograph showing multiple cystine stones in the right kidney, right ureter, and bladder. (B) Struvite stones: left staghorn calculus and a single bladder stone.

A

Periodic monitoring, if deemed necessary, should be obtained with an ultrasound scan rather than KUB or CT, whenever possible, to minimize radiation exposure. The combination of ultrasound and KUB is more sensitive in detecting stones than either test alone, while minimizing radiation compared with CT. Many patients with stones have recurrent disease and may require repeated imaging. Children and young adults are at higher risk for consequences from radiation exposure, and studies in this population should be limited. Especially when caring for patients who may father or subsequently carry offspring, every effort should be made to limit radiation exposure. In general, we do not order routine follow-up radiographic examinations and do not order radiographic examinations unless patients are symptomatic and the results will alter subsequent care. If radiographs are ordered, every effort should be made to limit radiation exposure, as the results of a noncontrast study alone are often sufficient to guide therapy.

Complete Evaluation

B

Fig. 60.5 Kidney Calculi. (A) Unenhanced computed tomography scan showing a nonobstructing left kidney stone (arrow) in a patient with right nephrectomy. (B) Ultrasound of the left kidney (sagittal view) from the same patient showing a stone with an acoustic shadow behind it (arrow).

A complete evaluation should be arranged for patients with multiple or metabolically active stones (i.e., stones that increase in size or number within a year), in all children, in patients from demographic groups not typically prone to stone formation, and in those with stones other than those containing calcium.23

The complete evaluation should include a measure of urine volume and the quantity of calcium, oxalate, phosphorus, uric acid, sodium, citrate, and creatinine excreted in a 24-hour urine collection (Table 60.2). Urine creatinine is useful in assessing adequacy of the collection; men should excrete more than 15 mg/kg (132.6 µmol/kg), and women should excrete more than 10 mg/kg (88.4 µmol/kg) daily. Patients should be encouraged to perform the urine collection on a typical day while eating their usual diet, although many patients prefer to collect the urine on weekends when their diet and habits may differ from those during usual workdays. Specialized testing, such as urine collections during high- or low-dietary calcium intake, is not recommended.

Careful instructions should be given to avoid overcollection or undercollection. Patients should be instructed to discard the first morning

TABLE 60.2 Optimal 24-Hour Urine Values in Recurrent Nephrolithiasis

24-Hour Urine Values	
Volume	>2–2.5 L
Calcium	<4 mg/kg (0.1 mmol/kg), ~300 mg (7.5 mmol) in men, ~250 mg (6.3 mmol) in women
Oxalate	<40 mg (0.36 mmol)
Uric acid	<750 mg (4.5 mmol) in women and <800 mg (4.7 mmol) in men (can be pH dependent)
Citrate	>320 mg (17 mmol)
Sodium	<2000 mg (87 mmol)
Phosphorus	<1100 mg (35 mmol)
Creatinine	>10 mg/kg (88 µmol/kg) in women and >15 mg/kg (132 µmol/kg) in men, if specimen is a complete collection
Urine Supersaturation Values	
Calcium oxalate supersaturation	<5
Calcium phosphate supersaturation	0.5–2
Uric acid supersaturation	0–1

urine at the start of the collection and collect all urine for the next 24 hours, including the first urine collection on the second morning.

A disadvantage of the standard 24-hour urine collection is that laboratories vary in the preservatives required to process the various constituents. Many laboratories require more than one collection to measure all the urinary constituents, reducing compliance and therefore the accuracy of the results, and supersaturation is often not calculated.

A better approach available in some speciality laboratories is to undertake a 24-hour urine collection for the relevant urinary constituents and calculation of supersaturation for the common solid phases of calcium oxalate, brushite (calcium phosphate), and uric acid (see Table 60.2). Urine for supersaturation analysis has been shown to correlate well with stone composition, and the risk for stone formation rises with increasing supersaturation. Determination of supersaturation is far more informative and helpful for planning proper therapy than evaluation of only the individual urinary constituents.

Patients can bring their specimens to a local laboratory or may send them to specialized laboratories that measure calcium, oxalate, citrate, uric acid, creatinine, sodium, potassium, magnesium, sulfate, phosphorus, chloride, urine urea nitrogen, and pH. Calculation of supersaturation from a 24-hour urine specimen will provide values lower than the peak postprandial supersaturation and peak nighttime supersaturation, either of which may initiate stone formation. Patients should stop taking any vitamin C or multivitamins containing more than 100 mg of vitamin C for at least 5 days before the urine collection because the antioxidants in the vitamin may interfere with the assay.

General Treatment

Intervention for stone removal may be required when pain, obstruction, and/or infection resulting from nephrolithiasis do not respond to conservative management. Surgical management of stones includes extracorporeal shock wave lithotripsy (ESWL) and both endoscopic and percutaneous surgical removal of stones, and is further discussed in Chapter 63. The risk for developing reduced glomerular filtration rate (GFR) varies with the type of stone, and this must be considered in planning management.

Medical Management

Patients who are seen by stone “specialists” often have a substantial decrease in stone recurrence even without pharmacologic intervention.[32] This phenomenon, termed the stone clinic effect, is likely a result of modifications in diet and fluid intake. These nonpharmacologic measures include an increase in fluid intake, which increases urine volume; restriction of dietary sodium, which leads to a reduction of urine calcium excretion; restriction of animal protein, which also leads to a reduction of urine calcium and uric acid excretion and an increase in excretion of the calcification inhibitor citrate; and ingestion of an age- and sex-appropriate amount of dietary calcium, which will bind oxalate in the intestine, preventing its absorption. Although dietary calcium restriction continues to be prescribed by many physicians, substantial evidence indicates that this is not beneficial and can actually increase the rate of stone formation (see later discussion of calcium stones) and can promote bone demineralization.[4,26]

Fluid intake. An increase in urine volume to more than 2 to 2.5 L daily has been proven to reduce the incidence of stones. Large urine volumes will reduce calcium oxalate supersaturation, as well as precipitation of other crystals. Increased fluid intake to augment urine volume is also a mainstay of therapy for patients with uric acid and cystine stones. The period of maximum risk for stone formation is at night, when urine concentration is physiologically increased. Patients should be encouraged to drink enough fluid in the evening to provoke nocturia and then drink further fluid before returning to bed. Patients should avoid calorie-containing beverages, such as sugar-sweetened beverages, which may lead to weight gain and are associated with a higher risk of stone formation.[27]

Salt intake. Urine sodium excretion correlated directly with urine calcium excretion;[2,3] thus, dietary salt restriction is associated with decreased urine calcium excretion. Patients should be instructed to limit daily sodium intake to a maximum of 2 g (87 mmol).

Dietary protein. Animal protein ingestion increases the frequency of kidney stone formation by a number of mechanisms. Metabolism of certain amino acids leads to generation of sulfate ions, which render urinary calcium ions less soluble.[33,34] The metabolic acidosis that results from excess protein ingestion causes calcium release from bone and a consequent increase in the filtered load of calcium.[33,34] Acidosis also decreases tubular calcium reabsorption, resulting in hypercalciuria. Urinary citrate excretion is also pH dependent, with acidosis leading to a decrease in citrate excretion. The result of increased animal protein intake is an increase in urinary calcium excretion that is rendered less soluble because of concomitant sulfate excretion and hypocitraturia. Low urine pH, coupled with increased uric acid excretion from the metabolism of animal protein, can result in uric acid lithiasis. Stone formers should be encouraged to consume a moderate protein intake. Dietary fructose may also increase uric acid lithiasis.

Dietary calcium. Despite conventional wisdom, several studies have demonstrated a decrease in stone incidence when people consume diets adequate, but not excessive, in calcium (>1500 mg/day of calcium).[35] This beneficial effect has been attributed to intestinal binding of ingested oxalate (which is highly lithogenic) by dietary calcium preventing oxalate absorption. Although women have reduced stone formation while ingesting an age-appropriate amount of dietary calcium, this benefit may not extend to those taking calcium in the form of calcium supplements.36 The data are inconsistent as to whether calcium supplements increase the risk for nephrolithiasis. Some have postulated that any increased risk may be a result of timing the supplemental calcium ingestion apart from meals, which would enhance calcium absorption without reducing oxalate absorption. In addition, the calcium supplements may dissociate rapidly, leading to rapid absorption, increased filtered calcium load, and transitory hypercalciuria, leading to increased supersaturation.

We advise patients that it is best to obtain calcium from dairy products rather than supplements.

Women ingesting calcium supplements may be at increased risk for cardiovascular disease and death compared with those not taking supplements, perhaps by promoting vascular calcification.[37] In one long-term study of more than 60,000 Swedish women, those with a dietary calcium intake exceeding 1400 mg/day had an increased risk for cardiovascular mortality with an HR of 1.49 (95% CI, 1.09–2.02). The risk for all-cause mortality rose to 2.57 (95% CI, 1.19–5.55) when any calcium tablet supplements were added to this high dietary intake.[38] A review of cardiovascular mortality in over 15 studies involving calcium supplementation versus placebo showed increased risk for myocardial infarction in those randomized to calcium supplements with an HR of 1.31 (95% CI, 1.02–1.67), which rose to 1.85 (95% CI, 1.28–2.67) in patients already taking more than 805 mg of dietary calcium daily.[37] In a 10-year follow-up of 5448 adults free of clinically diagnosed cardiovascular disease, calcium supplements increased the risk for incident coronary artery calcification (relative risk 1.22 [95% CI, 1.07–1.39]).[39]

The Institute of Medicine in the United States recently adjusted the recommended allowance of calcium to 1000 mg/day for adults older than 19 years and 1200 mg/day for women older than 50 years.[40] We recommend that women take the appropriate amount of calcium in the form of food with limited supplement intake, except in cases of severe osteoporosis with insufficient dietary intake.

Support for the use of an age- and sex-appropriate amount of dietary calcium was provided by a randomized prospective study comparing the rate of stone formation in men assigned a low-calcium diet with those assigned a normal-calcium, low-sodium, and low–animal protein diet.[26] The men assigned the low-calcium diet were twice as likely to have recurrent stones over 5 years compared with those on the normal-calcium, low-sodium, and low–animal protein diet. Urinary calcium oxalate supersaturation also diminished more rapidly in those on the higher-calcium diet and remained lower than that of men on the low-calcium diet for most of the 5-year study. This reduction in supersaturation was the result of a greater fall in urinary oxalate in the men eating the normal-calcium, low-sodium, and low–animal protein diet.[26,41]

Patients prescribed a low-calcium diet can avoid excessive hyperoxaluria when adequately instructed to also consume a low-oxalate diet.[42] Some contend that this approach may benefit patients with excessive intestinal absorption of calcium associated with severe hypercalciuria by allowing calcium restriction without the risk for significant osteopenia. We recommend, however, an age- and sex-appropriate calcium intake, best derived from a diet containing an adequate number of dairy products. Because stone formation can be reduced with normal calcium intake and there is a risk for bone demineralization and osteoporosis with calcium restriction, we consider the low-calcium diet to be obsolete.[24,38]

Vitamin D. Given the great degree of vitamin D deficiency and insufficiency in northern latitudes, vitamin D supplementation is very common.[43] There is concern that this might exacerbate nephrolithiasis, given the role of vitamin D in mineral metabolism. Active forms of vitamin D, such as calcitriol, may increase urinary calcium excretion.[44] However, studies have shown no association between vitamin D supplementation in the form of ergocalciferol, cholecalciferol, or levels of serum 25-hydroxyvitamin D and calcium excretion, nor an increased rate of stone formation in hypercalciuric patients on vitamin D supplementation. Thus, vitamin D therapy should not be withheld in patients with vitamin D deficiency (25-hydroxyvitamin D levels <20 ng/mL) on the basis of kidney stone disease.[45] If needed, we prefer cholecalciferol (D3) to ergocalciferol (D2) because of its more robust biologic activity and longer half-life.

SPECIFIC TYPES OF STONES

Calcium Stones

Calcium-containing kidney stones constitute approximately 70% of all stones formed. Most calcium stones are composed of calcium oxalate, either alone or in combination with calcium phosphate or uric acid. A small percentage of stones are composed entirely of calcium phosphate.2 Most calcium stones do not exceed 1 to 2 cm in width. Surgical intervention is often required for stones larger than 5 mm. Calcium-based stones most often develop as a result of hypercalciuria. Other causes of calcium stones are hyperoxaluria, hyperuricosuria, hypocitraturia, renal tubular acidosis, certain medications, and congenital abnormalities of the genitourinary tract (Fig. 60.6). Specific therapy for patients with calcium stones depends on the underlying metabolic abnormalities detected on evaluation. General therapy as outlined earlier always should be instituted; however, more definitive treatment is often required to significantly decrease the rate of recurrent stone formation.

Hypercalciuria

Etiology. Hypercalciuria for which a causative metabolic abnormality cannot be determined is called idiopathic hypercalciuria. Previously, hypercalciuric patients were divided into those with excessive kidney calcium excretion and those who absorbed excessive amounts of calcium via the gastrointestinal tract. However, hypercalciuric patients generally do not have a transport defect limited to a single site; they appear to have a systemic dysregulation of calcium transport at the major calcium transporting sites, the intestine, kidney, and bone. In both hypercalciuric rats and in humans placed on a low-calcium diet, there is a wide range of calcium excretion. Hypercalciuric patients may appear to have excessive excretion on one examination and excessive absorption on another.2,3 Some patients excrete more calcium than they consume, indicating a negative total body calcium balance. This calcium must be derived from the mineral phases of bone, which contain by far the largest repository of calcium in the body. The cause of this systemic disorder in calcium transport has, in hypercalciuric stone–forming rats and perhaps in humans, been linked to an increased number of biologically active receptors for vitamin D in the major calcium transporting organs (intestine, kidneys, and bone).46,47 Metabolic disorders leading to elevated levels of serum calcium, parathyroid hormone, or 1,25(OH)2D (1,25-dihydroxyvitamin D) also may result in hypercalciuria.

Treatment. For hypercalciuria the first-line therapy is a thiazide diuretic, which acts to reduce urinary calcium. In the United States, chlorthalidone 25 to 50 mg is the drug of choice because it requires only once-daily administration. Indapamide 1.25 to 2.5 mg/day does not tend to raise serum lipids as much as other thiazides and may be preferred for patients with cardiac risk factors or elevated serum lipids. On commencing these medications, patients should be instructed to increase their dietary potassium intake, and a serum potassium level should be checked 7 to 10 days later. If serum potassium is low, oral potassium supplementation should be initiated. Potassium citrate is generally preferred over potassium chloride. However, most patients find potassium citrate liquid preparations unpalatable. A wax matrix tablet of potassium citrate is well tolerated and is available in some countries. In general, patients are able to maintain a normal serum potassium level with potassium citrate 20 to 40 mmol/day. The serum potassium and bicarbonate levels should be rechecked 7 to 10 days later for further dosage adjustment. Because citrate is a base, potassium citrate may excessively raise the serum bicarbonate level and urinary pH, which could promote calcium phosphate stone formation. Urinary pH and supersaturation must be carefully monitored, and a

Etiology of Calcium Stones and Nephrocalcinosis
Hypercalciuria
Normal serum calcium
Idiopathic hypercalciuria
Elevated serum calcium
Malignancy
Primary hyperparathyroidism
Granulomatous diseases
(sarcoid, tuberculosis)
Immobilization
Hyperthyroidism

Hyperuricosuria
(see Box 60.5)

Hyperoxaluria
Dietary hyperoxaluria
High vitamin C intake
Enteric oxaluria
Malabsorptive disorders
Sprue (celiac disease)
Crohn disease
Chronic pancreatitis
Jejunoileal bypass
Biliary obstruction
Primary hyperoxaluria

Nephrocalcinosis and nephrolithiasis

Medications
(see Box 60.3)

Hypocitraturia
Metabolic acidosis
Hypokalemia
Hypomagnesemia
Starvation
Infection
Androgens
Exercise

Renal tubular
acidosis
(type 1, distal)
Anatomic genitourinary
abnormalities
Medullary sponge kidney
Congenital megacalyx
Tubular ectasia

Fig. 60.6 Etiology of calcium stones and nephrocalcinosis.

change to potassium chloride may be required if supersaturation of calcium phosphate worsens with increasing urinary pH in a patient with primarily calcium phosphate stones.

The 24-hour urine calcium, sodium, and citrate should be rechecked after several weeks to months. If the calcium excretion remains elevated, the thiazide dose should be increased. However, if the sodium excretion also remains high (i.e., >100 mEq/day), patients should be encouraged to limit their sodium intake further because they will not have an adequate response to the diuretic on a high-sodium diet. If serum potassium remains low despite supplementation or the calcium excretion remains high despite increased thiazide dosing, addition of a potassium-sparing diuretic may be required to increase serum potassium. Amiloride with a starting dose 5 mg/day is the preferred treatment for thiazide-induced hypokalemia.[2,3] Triamterene should not be used because it can precipitate into stones.

Dietary recommendations. See the discussion of general treatment.

Hyperoxaluria

Etiology. Elevated urinary oxalate results from excessive dietary intake (dietary oxaluria), gastrointestinal disorders that can lead to malabsorption (enteric oxaluria), or an inherited enzyme deficiency that results in excessive metabolism of oxalate (primary hyperoxaluria) (see Fig. 60.6).[48]

Dietary excess of oxalate generally does not raise urinary oxalate above 60 mg/24 h (0.54 mmol/24 h). Enteric oxaluria may occur when malabsorption results in excessive colonic absorption of oxalate, as a result of sprue (celiac disease), Crohn disease, chronic pancreatitis, or short bowel syndrome or after bariatric surgery. The anion exchange transporter Slc26a6 appears responsible for intestinal oxalate secretion, and mice with targeted inactivation of this transporter have hyperoxaluria.[49] It is not yet known whether patients with enteric hyperoxaluria have mutations in Slc26a6. Urinary oxalate is generally more than 60 mg/24 h (0.54 mmol/24 h) and can exceed 100 mg/24 h (0.9 mmol/24 h). In primary hyperoxaluria, the tremendous oxalate production results in widespread calcium oxalate deposition throughout the body at an early age. This infiltration of calcium oxalate into organs can result in cardiomyopathy, bone marrow suppression, and kidney failure. Urinary oxalate values may range from 80 to 300 mg/24 h (0.72–2.70 mmol/24 h).

There are three types of primary hyperoxaluria with unique enzymatic defects in the liver glyoxylate pathway. In type 1, the defective enzyme is alanine–glyoxylate aminotransferase, encoded by the gene AGXT on chromosome 2; this accounts for approximately 80% of cases. Type 2 tends to be milder and is caused by mutations in the GRHPR gene on chromosome 9, which results in failure of glyoxylate reduction to glycolate; this accounts for approximately 10% of the cases. Type 3 is a result of mutations in the gene that encodes the mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme, which catalyzes the cleavage of 4-hydroxy-2-oxoglutarate to pyruvate and glyoxylate and accounts for about half of the remaining cases.[50]

Treatment of dietary and enteric hyperoxaluria. Treatment of dietary oxaluria consists of dietary oxalate restriction. Patients should be given a list of foods that have high oxalate content to avoid or eat in moderation (see Box 60.4). Calcium-containing food may be included at each meal to bind intestinal oxalate and prevent its absorption. To evaluate the success of dietary modification, 24-hour urine oxalate and supersaturation of calcium oxalate can be used.

Specific therapy for the malabsorptive disorder, such as a glutenfree diet for patients with sprue, is the first-line treatment for enteric hyperoxaluria. More generalized therapy for steatorrhea, such as a low-fat diet, cholestyramine, and administration of medium-chain triglycerides, may reduce fat malabsorption as well as oxalate absorption and subsequent excretion. The low-oxalate diet and mealtime calcium carbonate prescribed for patients with dietary oxaluria is also helpful for these patients. The diarrhea associated with these disorders may result in low urine volumes, hypokalemia, hypocitraturia, and hypomagnesuria. Patients should therefore be advised to increase their fluid intake and take potassium citrate (in this case, the liquid, although unpalatable, is better absorbed than the tablets), as well as a magnesium supplement. Magnesium also serves as a urinary stone inhibitor and can be given as magnesium gluconate 0.5 to 1 g once or twice a day or as magnesium oxide 400 mg every 12 hours.

Treatment of primary hyperoxaluria. Primary hyperoxaluria type 1 (PH1) is a severe disorder that until recently could be cured only with liver transplantation to replace the defective hepatic enzyme. Traditional treatments for PH1 have included pyridoxine (vitamin B6) in doses ranging from 2.5 to 15 mg/kg/24 h in an attempt to reduce oxalate production. Efforts should be made to render the calcium and oxalate more soluble in the urine by raising the urinary pH (to at least 6.5) and giving supplemental citrate and magnesium. Orthophosphate is also an effective inhibitor of urinary calcium oxalate precipitation and can be safely administered in patients with a GFR greater than 50 mL/min/1.73 m2. Because oxalate is poorly excreted in CKD and is not removed well by dialysis, kidney transplantation serves not only to improve kidney function but also to improve oxalate excretion and diminish systemic oxalosis.16 Recently, a specific RNA interference therapeutic, lumasiran, has been approved in Europe and the United States for treatment of PH1. This therapy leads to decreased synthesis of glycolate oxidase, an enzyme upstream of the defect in PH1. Lumasiran leads to a prolonged and substantial reduction in urinary oxalate excretion and plasma oxalate concentration, both of which generally decrease to near normal levels in both children and adults.51 Lumasiran promises to be the standard of care for all patients with PH1. Hopefully with this important therapeutic advance, the devastating clinical consequences of PH1 will be avoided, including kidney failure and systemic oxalosis. Similar strategies to treat PH2 and PH3 are being developed.

Oxalobacter formigenes primarily uses oxalate for cellular metabolism.52 Calcium oxalate stone formers who are colonized with O. formigenes have lower urine oxalate levels than those who are not colonized.53 A small clinical trial involving administration of O. formigenes resulted in a modest decrease in urinary oxalate in some patients.52 Further studies with larger numbers of patients and assessing clinically relevant outcomes are required.

Hypocitraturia

Citrate inhibits stone formation. A number of conditions reduce urinary citrate excretion, predisposing to stone formation. Excessive protein intake, hypokalemia, metabolic acidosis, exercise, hypomagnesemia, infections, androgens, starvation, and acetazolamide have all been implicated in decreased urinary citrate excretion. Therapy involves treatment of the underlying condition and potassium citrate supplementation. The potassium salt is preferred to sodium citrate because sodium promotes kidney calcium excretion. Potassium citrate 15 to 25 mmol two to three times daily is required, and tablets are considered by most patients to be more palatable than the liquid preparation. In patients with reduced GFR, serum potassium should be monitored carefully, and dose reduction may be needed if hyperkalemia develops.16

Distal Renal Tubular Acidosis

Patients with distal (type 1) renal tubular acidosis have impaired distal tubular excretion of hydrogen ions with non–anion gap metabolic acidosis and alkaline urine. The acidosis causes calcium and phosphate to be released from bone with an ensuing increase in kidney excretion of these ions.33,34 The acidosis also leads to an increase in citrate reabsorption by the proximal tubule. The end result is a high urinary pH, hypocitraturia (urinary citrate generally <100 mg/24 h [0.53 mmol/24 h]), and increased kidney excretion of calcium and phosphate, all of which increase the propensity for calcium phosphate precipitation. Nephrocalcinosis in this setting is not uncommon, because calcium precipitates with phosphorus in the alkaline tubular fluid. The metabolic acidosis and hypocitraturia should be treated with a combination of sodium citrate (or bicarbonate) and potassium citrate (or bicarbonate). Often large amounts (e.g., 1–2 mmol/kg/day in 2 or 3 divided doses) are required to neutralize the acidosis.2 Citrate is generally preferred to bicarbonate by patients because it does not produce carbon dioxide on contact with stomach acid with resultant gastrointestinal bloating. However, citrate is usually more expensive than bicarbonate and promotes the absorption of aluminum.

Hyperuricosuria

Calcium oxalate crystals often nucleate around other crystal types such as uric acid. Hyperuricosuria contributes to nephrolithiasis in 10% to 15% of calcium stones. Patients with hyperuricosuric calcium oxalate nephrolithiasis may have hyperuricosuria with normal urinary calcium and oxalate, but often a higher urinary pH (>5.5) than patients with pure uric acid stones. Therapy for hyperuricosuria consists of increased fluid intake and reduced dietary purine intake. If uric acid excretion remains elevated, allopurinol should be initiated at 100 to 300 mg/day.2

Uric Acid Stones

Epidemiology

The prevalence of uric acid stones depends greatly on geographic location. In the United States, uric acid stones constitute 5% to 10% of all stones formed, whereas in Mediterranean and Middle Eastern countries, uric acid stones may constitute up to 75% of stones. The stones are radiolucent and therefore poorly visible on plain radiographs. They are detectable on ultrasound and CT and as filling defects on IVU (Fig. 60.7).

Etiology and Pathogenesis

Causes of hyperuricosuria include excessive dietary purine or protein intake, disorders associated with cellular breakdown (tumor lysis syndrome, myeloproliferative disorders, hemolytic anemia), gout, uricosuric medications, certain inborn errors of metabolism, and possibly excessive fructose intake.54

Three major factors influence uric acid stone formation: low urine pH, low urine volume, and elevated urinary uric acid levels (Box 60.5). Of the three, low urine pH is the principal metabolic disorder found in patients with uric acid nephrolithiasis. Uric acid is poorly soluble at pH below 5.5. Solubility increases with urine alkalinity such that at urine pH 6.5, urine can contain over 6 times the quantity of uric acid present at pH 5.3 without exceeding supersaturation. The rising incidence of obesity and insulin resistance in the United States led to a parallel increase in uric acid lithiasis. The urinary acidosis is likely a result of impaired ammoniagenesis, which results in excessive excretion of unbuffered acid and a very low urine pH.9,55 The geographic and ethnic variations in the incidence of uric acid stones may be due to diet, caused by environmental factors, or the result of genetic susceptibility in some populations.9

Treatment

Treatment of uric acid stones involves increasing urine pH and volume, and decreasing uric acid excretion. Alkaline urine not only can prevent uric acid stone formation but also may result in stone dissolution. To raise urine pH, potassium citrate is recommended. Although sodium bicarbonate alkalinizes the urine and enhances uric acid solubility, the added sodium increases sodium urate formation, which

serves as a nidus for calcium oxalate precipitation. Potassium citrate 40 to 50 mmol/day in divided doses is given, increasing the dose as necessary to achieve a urine pH of 6.5 to 7.0. Patients should monitor pH with urine dipsticks at various times of the day and adjust the dosage accordingly. If urine pH remains low despite potassium citrate exceeding 100 mmol/day, or if that dose results in hyperkalemia, acetazolamide may be added. This carbonic anhydrase inhibitor produces an alkaline urine similar to that seen in renal tubular acidosis. Patients should be cautioned not to exceed urine a pH of 7.0 because this may result in calcium phosphate precipitation.

A low-purine and low–animal protein diet is also useful in raising urinary pH and decreasing uric acid excretion (see Box 60.4). If uric acid excretion remains high despite dietary intervention, as in patients with disorders of cellular catabolism, allopurinol should be prescribed, 100 mg/day increasing to 300 mg/day as needed to keep urinary uric acid excretion lower than 750 mg/24 h (4.5 mmol/24 h). See Box 60.4 for high-purine foods to avoid.

Struvite Stones

Struvite stones are also referred to as infection stones or triple phosphate stones. The stones grow rapidly to a large size, can reduce GFR in the affected kidney, and are difficult to eradicate. Because of the significant morbidity in patients with struvite stones, they also have been termed stone cancer. Most staghorn calculi, large stones that penetrate more than one renal calyx, are composed of struvite. Their formation requires the presence of urease-producing bacteria in the urine (Box 60.6).56

Etiology and Pathogenesis

Fig. 60.7 Radiolucent Urate Calculi. Antegrade pyelogram showing multiple radiolucent uric acid stones (arrows) obstructing the lower ureter.

Factors Associated With Uric Acid Stone Formation

BOX 60.5

Low Urine pH (≤5.5)
- High–animal protein diet
- Diarrhea
- Insulin resistance (high body mass index, metabolic syndrome, type 2 diabetes)

Low Urine Volume
- Inadequate fluid intake
- Excessive extrarenal fluid losses
- Diarrhea
- Insensible losses (e.g., perspiration)

Hyperuricosuria
- Excessive dietary purine intake
- Hyperuricemia
- Gout
- Intracellular-to-extracellular uric acid shift
- Myeloproliferative disorders
- Tumor lysis syndrome
- Inborn errors of metabolism
- Lesch-Nyhan syndrome
- Glucose-6-phosphatase deficiency

Medications
- See Box 60.3

Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They form when urease production by certain urinary bacteria breaks down urea to ammonium (NH_4^+) and a carboxyl

(OH) group. The urine becomes quite alkaline; urinary phosphate becomes insoluble and forms a solid phase with magnesium, calcium, and the ammonium. Women are more prone to struvite nephrolithiasis than men because of an increased propensity for UTI. Others predisposed to developing struvite stones through infections or urinary stasis include patients with indwelling urinary catheters, neurogenic bladders, genitourinary tract anomalies, and spinal cord lesions. An alkaline urine (pH ≥7.0), urine culture of urease-producing bacteria, and large stones suggest the diagnosis of struvite nephrolithiasis.56

Certain gram-negative and gram-positive bacteria have been implicated in urease production and consequent struvite formation, with the most common being Proteus spp. (see Box 60.6). Escherichia coli, which is frequently present in urine cultures, is not a urease producer. If there is a strong suspicion for struvite stones but no organism is

Factors Associated With Struvite Stone Formation[a]

BOX 60.6

- Urease-producing bacteria
- Proteus
- Haemophilus
- Yersinia spp.
- Staphylococcus epidermidis
- Pseudomonas
- Klebsiella
- Serratia
- Citrobacter
- Ureaplasma
- Elevated urinary pH

[a] Escherichia coli is not a urease producer.

detected in the urine, a specific culture request for Ureaplasma urealyticum should be considered, because it does not grow on routine culture media.

Treatment

Struvite stones require aggressive medical and surgical management. Antibiotic therapy is important to reduce further stone growth and for stone prevention. Bacteria will remain in the stone interstices, however, and stones will continue to grow unless chronic antibiotic suppression is maintained or the calculi are completely eradicated. Given the need for complete stone removal to effect a cure, early urologic intervention is advised. Stones smaller than 2 cm may respond well to ESWL; however, larger stones will likely require percutaneous nephrolithotomy, often in combination with ESWL (see Chapter 63). Any stone fragments retrieved should be cultured and culture-specific antibiotics continued.57 Once the urine is sterile, usually approximately 2 weeks after initiation of therapy, the dose is halved. Monthly urine cultures should be obtained, and if they remain sterile for 3 consecutive months, antibiotics may be discontinued, although surveillance urine cultures should continue monthly for a full year.

Cystine Stones

Cystinuria is an autosomal disorder in which there is a tubular defect in dibasic amino acid transport, resulting in increased cystine, ornithine, lysine, and arginine excretion. It is also discussed in Chapter 50. The pattern of inheritance may be autosomal recessive or autosomal dominant with incomplete penetrance. The stone disease is usually clinically manifested by the second and third decades of life. Because of the high sulfur content of the cystine molecule, the stones are apparent on plain radiographs (see Fig. 60.4A) and often will manifest as staghorn calculi or multiple bilateral stones.

Cystine is poorly soluble, only approximately 300 mg/L (1.25 mmol/L) at a neutral pH. Normal cystine excretion of approximately 30 to 50 mg (0.12–0.21 mmol) per day is readily soluble in the usual daily urine output of approximately 1 L. However, homozygote cystinurics often excrete 250 to 1000 mg (1.04–4.20 mmol) of cystine per day, with heterozygotes excreting an intermediate amount. Treatment is directed at decreasing the urinary cystine concentration below the limits of solubility. Because the dietary precursor of cystine, methionine, is an essential amino acid, it is impractical to significantly reduce intake. Increasing urine volume so that cystine remains below the limits of solubility sometimes requires 4 L of urine per day. A low-sodium diet may reduce urine cystine excretion, although the mechanism by which this occurs is not clear.58 Increasing urine pH greater than 7.5 will increase cystine solubility, but this is difficult to achieve on a long-term basis. Tiopronin 800 mg/day in 3 divided doses or d-penicillamine with a starting dose 250 mg/day and maximum dose of 2 g/day will both bind cystine and reduce urinary supersaturation; however, side effects may limit their use. The angiotensin-converting enzyme inhibitor captopril may be effective by forming a thiol-cysteine disulfide bond that is more soluble than cystine.59

Stones Associated With Melamine Exposure

By late 2008, more than 50,000 Chinese children aged 3 years or younger had developed kidney stones associated with contaminated milk products. Powdered milk and infant formulas were noted to contain melamine, a nitrogenous substance synthesized from urea that increases the apparent protein content of the product.22 Risk factors for nephrolithiasis after melamine exposure may include volume depletion, small body size, uricosuria, and low urine pH.

Although affected children often presented with dysuria and hematuria, many children who were subsequently tested were asymptomatic

BOX 60.7

Causes of Nephrocalcinosis

Medullary

Disturbed Calcium Metabolism
- Hyperparathyroidism
- Sarcoidosis
- Milk-alkali syndrome
- Rapidly progressive osteoporosis
- Idiopathic hypercalciuria

Other Tubular Disease
- Distal (type 1) renal tubular acidosis
- Oxalosis[a]
- Dent disease (X-linked hypercalciuric nephrolithiasis)
- X-linked hypophosphatemic rickets
- Bartter syndrome
- Hypomagnesemia-hypercalciuria syndrome

Anatomic Disease
- Medullary sponge kidney
- Papillary necrosis

Medications
- Acetazolamide
- Amphotericin
- Triamterene

Cortical
- Cortical necrosis
- Transplant rejection
- Chronic glomerulonephritis
- Trauma
- Tuberculosis
- Oxalosis[a]

[a] Oxalosis typically causes both cortical and medullary nephrocalcinosis.

despite kidney stones identified on ultrasound.22 On urinalysis, some children exhibited fan-shaped crystals. The kidney stones formed were radiolucent and fragile. Many were composed of a combination of uric acid with melamine and were amenable to dissolution by hydration and alkalinization.

NEPHROCALCINOSIS

Nephrocalcinosis refers to increased calcium content within the kidney and may be unilateral or bilateral.

Etiology and Pathogenesis

Medullary Nephrocalcinosis

Medullary nephrocalcinosis in which the calcification tends to occur in the area of the renal pyramids accounts for most cases of nephrocalcinosis. It is typically associated with elevated urinary calcium, phosphate, and oxalate, or it can occur with alkaline urine (Box 60.7). Any disorder that can lead to hypercalcemia and/or hypercalciuria may be implicated. Instead of stone formation, smaller parenchymal calcifications deposit in the medulla, and they are usually bilateral and relatively symmetric (Fig. 60.8). Some metabolic disorders, particularly oxalosis caused by primary hyperoxaluria, can result in both medullary and cortical nephrocalcinosis (Fig. 60.9).

In adults, the most common causes of medullary nephrocalcinosis are primary hyperparathyroidism, distal renal tubular acidosis, and

Fig. 60.10 Cortical Nephrocalcinosis. Noncontrast computed tomgraphy scan showing cortical nephrocalcinosis (arrows) in the right kidney after cortical necrosis.

Fig. 60.8 Medullary Nephrocalcinosis. Plain radiograph showing bilateral metastatic medullary nephrocalcinosis in a patient with distal renal tubular acidosis.

Fig. 60.9 Nephrocalcinosis. Dense cortical and medullary calcification in the shrunken kidneys of a patient with oxalosis and long-standing kidney failure.

medullary sponge kidney, as well as medications, including acetazolamide, amphotericin, and triamterene (see Box 60.3).

In children, a similar range of disorders can be seen, but the most common associations are with furosemide and the hereditary disorders associated with hypercalciuria.[24] Furosemide, when used in premature neonates and older infants with congestive heart failure, can result in nephrocalcinosis with or without apparent hypercalciuria. The lesions often resolve with discontinuation of therapy. A normal ratio of calcium to creatinine at the time of diagnosis of nephrocalcinosis (~0.40 mg/mg in premature infants) appears to be a good predictor of resolution. There are many uncommon hereditary disorders associated with nephrocalcinosis, including Dent disease, X-linked hypophosphatemic rickets, hypomagnesemia-hypercalciuria syndrome, and Bartter syndrome.

Dent disease is an X-linked recessive disorder of proximal tubules characterized by low-molecular-weight proteinuria with hypercalciuria and nephrocalcinosis.[60] In most cases, it is due to mutations that inactivate a voltage-gated chloride transporter called CLC-5. A number of mutations affecting the CLCN5 gene on the X chromosome have been identified that lead to inactivation of CLC-5. The result is a clinical syndrome typically affecting young boys and usually including hypercalciuria, nephrocalcinosis, nephrolithiasis, and hematuria, as well as low-molecular-weight proteinuria, glycosuria, aminoaciduria, hypophosphatemia, kidney failure, and rickets. Dent disease is further discussed in Chapter 50

In X-linked hypophosphatemic rickets, the traditional treatment, with phosphate repletion and vitamin D, may itself result in hypercalcemia, hypercalciuria, and nephrocalcinosis. Recently, the monoclonal immunoglobulin antibody burosumab, which binds excess fibroblast growth factor 23, was approved for the treatment of this disorder. The drug normalized phosphorus levels in adults and children, and its use should prevent the calcific disorders caused by X-linked hypophosphatemic rickets.

Another cause of medullary nephrocalcinosis in children is primary hypomagnesemia-hypercalciuria syndrome.[3,61] This rare autosomal recessive condition results from defective production of the cellular tight-junction protein paracellin-1. This claudin family protein is necessary for adequate calcium and magnesium reabsorption in the thick ascending limb of the loop of Henle. Children typically present with symptoms of UTI (often with nephrolithiasis), polyuria, tetanic seizures (caused by hypomagnesemia), and muscle cramps and weakness. Hypercalciuria, hypermagnesuria, and a urinary concentrating defect also occur. Patients often have reduced GFR and may require kidney replacement therapy by the third decade of life. Sensorineural hearing disorders and ocular impairment may accompany the kidney manifestations in a subset of patients.

Cortical Nephrocalcinosis

Cortical nephrocalcinosis is usually the result of dystrophic calcification, which follows parenchymal tissue destruction, rather than the precipitation of excessive urinary constituents. It is secondary to infarction, neoplasm, and infection. It is typically asymmetric and is usually localized to the renal cortex (Fig. 60.10). Causes of cortical nephrocalcinosis include transplant rejection, cortical necrosis (mostly following hemorrhagic shock), tuberculosis, ethylene glycol toxicity, and chronic glomerulonephritis.

Clinical Manifestations

Treatment

Patients who do not have nephrolithiasis associated with nephrocalcinosis are often asymptomatic. Ultrasound and CT scanning are sensitive diagnostic tests for both cortical and medullary nephrocalcinosis, demonstrating the parenchymal calcifications before they can be visualized on plain radiographs. The extent of calcification correlates poorly with GFR.

Similar to nephrolithiasis, treatment of nephrocalcinosis relies on therapy for the underlying disease, as well as measures to reduce hypercalcemia, hyperphosphatemia, and oxalosis, if possible. The goal of treatment is usually to prevent further deposits, because therapy cannot eradicate existing calcium deposits.

SELF-ASSESSMENT QUESTIONS

1. A 49-year-old paraplegic man is referred for evaluation of nephrolithiasis. He has a suprapubic catheter and has had frequent urinary tract infections. He has reduced kidney function and is noted to have large staghorn calculi in both kidneys. On urinalysis, he has many white blood cells and bacteria. Urine culture grows Proteus. All statements regarding this patient’s kidney stones are true except:
A. His current stones can be treated with a course of antibiotics.
B. Stone formation is facilitated by the effects of urease-producing bacteria.
C. His stones are formed by a combination of phosphate with three cations.
D. Stone formation is potentiated by an elevated urine pH.
E. His current stones require surgical management.

2. A 35-year-old woman presents with her fourth kidney stone. Her father and brother have had stones as well. She was informed that her stones are composed of calcium. She tries to drink as much fluid as possible. Urine calcium excretion is elevated, but serum calcium is normal. All of the following dietary measures may be recommended for kidney stone prevention in this patient except:
A. Low-sodium diet

B. Reduction in animal protein intake
C. Reduction in dietary calcium intake
D. Low-oxalate diet

3. A 52-year-old obese man presents with flank pain and gross hematuria. Computed tomography reveals an obstructing left kidney stone and two other nonobstructing kidney stones in the right kidney measuring 0.5 mm. He passes the left kidney stone, which is found on analysis to be a uric acid stone. He was recently started on metformin for diabetes mellitus, his body mass index is 33, and he has normal kidney function; 24-hour urine reveals urine pH 5.3, volume 1.5 L, and uric acid excretion of 500 mg. Which of the following is a true statement regarding this patient’s kidney stones?
A. The patient’s right kidney stones can be followed by serial abdominal radiographic examination of the kidneys.
B. The patient’s insulin resistance may be contributing to his stone disease.
C. The patient should be treated with allopurinol.
D. Potassium citrate would not be beneficial.
E. The patient is drinking an adequate amount of fluid.

REFERENCES

1. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–344.
2. Bushinsky DA, Coe FL, Moe OW. Nephrolithiasis BM B. In: The Kidney. Philadelphia: W.B. Saunders; 2012:1455–1507.
3. Bushinsky DA. Nephrolithiasis. In: Goldman S, ed. Goldman-Cecil, Medicine. Elsevier; 2020:776–781.
4. Bushinsky DA. Kidney stones. In: Malmed P, Larsen and Kronenberg, eds. William’s Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier; 2019:689–703.
5. Scales Jr CD, Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–165.
6. Curhan GC, Willett WC, Rimm EB, et al. Body size and risk of kidney stones. J Am Soc Nephrol: JASN (J Am Soc Nephrol). 1998;9(9):1645–1652.
7. Chewcharat A, Curhan G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. Urolithiasis. 2021;49(1):27–39.
8. Soucie JM, Thun MJ, Coates RJ, et al. Demographic and geographic variability of kidney stones in the United States. Kidney Int. 1994;46(3):893–899.
9. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hyper. 2004;13(2):181–189.
10. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012;345:e5287.
11. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. JAMA. 2013;310(4):408–415.
12. Shavit L, Girfoglio D, Vijay V, et al. Vascular calcification and bone mineral density in recurrent kidney stone formers. CJASN. 2015;10(2):278–285.
13. Denburg MR, Leonard MB, Haynes K, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. Clin J Am Soc Nephro. 2014;9(12):2133–2140.
14. Sakhaee K, Maalouf NM, Kumar R, et al. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. Kidney Int. 2011;79(4):393–403.
15. Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol. 2016;12(9):519–533.
16. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest. 2005;115(10):2598–2608.
17. Arcidiacono T, Mingione A, Macrina L, et al. Idiopathic calcium nephrolithiasis: a review of pathogenic mechanisms in the light of genetic studies. Am J Nephrol. 2014;40(6):499–506.
18. Nazzal L, Blaser MJ. Does the receipt of antibiotics for common infectious diseases predispose to kidney stones? A cautionary note for all health care practitioners. J Am Soc Nephrol. 2018;29(6):1590–1592.
19. Tasian GE, Jemielita T, Goldfarb DS, et al. Oral antibiotic exposure and kidney stone disease. J Am Soc Nephrol. 2018;29(6):1731–1740.
20. Spetie DN, Nadasdy T, Nadasdy G, et al. Proposed pathogenesis of idiopathic loin pain-hematuria syndrome. Am J Kidney Dis. 2006;47(3):419–427.
21. Bass CM, Parrott H, Jack T, et al. Severe unexplained loin pain (loin pain haematuria syndrome): management and long-term outcome. Qjm-Int J Med. 2007;100(6):369–381.
22. Guan N, Fan Q, Ding J, et al. Melamine-contaminated powdered formula and urolithiasis in young children. N Engl J Med. 2009;360(11):1067–1074.
23. Pozdzik A, Maalouf N, Letavernier E, et al. Meeting report of the Symposium on kidney stones and mineral metabolism: calcium kidney stones in 2017. J Nephrol. 2019;32(5):681–698.
24. Moe OW, Bushinsky DA. Genetic hypercalciuria: a major risk factor in kidney stones. In: Thakker RVW,MP, Eisman JA, Igarashi T, eds. Genetics of Bone Biology and Skeletal Disease. Academic Press; 2013:585–604.
25. Daudon M, Jungers P. Drug-induced renal calculi - epidemiology, prevention and management. Drugs. 2004;64(3):245–275.
26. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the

prevention of recurrent stones in idiopathic hypercalciuria. New Engl J Med. 2002;346(2):77–84.

27. Ferraro PM, Taylor EN, Gambaro G, et al. Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol. 2013;8(8):1389–1395.
28. Johnson RJ, Perez-Pozo SE, Lillo JL, et al. Fructose increases risk for kidney stones: potential role in metabolic syndrome and heat stress. BMC Nephrol. 2018;19(1):315.
29. Perez-Pozo SE, Schold J, Nakagawa T, et al. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes (Lond). 2010;34(3):454–461.
30. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. Nat Rev Urol. 2016;13(11):654–662.
31. Smith-Bindman R, Aubin C, Bailitz J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. New Engl J Med. 2014;371(12):1100–1110.
32. Hosking DH, Erickson SB, Van den Berg CJ, et al. The stone clinic effect in patients with idiopathic calcium urolithiasis. J Urol. 1983;130(6):1115–1118.
33. Bushinsky DA, Kriefer NS. Effect of acid on bone. Kidney Int. 2022;101:1160–1170.
34. Lemann J, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. Am J Physiol-Renal. 2003;285(5):F811–F832.
35. Borghi L, Meschi T, Amato F, et al. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urology. 1996;155(3):839–843.
36. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. New Engl J Med. 2006;354(7):669–683.
37. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341.
38. Michaelsson K, Melhus H, Warensjo E, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346.
39. Anderson JJB, Kruszka B, Delaney JAC, et al. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 2016;5(10).
40. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–58.
41. Bushinsky DA. Recurrent hypercalciuric nephrolithiasis - does diet help? New Engl J Med. 2002;346(2):124–125.
42. Pak CYC, Odvina CV, Pearle MS, et al. Effect of dietary modification on urinary stone risk factors. Kidney Int. 2005;68(5):2264–2273.
43. Monk RD, Bushinsky DA. Making sense of the latest advice on vitamin D therapy. J Am Soc Nephrol. 2011;22(6):994–998.
44. Tsukamoto Y, Watanabe T, Nakagami T, et al. Effect of treatment with oral calcitriol on calcium metabolism and fasting serum 25(OH)- or 1,25(OH)2-vitamin D level in Japanese postmenopausal women. Endocr J. 2003;50(6):681–687.
45. Leaf DE, Korets R, Taylor EN, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. Clin J Am Soc Nephrol. 2012;7(5):829–834.
46. Bushinsky DA, Frick KK, Nehrke K. Genetic hypercalciuric stone-forming rats. Curr Opin Nephrol Hypertens. 2006;15(4):403–418.
47. Frick KK, Asplin JR, Favus MJ, et al. Increased biological response to 1,25(OH)(2)D-3 in genetic hypercalciuric stone-forming rats. Am J Physiol-Renal. 2013;304(6):F718–F726.
48. Asplin JR. Hyperoxaluric calcium nephrolithiasis. Endocrin Metab Clin. 2002;31(4):927.

49. Sakhaee K. Recent advances in the pathophysiology of nephrolithiasis. Kidney Int. 2009;75(6):585–595.
50. Hoppe B. An update on primary hyperoxaluria. Nat Rev Nephrol. 2012;8(8):467–475.
51. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384(13):1216–1226.

References

52. Hoppe B, Beck B, Gatter N, et al. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70(7):1305–1311.
53. Kwak C, Kim HK, Kim EC, et al. Urinary oxalate levels and the enteric bacterium Oxalobacter formigenes in patients with calcium oxalate urolithiasis. Eur Urol. 2003;44(4):475–481.
54. Cox CL, Stanhope KL, Schwarz JM, et al. Consumption of fructose- but not glucose-sweetened beverages for 10 weeks increases circulating concentrations of uric acid, retinol binding protein-4, and gammaglutamyl transferase activity in overweight/obese humans. Nutr Metab (Lond). 2012;9(1):68.
55. Cameron MA, Maalouf NM, Adams-Huet B, et al. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. J Am Soc Nephrol. 2006;17(5):1422–1428.

56. Rodman JS. Struvite stones. Nephron. 1999;81:50–59.
57. Flannigan R, Choy WH, Chew B, et al. Renal struvite stones-pathogenesis, microbiology, and management strategies. Nat Rev Urol. 2014;11(6):333–341.
58. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006;69(6):1041–1047.
59. Sakhaee K. Pathogenesis and medical management of cystinuria. Sem Nephrol. 1996;16(5):435–447.
60. Scheinman SJ. X-linked hypercalciuric nephrolithiasis: clinical syndromes and chloride channel mutations. Kidney Int. 1998;53(1):3–17.
61. Claverie-Martin F. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: clinical and molecular characteristics. Clin Kidney J. 2015;8(6):656–664.

61

Urinary Tract Obstruction

Kevin M. Gallagher, Jeremy Hughes

DEFINITIONS

Obstructive uropathy refers to the structural or functional changes in the urinary tract that impede normal urine flow. Obstructive nephropathy refers to the kidney disease caused by impaired flow of urine or tubular fluid. Hydronephrosis refers to dilation of the urinary tract. Hydronephrosis is not synonymous with obstructive uropathy because the former can occur without functional obstruction to the urinary tract and can be absent in established obstruction. Obstructive uropathy and nephropathy frequently coexist, and their management requires close collaboration between nephrologists and urologists. Some surgical aspects of obstruction to the urinary tract are discussed in Chapter 63.

Obstructive uropathy is classified according to the site, degree, and duration of the obstruction. Acute or chronic obstruction can occur anywhere in the urinary tract and includes intrarenal causes (casts, crystals) and extrarenal causes. Acute or chronic obstruction is further subdivided into obstruction of the upper urinary tract (the urinary tract above the vesicoureteral junction, often unilateral) and the lower urinary tract (usually bilateral obstruction located below the vesicoureteral junction). Complete obstruction of the urinary tract is termed high grade, whereas partial or incomplete obstruction is termed low grade.

Unilateral obstruction in a patient with two normal kidneys will not result in significant reduction in glomerular filtration rate (GFR) because the contralateral kidney compensates. However, bilateral obstruction or the obstruction of a single functioning kidney will result in kidney failure. In acute urinary tract obstruction, changes are mainly functional, whereas structural damage to the kidney results from more chronic obstruction. The kidney with acute functional changes may recover after effective release of the obstruction, but structural changes may be permanent and lead to chronic kidney disease (CKD). Urinary tract obstruction is a major cause of acute kidney disease and CKD worldwide in children and adults.

ETIOLOGY AND PATHOGENESIS

The causes of obstructive uropathy affecting the upper and lower urinary tracts are summarized in Boxes 61.1 and 61.2.

Congenital Urinary Tract Obstruction

Congenital urinary tract obstruction occurs most frequently in males, most commonly because of posterior urethral valves (PUV) or pelviureteral junction (PUJ) obstruction. If obstruction occurs early during development, the kidney fails to develop and becomes dysplastic. If the obstruction is bilateral, there is a high mortality rate from kidney failure. If the obstruction occurs later in gestation and is low grade or unilateral, hydronephrosis and nephron loss will still occur, but kidney

function may be sufficient to allow survival, and such patients may not present until later in childhood. Mild PUJ obstruction may not manifest until adulthood and in some patients may be an incidental finding (Fig. 61.1). However, with increased use and improved sensitivity of antenatal scanning, congenital abnormalities of the urinary tract are now frequently identified early, allowing prompt postnatal (and in some cases antenatal) intervention to relieve the obstruction and hence preserve kidney function. Congenital causes of obstruction are discussed further in Chapter 52.

Acquired Urinary Tract Obstruction

Acquired urinary tract obstruction may affect either the upper or lower urinary tract and can result from intrinsic or extrinsic causes. Intrinsic causes of obstruction may be intraluminal or intramural.

Intrinsic Obstruction

Intraluminal obstruction. Intrarenal intraluminal obstruction may result from tubular obstruction, such as the deposition of uric acid crystals after treatment of hematologic malignancies (tumor lysis syndrome), the precipitation of Bence Jones protein in myeloma, or the precipitation or crystal formation of certain drugs (e.g., sulfonamides, acyclovir, methotrexate, indinavir). Uncommonly, patients with glomerulonephritis such as immunoglobulin A (IgA) nephropathy may develop severe glomerular hematuria with tubular obstruction from erythrocytes and acute kidney injury (AKI) that typically resolves. Extrarenal intraluminal obstruction in young adults is most commonly caused by urinary calculi (see Chapter 60). Calcium oxalate stones are the most common and typically cause intermittent acute unilateral urinary tract obstruction. Any stone formation is a significant and independent risk factor for CKD, although end-stage kidney disease (ESKD) because of urinary stones is rare.1 Less common causes of urinary lithiasis, such as struvite stones, uric acid stones, and cystinuria are often bilateral and recurrent and therefore more likely to cause CKD. Kidney calculi lodge more commonly in the calyx, PUJ, or vesicoureteral junction and at the level of the pelvic brim. Surgical management of stones is discussed in Chapters 60 and 63. Intraluminal obstruction can also result from a sloughed papilla after papillary necrosis or blood clots after macroscopic hematuria (“clot colic”). Papillary necrosis may occur in diabetes mellitus, sickle cell trait or disease, analgesic nephropathy, amyloidosis, and acute pyelonephritis. Clot colic can occur with bleeding from kidney tumors (benign and malignant) or arteriovenous malformations, after kidney trauma or surgery, and in patients with polycystic kidney disease.

Intramural obstruction. Intramural obstruction can result from either functional or anatomic changes. Functional disorders include adynamic ureteral segments (usually at the junction of the ureter with the pelvis or bladder) and neurologic disorders. The latter may result in a contracted (hypertonic) bladder or a flaccid (atonic) bladder,

CHAPTER 61 Urinary Tract Obstruction

BOX 61.1

Causes of Lower Urinary Tract
Obstruction[a]

BOX 61.2

Urethral Anatomic Causes
- Urethral strictures: trauma, postinstrumentation, infections such as gonococcal urethritis, nongonococcal urethritis, tuberculosis
- Posterior urethral valves
- Stones
- Blood clots
- Periurethral abscess
- Phimosis
- Paraphimosis
- Meatal stenosis

Intrinsic Causes
Intraluminal
- Intratubular deposition of crystals (uric acid, drugs)
- Stones
- Papillary tissue
- Blood clots
- Fungal ball

Urethral Functional Causes
- Anticholinergic drugs, antidepressants, levodopa

Prostate
- Benign prostatic hypertrophy
- Prostatic carcinoma

Bladder Anatomic Causes
- Bladder cancer
- Schistosomiasis (Schistosoma haematobium infection)
- Bladder calculi
- Bladder trauma, pelvic fracture

Bladder Functional Causes
- Neurogenic bladder: spinal cord defects or trauma, diabetes, multiple sclerosis, Parkinson disease, cerebrovascular accidents

[a] The

most common causes are in italics.

depending on whether the lesion affects upper or lower motor neurons, and may lead to impaired bladder emptying with vesicoureteral reflux. Bladder dysfunction is very common in patients with multiple sclerosis and after spinal cord injury and is also seen in diabetes mellitus, Parkinson disease, and after cerebrovascular accidents. Some drugs (anticholinergics, levodopa) can alter neuromuscular activity of the bladder and result in functional obstruction, especially if there is preexisting bladder outflow obstruction (e.g., prostatic enlargement). Anatomic causes of intramural obstruction of the upper urinary tract include transitional cell carcinoma of the renal pelvis and ureter and ureteral strictures secondary to radiotherapy, previous stones or endoscopic stone surgery, or retroperitoneal surgery. Rarely, obstruction may result from ureteral valve malfunction, polyps, or strictures after therapy for tuberculosis. Intramural obstruction of the lower urinary tract can result from urethral strictures, which are usually secondary to instrumentation or previous urethritis, or malignant and benign tumors of the bladder. Infection with Schistosoma haematobium when the ova lodge in the distal ureter and bladder is a common cause of obstructive uropathy worldwide; up to 50% of chronically infected patients develop ureteral strictures and fibrosis, with calcifications and contraction of the bladder.

Extrinsic Obstruction

The most common cause of extrinsic compression in females is pressure from a gravid uterus on the pelvic rim; the right ureter is more commonly affected. It is usually asymptomatic, and the changes resolve rapidly after delivery. Rarely, bilateral obstruction and AKI may occur. Ureteral dilation frequently may be seen in pregnancy as a result of hormonal effects (especially progesterone) on smooth muscle, but this does not indicate functional obstruction (see Chapter 44). Carcinoma of the cervix also may cause extrinsic obstruction secondary to direct extension of the tumor to involve the urinary tract. Other pelvic pathologic processes that can cause ureteral compression include benign and malignant uterine and ovarian masses, endometriosis, and pelvic inflammatory disease. Compression of the ureters outside the bladder also may occur with uterine prolapse. Rarely, inadvertent ureteral ligation may occur during surgical procedures, particularly those related to obstetrics and gynecology and colorectal surgery. Unilateral ligation may go undetected, but AKI will result from bilateral ligation.

Causes of Upper Urinary Tract Obstruction[a]

Intramural
- Functional: pelviureteral or vesicoureteral junction dysfunction
- Anatomic: tumors (benign or malignant)
- Infections, granulomas, strictures

Extrinsic Causes

Reproductive System
- Cervix: carcinoma
- Uterus: pregnancy, tumors, prolapse, endometriosis, pelvic inflammatory disease
- Ovary: tumor, cysts
- Prostate: carcinoma

Vascular System
- Aneurysms: aorta, iliac vessels
- Aberrant arteries: pelviureteral junction
- Venous: ovarian veins, retrocaval ureter

Gastrointestinal Tract
- Crohn disease
- Pancreatitis
- Appendicitis
- Diverticulitis
- Tumors

Retroperitoneal Space
- Lymph nodes
- Fibrosis: idiopathic, drugs, inflammatory or immunoglobulin G4–related disease
- Tumors: primary or metastatic
- Hematomas
- Radiation therapy

Other
- Surgical disruption or ureteral ligation

[a] The most common causes are in italics.

In males, the most common cause of extrinsic obstruction of the lower urinary tract is benign prostatic hypertrophy. Carcinoma of the prostate can result in obstruction either from direct tumor extension to the bladder outlet or ureters or from metastatic spread.

Fig. 61.2 Retrograde Pyelogram Showing Idiopathic Retroperitoneal Fibrosis. Dilation of the pelvicalyceal system is clearly demonstrated. The ureters, however, are not dilated, and the left ureter can be seen displaced medially as a result of being encased in thick fibrous tissue.

vessels such as an aberrant anterior crossing accessory renal artery causing PUJ obstruction in adults, and anatomic variations in the location of the ureter (retrocaval ureter).

Fig. 61.1 Intravenous Urogram Demonstrating Pelviureteral Junction Obstruction. The study was performed in a previously asymptomatic adult to investigate nonspecific right loin pain. There is unilateral dilation of the pelvicalyceal system. The ureter has not been visualized.

Retroperitoneal pathology may result in extrinsic obstruction of the ureters, as can metastases or extension of tumors from the cervix, prostate, bladder, colon, ovary, and uterus. Primary tumors of the retroperitoneum, such as lymphomas and sarcomas, commonly cause obstruction. Obstruction can also result from inflammatory conditions affecting the retroperitoneum, such as Crohn disease and large bowel diverticulitis. In Crohn disease, the obstruction is usually right-sided as a result of ileocecal disease. Less common pathologic processes include retroperitoneal fibrosis, in which thick fibrous tissue encases the ureters and draws them medially (Fig. 61.2). Retroperitoneal fibrosis may be idiopathic but can result from inflammatory aortic aneurysms, certain drugs (e.g., β-blockers, bromocriptine, methysergide), previous irradiation, trauma or surgery, and granulomatous disease (e.g., tuberculosis, sarcoidosis). Retroperitoneal fibrosis is also associated with IgG4-related disease (see Chapter 65), which typically presents with autoimmune pancreatitis, and elevated serum IgG4 levels suggest this diagnosis.2 IgG4-related disease may be diagnosed after retroperitoneal biopsy material with an IgG4-positive plasma cell infiltrate, fibrosis with a whorled (cartwheel) appearance, and an obliterative venous phlebitis evident.3 The main differential diagnosis for idiopathic or benign retroperitoneal fibrosis is lymphoma or other malignant mimics and therefore consideration should be given to the need for biopsy. Computed tomography (CT) positron emission tomography (PET) can help with the distinction between benign retroperitoneal fibrosis and malignant disease.4

Ureteral compression may be a result of vascular abnormalities, including aneurysmal dilation of the aorta or iliac vessels, aberrant

Pathophysiology

Obstruction of the urinary tract causes profound functional and structural changes of the kidney. Initially, changes are predominantly functional and potentially reversible, but with time, chronic and irreversible structural changes occur. Our understanding of the consequences of urinary tract obstruction stems mainly from the study of animal models.5 Although many studies have focused on the effects of complete ureteral obstruction in rodents, investigators have also examined models of chronic complete, partial, or reversible obstruction in adult and neonatal animals.5 Available experimental data show little species-tospecies variation in the response to acute obstruction, suggesting that similar changes are likely to occur in humans. The complex effects of urinary tract obstruction on the kidney affect both glomerular hemodynamics and tubular function.

Changes in Glomerular Function

GFR declines progressively after the onset of complete ureteral obstruction. After complete ureteral obstruction, there is an initial rise in proximal tubular pressure. This is accompanied by afferent arteriolar dilation as a result of the generation of vasodilatory prostaglandins. Although this increases glomerular capillary hydraulic pressure, it does not offset the rise in tubular pressure, and there is a decrease in the hydraulic pressure gradient across glomerular capillaries, resulting in a dramatic decline in GFR. The relative changes in ureteral pressure, renal plasma flow, and GFR are summarized in Fig. 61.3. With ongoing obstruction, there is a progressive fall in renal blood flow secondary to the generation of angiotensin II (Ang II) and thromboxane A_2, the release of vasopressin (antidiuretic hormone), and decreased nitric oxide production. An interstitial leukocyte infiltrate develops, predominantly macrophages, and promotes the late structural changes that occur after obstruction as macrophage depletion limits experimental interstitial fibrosis.[6]

The extent to which glomerular function recovers after the release of ureteral obstruction depends on the duration of the obstruction. Whole-kidney GFR may return to normal after short-term obstruction (days), whereas recovery may be incomplete after prolonged obstruction.

Changes in Tubular Function

Abnormalities in tubular function are common in urinary tract obstruction and manifest as altered kidney handling of electrolytes and changes in the regulation of water excretion. The degree and nature of the tubular defects after obstruction depend in part on whether the obstruction is bilateral or unilateral. These differences could result from the dissimilar hemodynamic responses, different intrinsic changes within the nephron, or differences in extrinsic factors (e.g., volume expansion and accumulation of natriuretic substances in bilateral obstruction) between the two states.

After ureteral obstruction, the ability to concentrate the urine is impaired with causative factors including a loss of medullary tonicity and reduced expression of sodium transporters. Also, the collecting duct is unresponsive to vasopressin because of reduced expression of kidney aquaporins.

Rats exhibit reduced expression of multiple acid-base transporters after ureteral obstruction,7 and patients with urinary tract obstruction often have urinary acidification defects. These defects may be detected only by exogenous acid loading, but hyperchloremic acidosis caused by impaired distal acid secretion, hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis), and a combination of these findings has been described. This acidifying defect results from a marked increase in bicarbonate excretion or from a distal acidification defect, possibly as a result of abnormalities of the H+-ATPase activity of intercalated cells of the collecting duct after ureteral obstruction.

Obstruction also alters kidney potassium handling. In the presence of a normal functioning contralateral kidney, potassium excretion is reduced after relief of obstruction, either in proportion to or perhaps even greater than the fall in GFR (i.e., fractional excretion of potassium is unaltered or slightly reduced). There is a defect in the distal potassium secretory mechanism after unilateral obstruction that may be secondary to reduced responsiveness of that nephron segment to aldosterone. By contrast, after release of bilateral ureteral obstruction, there is a marked increase in both net and fractional potassium excretion. The major mechanism by which potassium losses occur in this setting is an increased delivery of sodium to the distal tubule, resulting in increased sodium-potassium exchange.

Percentage of control values

The Effects of Complete
Ureteral Obstruction
200
180
160
140
120
100
80
60
40
20
0

Recovery of tubular function after release of obstruction is slow and may remain abnormal even after whole-kidney GFR has returned to normal. In rats, acidification and potassium-handling abnormalities persist for at least 14 days and urinary concentrating ability is abnormal for up to 60 days after the release of 24 hours of unilateral ureteral obstruction. These observations are consistent with persistent alterations in distal tubular and collecting duct function or a loss in functioning juxtaglomerular nephrons after the release of the obstruction.

HISTOPATHOLOGIC CHANGES

The morphologic alterations in kidney architecture are similar irrespective of the cause of the obstruction. Initially, there is kidney enlargement and edema with pelvicalyceal dilation (Fig. 61.4). Tubular dilation that predominantly affects the collecting duct and distal tubular segments is seen microscopically with cellular flattening and atrophy of proximal tubular cells. Glomerular structures are usually preserved initially, although the Bowman space may be dilated and some periglomerular fibrosis may ultimately develop.

Inadequately treated urinary tract obstruction eventually causes irreversible structural changes. The renal pelvis becomes widely dilated, with the papillae either flattened or hollowed out. The cortex and medulla become grossly thinned, such that the kidney becomes a thin rim of kidney tissue surrounding a large saccular pelvis (Fig. 61.5). Histologic examination demonstrates tubulointerstitial fibrosis and profound nephron loss. Tubular proliferation and apoptosis, interstitial myofibroblast accumulation, increased extracellular matrix deposition, and tubular atrophy occur. Ischemia as a result of the decreased renal blood flow and the rarefaction of peritubular capillaries contributes to parenchymal damage after obstruction. In both genetic and interventional studies, an important pathologic role for Ang II and transforming growth factor-β (TGF-β) has been established.[5] Infiltrating macrophages release profibrogenic factors (e.g., TGFβ, galectin-3) and play a pivotal role in the chronic tissue injury and fibrosis that result from prolonged ureteral obstruction[6 8] (Fig. 61.6). Local Ang II generation also may stimulate tubular cell production of TGF-β. Treatments shown to ameliorate chronic interstitial damage in experimental obstructive uropathy include angiotensin receptor

Ureteral pressure
Renal plasma flow
Glomerular filtration rate

0

2

4

6

8

10

12

14

16

18

Time postobstruction (hours)

Fig. 61.3 Effects of Complete Ureteral Obstruction. The relative changes in ureteral pressure, kidney plasma flow, and glomerular filtration rate

are shown using data from experimental studies of unilateral ureteral obstruction in rats.

Fig. 61.4 Autopsy Specimen of a Kidney Showing the Early Effects of Ureteral Obstruction. The kidney is enlarged and edematous with pelvicalyceal dilation. There is good preservation of the kidney parenchyma.

blockers (ARBs), pentoxifylline, simvastatin, and various growth factors with beneficial effects including reduced tubulointerstitial inflammation, tubular cell apoptosis, and fibrosis.5 However, differences have been noted in the responses of adult and neonatal rodents to experimental therapeutic interventions, and it is unclear whether such differences might occur in humans.

EPIDEMIOLOGY

Fig. 61.5 Chronic Ureteral Obstruction. Surgical specimen of a kidney showing gross dilation of the pelvicalyceal system and the reduction of the kidney cortex to a thin fibrotic rim of tissue. There would have been no prospect for any significant functional recovery in this kidney after the relief of the obstruction.

Obstructive uropathy is common and can occur at all ages, with the prevalence of hydronephrosis at autopsy being 3.5% to 3.8%, although this underestimates the true incidence because these figures exclude transient obstruction. The frequency and cause of obstruction vary in both sexes with age. Antenatal ultrasound has significantly increased the detection rate of lower urinary tract obstruction in the fetus.9 In children aged younger than 10 years, obstruction is more common in males; congenital urinary tract anomalies, such as PUV and pelviureteral obstruction, account for most cases. In North America, obstructive uropathy is a common cause of ESKD in children and accounts for 11.4% of cases.10 In addition, congenital obstructive uropathy accounts for 0.7% of all patients (median age, 31 years) treated with maintenance kidney replacement therapy,

Impairment of Function and Structural Damage in Obstructive Nephropathy

Obstruction of urinary tract

Abrupt fall in GFR

Mechanical stimulation
Membrane stretch

Release of chemoattractants

Stimulation of intrinsic renal cells

Macrophage infiltration and interstitial inflammation

Generation of vasoactive substances, e.g., Ang II, TXA2

Mediator and cytokine generation, e.g., nitric oxide, TNF-α, TGF-β

Altered renal hemodynamics

Peritubular
capillary loss
and ischemia

Tubular cell
apoptosis
and tubular
atrophy

Myofibroblast
accumulation and
interstitial fibrosis

Acute
kidney injury
Nephron loss

Irreversible renal injury and
scarring with resultant chronic
kidney disease

Fig. 61.6 Events leading to acute impairment of kidney function and chronic structural damage in obstructive nephropathy. Ang II, Angiotensin II; GFR, glomerular filtration rate; TGF-β, transforming growth factor-β; TNFα, tumor necrosis factor α; TXA2, thromboxane A2.

demonstrating the continued impact of this disease into adult life.11 In adults younger than 20 years, the frequency of urinary tract obstruction is similar in males and females. Beyond 20 years of age, obstruction becomes more common in females, mainly because of pregnancy and gynecologic malignancy. The peak incidence of kidney calculi occurs in the second and third decades of life, with a threefold increased incidence in males. After the age of 60 years, obstructive uropathy occurs more frequently in males secondary to benign prostatic hypertrophy and prostatic carcinoma. About 30% of males older than 50 years have some symptoms of bladder outflow obstruction and acquired urinary tract obstruction can lead to ESKD in elderly patients with most resulting from prostatic disease.12 In the United States, 1.4% of prevalent patients with ESKD have kidney failure secondary to acquired obstruction.11

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract can present with a wide range of clinical symptoms, depending on the site, degree, and duration of obstruction. The clinical manifestations of upper and lower urinary tract obstruction differ. Symptoms can be caused by mechanical obstruction of the urinary tract (usually pain) or can result from the complex alterations in glomerular and tubular function that may occur in obstructive nephropathy. The latter commonly manifests as alterations in urine volume and as kidney failure, which can be acute or chronic. For example, patients with complete obstruction present with anuria and AKI, whereas those with partial obstruction may present with polyuria and polydipsia secondary to acquired vasopressin resistance. Alternatively, there may be a fluctuating urine output, alternating from oliguria to polyuria. However, obstructive uropathy and hence obstructive nephropathy can occur without symptoms and with minimal clinical manifestations. Therefore, obstruction of the urinary tract must be considered in the differential diagnosis of any patient with reduced GFR.

Pain

Pain is a frequent complaint in patients with obstructive uropathy, particularly in those with ureteral calculi. The pain is believed to result from stretching of the collecting system or the renal capsule. The location of the pain may help determine the site of obstruction. With upper ureteral or pelvic obstruction, flank pain and tenderness typically occur, whereas lower ureteral obstruction causes pain that radiates to the groin, the ipsilateral testicle, or the labia. Acute high-grade ureteral obstruction may be accompanied by a steady and severe crescendo flank pain radiating to the labia, the testicles, or the groin (classic kidney colic). The acute attack may last less than half an hour or as long as a day. By comparison, patients with chronic slowly progressive obstruction may have no pain or minimal pain; in such patients, any pain that does occur is rarely colicky. In PUJ obstruction, pain may occur only after fluid loading to promote a high urine flow rate (often reported after drinking alcohol, for example).

Lower Urinary Tract Symptoms

Obstructive lesions of the urethra or bladder neck or bladder disease may cause a decrease in the force or caliber of the urine stream, intermittency, hesitancy, straining (voiding lower urinary tract symptoms), postmicturition dribbling, or nocturia. Urgency, frequency, and urinary incontinence can result from incomplete bladder emptying. Indeed, the development of nocturnal incontinence suggests chronic urinary retention and should be considered a red flag that may be associated with painless kidney failure. Such symptoms commonly result from prostatic hyperplasia (a histologic diagnosis; benign prostatic enlargement [BPE] is the preferred clinical term) and are frequently referred to as prostatism. The preferred clinical term is lower urinary tract symptoms (LUTS), caused by BPE, resulting in benign prostatic obstruction (BPE with evidence of bladder obstruction). However, lower urinary tract symptoms have many causes and are not pathognomonic of benign prostatic enlargement.

Urinary Tract Infections

Urinary stasis resulting from obstruction predisposes to urinary tract infections (UTIs), and patients may develop cystitis with dysuria and frequency or pyelonephritis with loin pain and systemic symptoms. Infection occurs more often in patients with lower urinary tract obstruction than in those with upper urinary tract obstruction.

UTI in males or young children of either sex, recurrent or persistent infections in females, infections with unusual organisms such as Pseudomonas or Proteus spp., and a single attack of acute pyelonephritis require further investigation to exclude obstruction or stone disease. Also, the presence of obstruction makes effective eradication of the infection difficult. Infections of the urinary tract with a urease-producing organism such as Proteus mirabilis predispose to stone formation. These organisms generate ammonia, which results in urine alkalinization and favors the development of magnesium ammonium phosphate (struvite) stones. Struvite calculi can fill the entire renal pelvis to form a staghorn calculus that eventually leads to loss of the kidney if untreated. Thus, stone formation and papillary necrosis can be consequences of urinary tract obstruction and causes of obstruction.

Hematuria

Calculi may cause trauma to the urinary tract uroepithelium and result in either macrohematuria or microhematuria. Any neoplastic lesion that obstructs the urinary tract, especially uroepithelial malignancies, may bleed, resulting in macrohematuria. Urinary tract bleeding may result in obstruction, giving rise to clot colic when it is in the ureter, or clot retention when it is in the bladder. Clot obstruction of the ureter is usually (but not always) transient.

Changes in Urine Output

Complete bilateral obstruction or unilateral obstruction of a single functioning kidney such as a kidney transplant will result in anuria. However, in partial obstruction, the urine output may be normal or increased (polyuria). A pattern of alternating oliguria and polyuria or the presence of anuria strongly suggests obstructive uropathy.

Abnormal Physical Findings

Physical examination can be completely normal. Some patients with upper urinary tract obstruction may have flank tenderness. Longstanding obstructive uropathy may result in an enlarged palpable kidney in children. Lower urinary tract obstruction causes a distended, palpable, and occasionally painful bladder. However, in severe chronic bladder outflow obstruction (which is most likely to cause kidney failure), there may be no tenderness and no discrete palpable bladder because the bladder has stretched to such an extent that it is now “baggy.” Ultrasound scan, or catheterization with careful documentation of residual bladder volume and subsequent urine output, may be required to clinch the diagnosis. A rectal examination and, in females, a pelvic examination should be performed because they may reveal a local malignancy, prostatic enlargement, or neurologic deficit suggesting cauda equina pathology.

Acute or chronic hydronephrosis, either unilateral or bilateral, may cause hypertension secondary to impaired sodium excretion with expansion of extracellular fluid volume or from the abnormal release

of renin. On occasion, in patients with partial urinary tract obstruction, polyuria and volume depletion lead to hypotension.

Abnormal Laboratory Findings

Urinalysis may show hematuria, bacteriuria, pyuria, crystalluria, and low-grade proteinuria, depending on the cause of obstruction. However, urinalysis may be completely negative despite advanced obstructive nephropathy. In the acute phase of obstruction, urinary electrolyte values are similar to those seen in a prerenal state, with a low urinary sodium concentration (<20 mmol/L), a low fractional excretion of sodium (<1%), and a high urinary osmolality (>500 mOsm/kg). However, with more prolonged obstruction, a decreased ability to concentrate the urine and an inability to reabsorb sodium and other solutes occur. These changes are particularly marked after the release of chronic obstruction and give rise to the syndrome commonly referred to as "postobstructive diuresis."

Increases in serum urea and creatinine are the most significant laboratory abnormalities in patients with obstructive uropathy. Electrolyte abnormalities may occur, including hyperchloremic hyperkalemic (type 4) metabolic acidosis or hypernatremia from acquired nephrogenic diabetes insipidus. The development of obstruction in patients with underlying CKD may accelerate the rate of progression. ESKD may occasionally be caused by chronic obstructive uropathy that had been asymptomatic.

Obstruction in Neonates or Infants

With the advent of routine antenatal scanning, the diagnosis of hydronephrosis and genitourinary abnormalities is now frequently made antenatally; however, unsuspected obstructive uropathy may present in the postnatal period with failure to thrive, voiding difficulties, fever, hematuria, or symptoms of kidney failure. Oligohydramnios at the time of delivery should raise the suspicion of obstructive uropathy, as should the presence of congenital anomalies of the external genitalia. Nonurologic anomalies such as ear deformities, a single umbilical artery, imperforate anus, or a rectourethral or rectovaginal fistula should prompt investigation for urinary tract obstruction. Any infant with neurologic abnormalities may have a neurogenic bladder with associated obstructive uropathy.

DIAGNOSIS

Prompt diagnosis of urinary tract obstruction is essential to allow timely treatment. Symptoms such as kidney colic may suggest the diagnosis and prompt appropriate investigation. However, urinary tract obstruction should be considered in any patient with unexplained acute or chronic kidney impairment. The diagnostic approach must be tailored to the clinical presentation (Fig. 61.7), but a careful history and thorough physical examination are mandatory in all patients.

Urinalysis may provide valuable diagnostic information. Hematuria suggests that the obstructing lesion is a calculus, sloughed papilla, or tumor. Bacteriuria suggests urinary stasis, especially in males or pregnant females, but it also may be a complication of chronic obstruction. The presence of crystals in the urine sediment (cystine or uric acid) may be an indication of the type of stone causing the ureteral obstruction or the intrarenal obstruction resulting in AKI. Laboratory studies must include assessment of GFR and serum electrolytes.

Imaging

Because the sites, causes, and consequences of obstruction to the urinary tract are so variable, no single imaging investigation can diagnose or exclude urinary tract obstruction with certainty. Therefore, if the clinical suspicion of obstruction is high, the patient may require investigation with multiple imaging techniques.

Ultrasound is the most widely used imaging modality, but CT scanning (with urographic phase) and magnetic resonance (MR) urography are increasingly used to accurately diagnose both the site and cause of obstruction. Although much less commonly used, older imaging techniques, such as intravenous urography (IVU), can be used to evaluate patients with obstructive uropathy. None of these modalities provides a functional kidney excretory or voiding profile, and where doubt still exists as to the existence of kidney obstruction (e.g., in cases of nonobstructive hydronephrosis [“baggy renal pelvis”], vesicoureteral reflux, or hypertonic bladder), functional investigations are required such as radioisotope excretory renography (mercaptoacetyltriglycine [MAG3] renogram), micturating cystoureterogram, or pressure-voiding studies (cystometrogram [CMG]), respectively. The role of imaging techniques is shown in Fig. 61.7 and discussed further in Chapters 5 and 6.

Ultrasound

Ultrasound can define kidney size and demonstrate calyceal dilation but depends on the expertise of the operator (Fig. 61.8). Although it is sensitive for detection of hydronephrosis, ultrasound often will not determine its cause. Pathologic change within the ureter is difficult to demonstrate, and tiny stones will not generate acoustic shadows. However, unilateral hydronephrosis suggests obstruction of the upper urinary tract by stones, blood clots, or tumors. Bilateral hydronephrosis is more likely to result from a pelvic problem obstructing both ureters or obstruction of the bladder outlet, in which case the bladder will also be enlarged. Ultrasound should be combined with radiographic examination of the kidneys, ureters, and bladder (KUB) to ensure that ureteral stones or small kidney stones are not overlooked.

Ultrasound produces false-negative results in cases of nondilated obstructive uropathy. Immediately after acute obstruction (within 24 hours), the relatively noncompliant collecting system may not have dilated, so ultrasound examination findings may be normal. Furthermore, if urine flow is low, as in severe dehydration or kidney failure, there may be little dilation of the urinary tract. Dilation also may be absent in slowly progressive obstruction when the ureters are encased by fibrous tissue (as in retroperitoneal fibrosis) or by tumor, and in some kidney transplants in which there is dense surrounding scar tissue. The acoustic shadow of a staghorn calculus also can mask dilation of the upper urinary tract. In view of this, it is advisable to repeat the kidney ultrasound if suspicion of obstruction is high. The sensitivity of ultrasound for diagnosis of obstruction can be improved by measuring the resistive index with color Doppler sonography. A resistive index above 0.7 reflects the increased vascular resistance present in obstruction and can assist discrimination between obstructed and nonobstructed kidneys, although the resistive index can be increased in other conditions.13 Such ultrasound techniques are particularly useful when it is especially important to minimize radiation exposure, such as in pregnant patients and in children, and in the follow-up of patients requiring repeated imaging, such as after extracorporeal shock wave lithotripsy.

Even in experienced hands, ultrasound may have a significant falsepositive rate, especially if minimal criteria are adopted to diagnose obstruction. In addition, the echogenicity produced by multiple kidney cysts may be mistaken for hydronephrosis.

Ultrasound scanning can be used to assess bladder emptying and should be undertaken in patients with lower urinary tract symptoms, being performed at the bedside if necessary. The normal postmicturition (postvoid) residual volume is less than 50 mL (<100 mL is usually acceptable in patients > 65 years), and a large postmicturition residual volume suggests bladder outflow obstruction or detrusor muscle failure, which should prompt further urologic investigation and treatment.

Investigation and Management of Suspected Urinary Tract Obstruction

Suspected obstruction

History/examination
Urinalysis and urine
culture
Assessment of renal
function
Lower tract
symptoms

Flank pain
? Renal colic

Ultrasound scan ±
plain abdominal x-ray

Bladder
ultrasound
scan

CT scan
(or IVU)

Dilation of PC system

Large residual
volume

Reduced
glomerular
filtration rate

Normal
renal function

Nephrostomy

Further imaging
to define lesion
(CT or MR scan)

Catheterize

Nondilated
PC system

Obstruction
still suspected

Consider
retrograde
pyelography

Consider diuresis
renogram

Nephrostogram to
define lesion

Plan definitive therapy

Fig. 61.7 Investigation and Management of Suspected Urinary Tract Obstruction. A full history and examination should be performed, together with urinalysis, urine microscopy and culture, and measurement of kidney function and serum electrolytes. Ultrasound is a useful first-line investigation for any patient with suspected urinary tract obstruction. Computed tomography (CT) is now the preferred imaging technique when kidney calculi are suspected. Either CT or magnetic resonance (MR) urography can accurately diagnose both the site and cause of obstruction in most cases. If there is reduced glomerular filtration rate, a nephrostomy or stenting allows the effective relief of the obstruction and time for kidney function to recover while definitive therapy is planned. IVU, Intravenous urography; PC, pelvicalyceal.

The investigation of neonates with hydronephrosis diagnosed antenatally depends on the grade of hydronephrosis identified. Neonates with grade 1 or 2 hydronephrosis (no calyceal dilation) undergo ultrasound scanning; neonates with grade 3 or 4 hydronephrosis (indicating increasingly severe pelvicalyceal dilation) require both ultrasound scanning and voiding cystourethrography.14 This combination can distinguish megaureter resulting from obstruction or reflux and enable the diagnosis of PUV and UPJ obstruction. Measurements of both calyceal dilation and the anteroposterior diameter of the kidney pelvis at the first postnatal ultrasound may be able to distinguish those children who will require surgery, but this grading system will require further validation.15

Plain Abdominal Radiography

A plain abdominal radiograph (or KUB) allows an assessment of kidney size and contour and frequently demonstrates kidney calculi because about 90% of calculi are radiopaque.

Intravenous Urography

IVU was formerly the first-choice investigation for suspected upper urinary tract obstruction. In patients with normal GFR, it can usually define both the site and the cause of the obstruction. However, the excretion of contrast material may be poor or delayed in patients with low GFR because of a decreased filtered load of the contrast agent. IVU is no longer a first-line investigation to diagnose urinary tract obstruction, especially in patients with reduced GFR.

Computed Tomography

Non–contrast-enhanced spiral CT scanning is used increasingly as the primary imaging modality for the evaluation of patients with acute flank pain16 and uses a low-dose protocol compared with conventional CT scanning of abdomen and pelvis. Stones are easily detected because of their high density; CT can provide an accurate and rapid diagnosis of an obstructing ureteral calculus, with a stone being found more commonly in males.17 In addition, it provides useful information

Fig. 61.8 Kidney Ultrasound Scan of a Patient with Obstruction of the Urinary Tract Causing Hydronephrosis. The kidney is hydronephrotic with dilation of the pelvicalyceal system; dilation of the upper ureter is also clearly seen (arrows).

Fig. 61.9 Computed Tomography Scan of the Abdomen Showing a Grossly Hydronephrotic Kidney on the Left. Arrows mark dilated kidney pelvis. Dilated loops of small bowel are seen in the right hypochondrium. Sequential sections demonstrated that the ureter was dilated along its length and that there was a pelvic mass, which was responsible for both bowel and left ureteral obstruction. The mass was subsequently shown to be arising from a carcinoma of the colon.

about the site and nature of the obstructing lesion, especially when this is extrinsic to the urinary tract (Fig. 61.9), although a higher dose CT scan with intravenous (IV) contrast may be required for a full diagnostic study. CT demonstrates retroperitoneal disease, such as paraaortic and paracaval lymphadenopathy; retroperitoneal fibrosis is evident as increased attenuation within the retroperitoneal fat, with encasement of one or both ureters. Hematomas, primary ureteral tumors, and polyps are also detectable. The diagnostic potential of CT is enhanced by the administration of contrast material, but this may limit its use in patients with reduced GFR. CT urogram (IV contrast with delayed [usually 10 minutes] excretory phase images) is the gold standard imaging modality for diagnosis of intraluminal or intramural obstructing lesions such as upper tract urothelial malignancy. It should be noted that CT involves exposure to ionizing radiation, especially if patients require multiple CT scans over time.

Magnetic Resonance Urography

MR urography (combined with KUB) can enable the diagnosis of ureteral obstruction caused by kidney calculi with accuracy similar to that of spiral CT scanning but without exposure to contrast medium or ionizing radiation. The technique has less observer variability and is more accurate than CT in detecting indirect evidence of obstruction, such as perirenal fluid. MR urography can rapidly and accurately depict the morphologic features of dilated urinary tracts and provide information about the degree and level of obstruction[18] (Fig. 61.10). MR urography is a particularly attractive imaging modality for the evaluation of hydronephrosis in children because it provides both anatomic and functional data and can indicate whether the hydronephrosis is compensated (symmetric changes of signal intensity of the nephrogram) or decompensated.[19] Signs of decompensation (acute on chronic obstruction) include edema of the kidney parenchyma, a delayed and increasingly dense nephrogram, a delayed calyceal transit time, and a more than 4% difference in the calculated differential kidney function. MR urography is likely to be increasingly used in the future.

Retrograde Pyelography

Retrograde pyelography (Fig. 61.11; see also Fig. 61.2) usually requires a general anesthetic and cystoscopy but may be particularly useful to

Fig. 61.10 Magnetic Resonance (MR) Urography Showing Obstructive Uropathy. T2-weighted MR image showing a proximal right-sided ureteric ureteral obstruction with an associated mild hydronephrosis. The obstruction was secondary to a ureteral calculus.

identify both the site and the cause of the obstruction because intervention (by stenting or dilation) and biopsy of a suspected tumor (by ureteroscopy) are both possible. It is also helpful when nondilated urinary tract obstruction is suspected or when there is a history of allergic reactions to contrast material.

Diuresis Renography

A diuresis renogram using technetium-99m MAG3 (99mTc-MAG3), combined with IV furosemide administered 20 to 30 minutes after injection of the isotope (diuretic isotopic renography), can be used to distinguish between simple dilation of the collecting system and true

Diuretic Isotopic Renography

Renal isotope
activity

Normal uptake and excretion of isotope

Time

Renal isotope
activity

Obstruction: delayed excretion

Furosemide

Time

Renal isotope
activity

Dilation without obstruction

Fig. 61.11 Ureteral Obstruction by a Tumor. A retrograde pyelogram shows the tumor is within and obstructing the ureter (arrows). Above the tumor, there is dilation of the ureter, but below it, the ureter is of a normal caliber.

obstruction.[20] Normally, there is a rapid washout of the isotope from the kidney, and persistence of the isotope suggests a degree of obstruction (Fig. 61.12). Severely reduced GFR significantly limits the usefulness of renography because the diuretic response to furosemide may be absent. Diuresis renography also may be used for follow-up of patients who have undergone surgical procedures to relieve obstruction, such as a pyeloplasty.

Pressure Flow Studies

A pressure flow study (Whitaker test) involves puncture of the collecting system with a fine-gauge needle to perfuse fluid (at 10 mL/min) with concurrent measurement of the differential pressure between the bladder and the collecting system; a pressure greater than 20 cm H_2O indicates obstruction. Although this test is rarely required, it may be informative in patients with potential upper tract obstruction when other, less invasive tests have generated equivocal results.[21]

Other Evaluations

Lower urinary tract obstruction may be evaluated by cystoscopy, which allows a visual inspection of the entire urethra and the bladder. Urodynamic studies, also known as cystometrogram (CMG; see Chapter 50, Fig. 50.14), are most useful where the distinction between obstructive (e.g., BPE) and functional (e.g., detrusor muscle failure) impaired bladder emptying needs to be determined. High pressure voiding and vesicoureteral reflux can also be assessed with the use of fluoroscopy during urodynamics (known as video urodynamics).

Furosemide

Time

Fig. 61.12 Diuretic Isotopic Renography. Idealized tracings for normal,

obstructed, and dilated kidneys without obstruction of the upper urinary tract. In obstruction, there is delayed excretion of technetium-99m mercaptoacetyltriglycine despite administration of furosemide. When there is dilation of the upper urinary tract without obstruction, the isotope is retained but is rapidly excreted after the administration of furosemide.

DIFFERENTIAL DIAGNOSIS

Diagnostic uncertainty arises with nonobstructive dilation of the upper urinary tract, which may be seen with vesicoureteral reflux, diuretic administration, diabetes insipidus, congenital megacalyces, chronic pyelonephritis, and postobstructive atrophy. Diuresis renography or retrograde pyelography may be required to exclude obstruction.

NATURAL HISTORY

Obstructive uropathy is potentially curable but will result in progressive irreversible loss of nephrons and kidney scarring if left untreated (Fig. 61.13). ESKD will result if both kidneys are affected or if there is only a solitary kidney. Outcome data for obstructive uropathy are limited, but the exact prognosis will depend on the pathologic process responsible for the obstruction, the duration and grade of the obstruction (complete or partial), and the presence or absence of urosepsis.

Relief of short-term obstruction (<1–2 weeks) usually results in an adequate return of kidney function. With chronic progressive obstruction (>12 weeks), there is often irreversible and severe kidney damage, and kidney functional recovery may be limited even after relief of the obstruction. A single-center study identified 104 patients who presented with obstructive nephropathy.[22] The mean GFR at presentation and at 3, 12, and 36 months was 9, 28, 29, and 30 mL/min, respectively

Fig. 61.13 Pathology of Chronic Ureteral Obstruction. Section of the rim of kidney tissue from the kidney shown in Fig. 61.7. The kidney capsule is at the top, the urinary space at the bottom. The cortex is considerably thinned, and only a few atrophic tubules remain (arrows) within an interstitium comprising dense fibrous tissue and a mononuclear cell infiltrate (blue staining nuclei). No glomeruli can be seen. This demonstrates why there would be no prospect for any significant functional recovery in this kidney even after the relief of the obstruction.

(patients on dialysis excluded), demonstrating significant but nonprogressive kidney impairment after relief of obstruction. It is likely that the prognosis for kidney functional recovery is better after earlier diagnosis and relief of the obstruction.

TREATMENT

General Considerations

Treatment is dictated by the location of the obstruction, the underlying cause, and the degree of any kidney impairment. If kidney impairment is present, the treatment of obstruction requires close collaboration between nephrologists and urologists to reduce the risks associated with the metabolic and electrolyte consequences of kidney failure and to optimize the chances for long-term recovery of kidney function. For example, complete bilateral ureteral obstruction (or obstruction of a single kidney) manifesting as AKI is a medical emergency and requires rapid intervention to salvage kidney function. Prompt intervention to relieve the obstruction should result in a rapid improvement in kidney function. Dialysis is rarely required in patients with AKI secondary to obstruction except to make the patient fit for intervention, such as by improving life-threatening hyperkalemia or severe fluid overload. The rapid relief of obstruction will limit permanent kidney damage, but kidney function may not recover immediately if acute tubular injury has resulted from obstruction or any accompanying sepsis.

Some surgical aspects of the management of obstructive uropathy are discussed in Chapter 63. The site of obstruction frequently determines the approach. If the obstruction is distal to the bladder, a urethral catheter or, if this cannot be passed, a suprapubic cystostomy will effectively decompress the kidneys. Placement of nephrostomy tubes or cystoscopy and passage of a retrograde ureteral stent will relieve upper urinary tract obstruction. Percutaneous nephrostomy (PCN) is generally the appropriate emergency treatment for upper urinary tract obstruction, especially in the setting of AKI. PCN can be achieved with local anesthetic and should allow for rapid recovery of kidney function in most patients (>70%), avoiding the need for dialysis. After relief of the obstruction by a nephrostomy, the exact site and nature of the obstructing lesion can be determined by an antegrade study infusing radiographic contrast material into the nephrostomy tube (nephrostogram), and time can be taken to plan definitive therapy (Fig. 61.14).

The benefit of PCN insertion is that it can be achieved under local anesthetic, whereas ureteral stenting usually requires a general anesthetic. However, PCN is usually not possible where patients are therapeutically anticoagulated, potentially limiting its use where it is required urgently, and anticoagulation cannot be reversed. Major complications of nephrostomy insertion (abscess, infection, and hematoma) occur in less than 5% of patients. If both kidneys are obstructed, the nephrostomy should initially be placed in the kidney with the most preserved kidney parenchyma, although bilateral nephrostomies may be required to maximize the potential for the recovery of kidney function. If infection occurs above a ureteral obstruction (pyonephrosis), drainage of the kidney by PCN can play an important therapeutic role together with appropriate antibiotics.

A nephrostomy can be used to gauge the potential for functional recovery in patients with chronic obstruction. Failure of kidney recovery after several weeks of nephrostomy drainage strongly suggests irreversible structural damage and thus no likely benefit from undertaking a more definitive surgical correction of the obstructing lesion. Longterm nephrostomy or stenting may be used as a definitive therapy for patients who are unsuitable for major surgical intervention and those with incurable malignant disease, although patient selection is important in the latter23 (see Chapter 63 for further discussion). Various types of stent are available, and there is some evidence that metallic stents may provide more durable functional decompression in patients with malignant ureteric obstruction.24

Where stents have failed or the ureters have become impassable because of disease, it is possible where expertise exists to insert “extraanatomic stents.” These stents are tunneled from the kidney to the bladder percutaneously in the abdominal wall, thus bypassing any intraabdominal pathology.25

Ureteral obstruction requiring intervention occurs in up to 3% of kidney transplant recipients.26 It can be treated by nephrostomy and ureteral stenting, percutaneous incision or balloon dilation of the stricture, or open surgical repair (see Chapter 108).

Specific Therapies

Calculi are the most common cause of ureteral obstruction, and their treatment includes relief of pain, elimination of obstruction, and treatment of infection (see Chapters 60 and 63). Ureteral obstruction by papillary tissue, blood clots, or a fungus ball is treated by procedures similar to those used for calculi. When obstruction is caused by neoplastic, inflammatory, or neurologic disease, there is unlikely to be spontaneous remission of the obstruction, and some form of urinary diversion, such as an ileal conduit, long-term intermittent ureteral stenting, or extra-anatomic stenting should be considered. Some obstructing neoplastic lesions, such as lymphadenopathy from lymphoma, may respond to chemotherapy. A “realistic medicine” approach should be taken in management of ureteric obstruction because surgical management can reduce quality of life and carries risks of complications. Management of malignant urinary tract obstruction is discussed further in Chapter 59

In idiopathic retroperitoneal fibrosis, ureterolysis (in which the ureters are surgically freed from their fibrous encasement) may be beneficial, especially if combined with corticosteroid therapy to prevent recurrence. The procedure can be performed minimally invasively using robotic technology in specialist centers and may represent a durable treatment preferable to long-term ureteric stents and steroids.27

A

B

C

Fig. 61.14 Nephrostogram. A nephrostomy has been placed percutaneously into the dilated collecting system of the kidney under ultrasound control (A). After infusion of contrast material down the nephrostomy, the dilated pelvicalyceal system and upper ureter (B) and the lower ureter (C) are outlined. The ureter is dilated along its length but tapers abruptly at the vesicoureteral junction (arrow). In this case the obstruction was caused by a radiolucent stone.

Although ureteral stent insertion and corticosteroids can provide relief of obstruction in idiopathic retroperitoneal fibrosis,28 these treatments come with long-term adverse effects, whereas surgery may offer the chance of cure.27 29 Retroperitoneal fibrosis complicating IgG4 disease may respond to corticosteroid treatment.3 Although kidney obstruction per se results in kidney inflammation involving multiple immune cells irrespective of the underlying cause, there are no published trials of therapies that target the immune system in this patient cohort.

Although pharmacologic blockade of the renin-angiotensin system is not instituted in the acute setting, it is reasonable to employ ARBs or angiotensin-converting enzyme inhibitors in patients with residual CKD.

Functionally significant PUJ obstruction should be corrected surgically; minimally invasive and robotic techniques have largely replaced the open (Anderson-Hynes) pyeloplasty. The laparoscopic approach results in significantly less morbidity and has good long-term outcomes that are comparable to those of the open procedure.30 Balloon dilation of the abnormal segment of the ureter is also possible, but the recurrence rate is high. The severity of kidney fibrosis and atrophy as assessed on intraoperative wedge kidney biopsy in patients undergoing open PUJ surgery can be used to predict functional outcome.31

There is increasing interest in the usefulness of urine proteomics to identify neonates with PUJ obstruction who require surgical intervention,32 although a subsequent small study indicated that this approach was less specific and sensitive in older children.33 Urinary biomarkers that show altered levels in children or adult patients with obstructive nephropathy include established well-studied AKI biomarkers (kidney injury molecule-1, neutrophil gelatinase–associated lipocalin, and liver-type fatty acid binding protein),34 aquaporin-2, and TGF-β, as well as epidermal growth factor, monocyte chemotactic protein-1, and β2-microglobulin.35 Interestingly, a reduction in urinary epidermal growth factor is also seen in patients with CKD and is a predictor of CKD progression,36 suggesting that urinary biomarkers may well facilitate the future stratification of patients with obstructive nephropathy and assist with predicting functional outcome after intervention.

Benign prostatic enlargement is the most common cause of lower urinary tract obstruction in males and may be mild and nonprogressive. Patients with minimal symptoms, no infection, and a normal upper urinary tract can continue with assessment until they and their physician agree that further treatment is desirable. Medical therapy with either α-adrenergic blockers (e.g., tamsulosin) or 5α-reductase inhibitors (e.g., finasteride) may be used in patients with moderate symptoms.37 α-Blockers relax the smooth muscle of the bladder neck and prostate and decrease urethral pressure and outflow obstruction.

5α-Reductase inhibitors inhibit the conversion of testosterone to the active metabolite dihydrotestosterone and reduce prostatic hypertrophy. Combination therapy with these agents may be synergistic.

Medical therapy is not appropriate for patients with outflow obstruction caused by BPE who have had upper urinary tract obstruction and loss of GFR. In these patients, definitive bladder drainage is mandatory and therefore will entail either long-term urethral catheter, intermittent self-catheterization, or definitive bladder outflow surgery according to individual patient risks and benefits. Surgical intervention for benign prostatic obstruction is generally required for failed medical treatment, debilitating symptoms, urinary retention, recurrent infection, or evidence of kidney parenchymal damage. A multitude of surgical modalities are available to treat benign prostatic obstruction, with transurethral resection of the prostate (TURP) still considered the gold standard; however, discussion with a urologist is recommended for all patients with significant BPE, even those who may traditionally have been considered “unfit for surgery.”[38]

Urethral strictures in males can be treated by dilation or directvision internal urethrotomy before definitive urethroplasty, although urethral stenting is evolving. The incidence of bladder neck and urethral obstruction in females is low and treatment rarely required. Suprapubic cystostomy may be necessary for bladder drainage in patients unable to void after injury to the urethra or in those who have an impassable urethral stricture.

When obstruction results from neuropathic bladder dysfunction, urodynamic studies are essential to guide therapy. The goals of therapy are to establish the bladder as a urine storage organ without causing kidney parenchymal injury and provide a mechanism for bladder emptying acceptable to the patient. Patients may have either a flaccid atonic or an unstable hypertonic bladder. Ureteral reflux and parenchymal damage may develop in both cases, although it is more common in patients with a hypertonic bladder. Asking the patient to void at regular intervals may achieve satisfactory emptying of the bladder. Patients with an atonic bladder and significant residual urine retention associated with recurrent urosepsis need to undertake clean intermittent self-catheterization. The aim should be to catheterize four or five times per day to ensure the amount of urine drained from the bladder on each occasion is less than 400 mL. In patients with a hypertonic bladder, improvement in the storage function of the bladder may be obtained with anticholinergic agents or intermittent detrusor injection with botulinum toxin. Occasionally, chronic clean intermittent selfcatheterization is necessary.

Whenever possible, chronic indwelling catheters should be avoided in patients with a neurogenic bladder because they may lead to the formation of bladder stones, urosepsis, and urethral erosion, and they predispose to squamous cell carcinoma of the bladder. Patients who have chronic indwelling catheters for more than 5 years should have annual cystoscopic examinations. If deterioration in GFR occurs despite conservative measures or there is intractable incontinence or a small contracted bladder, an upper urinary tract diversion procedure such as an ileal conduit may be required or a bladder augmentation procedure such as a clam ileocystoplasty.

Management of Postobstructive Diuresis

Marked polyuria (postobstructive diuresis) is frequently seen after the release of bilateral obstruction or obstruction of a single functioning kidney. Indeed, a diuresis of greater than 7 L/day is associated with a good functional outcome.39 Release of unilateral obstruction rarely results in a postobstructive diuresis despite the presence of tubular dysfunction and a concentrating defect. This is because of intrinsic differences in the tubular response to unilateral and bilateral obstruction and, more importantly, the salt and water retention and kidney impairment that occurred in bilateral obstruction (not evident in unilateral obstruction because of the contralateral normal kidney). The resultant increase in natriuretic factors (including atrial natriuretic peptide) and substances able to promote an osmotic diuresis, such as urea, promote an appropriate postobstructive diuresis to excrete water and electrolytes that were retained during the period of obstruction. However, the postobstructive diuresis also may be inappropriate because of tubular dysfunction and, if not managed correctly, may result in severe volume depletion and electrolyte imbalance with continued kidney dysfunction. The key to correct management is clinical fluid assessment because appropriate diuresis may not require treatment, whereas inappropriate diuresis requires treatment to prevent hypovolemia and electrolyte imbalance. IV and oral fluid replacement is usually required in cases of inappropriate diuresis with careful and regular assessment of the fluid balance and serum electrolytes to tailor the fluid replacement regimen appropriately. Once the patient is deemed euvolemic, urine losses plus an allowance for insensible losses should be replaced. Urine volume should be measured regularly (hourly) to facilitate fluid administration, and serum electrolytes should be measured at least daily and as frequently as every 6 hours when there is a massive diuresis. Daily weighing of the patient is also helpful. Replacement fluid regimens should include sodium chloride and a source of bicarbonate and potassium. Calcium, phosphate, and magnesium replacement also may be necessary.

If fluid administration is overzealous, the kidney will not recover its concentrating ability, and a continued “driven” diuresis will result. It may then be necessary to decrease fluid replacement to levels below those of the urine output and observe the patient carefully for signs of volume depletion.

Future Prospects

Understanding the pathophysiologic changes that follow ureteral obstruction has allowed the development of rational interventional therapies to hasten the recovery of kidney function and limit permanent kidney damage. Although the best treatment option in humans remains prompt and effective relief of the obstruction, development and implementation of improved imaging modalities that provide more sophisticated anatomic and functional information (including intrarenal oxygen content40) and future advances in urine proteomics will undoubtedly refine patient management and increase the data available for making key clinical decisions, such as whether and when surgical intervention is required.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements are correct?
A. The presence of hydronephrosis does not always indicate significant obstruction.
B. Despite the effective relief of urinary tract obstruction, the majority of patients slowly progress to ESKD.
C. Urinary tract obstruction is always associated with oliguria.
D. Patients with urinary tract obstruction typically exhibit microscopic hematuria on urinalysis.
E. Urinary tract obstruction is a risk factor for urinary infections.
2. Which of the following statements are correct?
A. The development of marked diuresis after relief of urinary tract obstruction is a poor prognostic indicator and is associated with the eventual development of ESKD.
B. Urinary tract obstruction may complicate neurologic disease.
C. Retroperitoneal disease may result in urinary tract obstruction.

D. Urinary tract obstruction leads to inflammation and scarring of the kidney.
E. Urinary tract obstruction may complicate IgA nephropathy.
3. Which of the following statements are correct?
A. Defective tubular function may persist after relief of urinary tract obstruction.
B. Urinary tract obstruction is associated with a reduction in the glomerular filtration rate but preservation of kidney blood flow.
C. Non–contrast-enhanced spiral CT scanning is now established as the first-line imaging investigation in patients with suspected urinary tract obstruction.
D. A diuresis renogram accurately assesses kidney function but is unlikely to indicate the presence of obstruction.
E. Urinary tract obstruction may occur in the absence of hydronephrosis.

REFERENCES

1. Chuang TZ, Hung HC, Li SF, et al. Risk of chronic kidney disease in patients with kidney stones – a nationwide cohort study. BMC Nephrol. 2020;21:292–298.
2. Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. Medicine (Baltim). 2013;92:82–91.
3. Fujimori N, Ito T, Igarashi H, et al. Retroperitoneal fibrosis associated with immunoglobulin G4-related disease. World J Gastroenterol. 2013;19:35–41.
4. Wang Y, Guan Z, Gao D, et al. The value of 18 F-FDG PET/CT in the distinction between retroperitoneal fibrosis and its malignant mimics. Semin Arthritis Rheum. 2018;47:593–600.
5. Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int. 2009;75:1145–1152.
6. Henderson NC, Mackinnon AC, Farnworth SL, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. Am J Pathol. 2008;172:288–298.
7. Wang G, Li C, Kim SW, et al. Ureter obstruction alters expression of renal acid-base transport proteins in rat kidney. Am J Physiol Renal Physiol. 2008;295:F497–F506.
8. Ricardo SD, Diamond JR. The role of macrophages and reactive oxygen species in experimental hydronephrosis. Semin Nephrol. 1998;18:612–621.
9. Lissauer D, Morris RK, Kilby MD. Fetal lower urinary tract obstruction. Semin Fetal Neonatal Med. 2007;12:464–470.
10. U.S. Renal Data System U. Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
11. U.S. Renal Data System U. Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2005.
12. Sacks SH, Aparicio SA, Bevan A, et al. Late renal failure due to prostatic outflow obstruction: a preventable disease. BMJ. 1989;298:156–159.
13. Granata A, Zanoli L, Clementi S, et al. Resistive intrarenal index: myth or reality?. Br J Radiol. 2014;87. 20140004.
14. Belarmino JM, Kogan BA. Management of neonatal hydronephrosis. Early Hum Dev. 2006;82:9–14.
15. Dos Santos J, Parekh RS, Piscione TD, et al. A new grading system for the management of antenatal hydronephrosis. Clin J Am Soc Nephrol. 2015;10:1783–1790.
16. Pfister SA, Deckart A, Laschke S, et al. Unenhanced helical computed tomography vs intravenous urography in patients with acute flank pain: accuracy and economic impact in a randomized prospective trial. Eur Radiol. 2003;13:2513–2520.
17. Patatas K, Panditaratne N, Wah TM, et al. Emergency department imaging protocol for suspected acute renal colic: re-evaluating our service. Br J Radiol. 2012;85:1118–1122.
18. Semins MJ, Feng Z, Trock B, et al. Evaluation of acute renal colic: a comparison of non-contrast CT versus 3-T non-contrast haste MR urography. Urolithiasis. 2013;41:43–46.
19. Grattan-Smith JD, Little SB, Jones RA. MR urography evaluation of obstructive uropathy. Pediatr Radiol. 2008;38:S49–S69.
20. O'Reilly PH. Standardization of the renogram technique for investigating the dilated upper urinary tract and assessing the results of surgery. BJU Int. 2003;91:239–243.

21. Johnston RB, Porter C. The Whitaker test. Urol J. 2014;11:1727–1730.
22. Ravanan R, Tomson CR. Natural history of postobstructive nephropathy: a single-center retrospective study. Nephron Clin Pract. 2007;105:c165–c170.
23. Misra S, Coker C, Richenberg J. Percutaneous nephrostomy for ureteric obstruction due to advanced pelvic malignancy: have we got the balance

right? Int Urol Nephrol. 2013;45:627–632.
24. Chow PM, Chiang IN, Chen CY, et al. Malignant ureteral obstruction: functional duration of metallic versus polymeric ureteral stents. PLoS One. 2015;10. e0135566.
25. Laso-Garcia I., Lorca-Alvaro J., Arias-Funez F., et al. Central European J Urol. Long-term results of the treatment of complex ureteral stenosis with extra-anatomic ureteral bypasses. 73:213–219
26. Faenza A, Nardo B, Catena F, et al. Ureteral stenosis after kidney transplantation. A study on 869 consecutive transplants. Transpl Int. 1999;12:334–340.
27. Keehn AY, Mufarrij PW, Stifelman MD. Robotic ureterolysis for relief of ureteral obstruction from retroperitoneal fibrosis. Urology. 2011;77:1370–1374.
28. Fry AC, Singh S, Gunda SS, et al. Successful use of steroids and ureteric stents in 24 patients with idiopathic retroperitoneal fibrosis: a retrospective study. Nephron Clin Pract. 2008;108:c213–c220.
29. Bozaci AC, Altan M, Haberal HB, et al. Outcomes of ureterolysis for primary retroperitoneal fibrosis: a single-center experience. Int J Urol. 2021;28:520–525.
30. Uberoi J, Disick GI, Munver R. Minimally invasive surgical management of pelvic-ureteric junction obstruction: update on the current status of robotic-assisted pyeloplasty. BJU Int. 2009;104:1722–1729.
31. Bhat GS, Maregowda S, Jayaram S, et al. Is renal biopsy a better predictor of the outcome of pyeloplasty in adult ureteropelvic junction obstruction? Urology. 2012;79:321–325.
32. Decramer S, Wittke S, Mischak H, et al. Predicting the clinical outcome of congenital unilateral ureteropelvic junction obstruction in newborn by urinary proteome analysis. Nat Med. 2006;12:398–400.
33. Drube J, Zurbig P, Schiffer E, et al. Urinary proteome analysis identifies infants but not older children requiring pyeloplasty. Pediatr Nephrol. 2010;25:1673–1678.
34. Xie Y, Xue W, Shao X, et al. Analysis of a urinary biomarker panel for obstructive nephropathy and clinical outcomes. PLoS One. 2014;9. e112865.
35. Bartoli F, Penza R, Aceto G, et al. Urinary epidermal growth factor, monocyte chemotactic protein-1, and beta2-microglobulin in children with ureteropelvic junction obstruction. J Pediatr Surg. 2011;46:530–536.
36. Ju W, Nair V, Smith S, et al. Tissue transcriptome-driven identification of epidermal growth factor as a chronic kidney disease biomarker. Sci Transl Med. 2015;7. 316ra193.
37. Beckman TJ, Mynderse LA. Evaluation and medical management of benign prostatic hyperplasia. Mayo Clin Proc. 2005;80:1356–1362.
38. Magistro G, Chapple CR, Elhilali M, et al. Emerging minimally invasive treatment options for male lower urinary tract symptoms. Eur Urol. 2017;72:986–997.
39. Hamdi A, Hajage D, Van Glabeke E, et al. Severe post-renal acute kidney injury, post-obstructive diuresis and renal recovery. BJU Int. 2012;110:E1027–E1034.
40. Thoeny HC, Kessler TM, Simon-Zoula S, et al. Renal oxygenation changes during acute unilateral ureteral obstruction: assessment with blood oxygen level-dependent MR imaging–initial experience. Radiology. 2008;247:754–761.

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Primary Vesicoureteral Reflux and Reflux Nephropathy

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INTRODUCTION

Vesicoureteral reflux (VUR) may be primary or secondary. Primary VUR is diagnosed mostly after a urinary tract infection (UTI) or during work-up for antenatal hydronephrosis. Secondary VUR results mostly from increased bladder pressure because of obstructive uropathy or neurogenic bladder. In this chapter, we discuss primary VUR only.

Prenatal kidney injury in the form of dysplasia has been noted with high-grade primary VUR. The presence of VUR increases the risk for postnatal upper tract infection (pyelonephritis), and the two together can cause kidney injury leading to scarring of the kidney termed reflux nephropathy (RN). RN may manifest as proteinuria, hypertension, preeclampsia, chronic kidney disease (CKD), and even end-stage kidney disease (ESKD). Some patients present with proteinuria as a result of secondary focal segmental glomerulosclerosis (FSGS).

CLASSIFICATION

VUR is classified by radiologic evaluation on voiding cystourethrography (VCU) into five grades as defined by the International Reflux Study in Children (Fig. 62.1 and Table 62.1).[1] An example of grade V reflux is shown in Fig. 62.2. Grades I and II are considered low-grade VUR, and grades III to V are considered high-grade VUR. Grading of VUR is necessary to standardize management strategies and compare clinical outcomes. Although widely used, there is interobserver variability in the application of the grading system.[2]

EPIDEMIOLOGY

The reported incidence of VUR depends on the age of presentation and sex. VUR is often first suggested by dilation of the fetal kidney during ultrasound examination. It is suspected when the fetal kidney pelvis is more than 5 mm in anteroposterior diameter; a diameter of more than 10 mm is suggestive of high-grade VUR. In neonates who had evidence of fetal kidney pelvis dilation, as many as 13% to 22% have VUR. Indeed, it is estimated that 1% to 2% of neonates have VUR, with a higher frequency in boys and premature infants.[3] The incidence of kidney dysplasia is also greater in male infants with VUR.[4] Although some studies show that there is a higher incidence of VUR in females compared with males, this may be attributable to the higher predisposition of UTIs in females, therefore leading to greater diagnosis of VUR in females.

VUR is identified in 30% to 40% of children presenting with UTI, predominantly in girls. VUR may also be identified in as many as 40% of siblings of index patients. When identified using sibling screening protocols, VUR was felt to be less likely to be associated with infection or long-term kidney injury.[5] VUR is less common and less severe in Black children.[6] Only about one-third as many Black girls as White girls with UTI have VUR, and no significant differences in age or mode of presentation exist between the two races.

EMBRYOLOGY AND PATHOLOGY

Primary VUR is a congenital anomaly of the ureterovesical junction caused by shortening of the intravesical submucosal length of the ureter, leading to an incompetent valve mechanism (Fig. 62.3). The formation of the ureteral bud from the mesonephric duct signals the initial development of the metanephric kidney, the final stage of kidney development. The ureteral bud interacts with the mesenchyme to give rise to the metanephric kidney. As the mesonephric duct is gradually absorbed into the enlarging urogenital sinus (the precursor of the developing bladder), the location of the ureteral bud on the mesonephric duct plays a role in the eventual location of the ureteral meatus within the bladder. If the ureteral bud reaches the urogenital sinus too early because of the absorption pattern of the mesonephric duct, it is eventually located more laterally and proximally in the bladder. This location is associated with reduction in the intravesical submucosal length of the ureter, leading to VUR.

The ureterovesical junction is designed to prevent free reflux of urine from the bladder to the kidney. The ureters pass into the bladder through the detrusor in an oblique path. The distal end of the ureter is located submucosally within the bladder. The length of the submucosal ureter is critical for preventing VUR. The muscles of the ureter extend into the trigone of the bladder and mesh with the fibers from the opposite ureter. This intermingling of fibers helps anchor the ureters into the trigone of the bladder. The distal submucosal segment is compressed against the muscular bladder wall with bladder filling, acting as an additional mechanism to prevent reflux. Because urine is propelled antegrade down the ureter, the tone of the ureter and the meatus in the bladder also help prevent reflux.

CLINICAL MANIFESTATIONS

Presentation of Primary Vesicoureteral Reflux

The three most common presentations are during follow-up for antenatal hydronephrosis, after a diagnosis of UTI, and on screening of siblings of a patient with VUR (Box 62.1).

Reflux Identified Secondary to Antenatal Hydronephrosis

Diagnosis of VUR may be suspected in utero with unilateral or bilateral hydronephrosis and confirmed after birth with VCU. There is a higher incidence of male infants diagnosed with VUR after identification of antenatal hydronephrosis.7 Spontaneous resolution of the VUR occurs more commonly in boys with lower grades and unilateral reflux; infection rates are also lower in this cohort.8 Female infants are more likely to have lower grades of VUR and are also less likely to develop kidney

Grades of Vesicoureteral Reflux

I

II

III

IV

V

Fig. 62.1 Grades of vesicoureteral reflux.

TABLE 62.1 Classification of VUR[a]

Grade	Degree of VUR
I	Ureter only
II	Reflux into ureter, pelvis, and calyces with no dilation and with normal calyceal fornices
III	Mild or moderate dilation and/or tortuosity of the ureter and mild or moderate dilation of the pelvis; no or slight blunting of the fornices
IV	Moderate dilation and/or tortuosity of the ureter and moderate dilation of the pelvis and calyces; complete obliteration of the pelvis and calyces; complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions in the majority of the calyces (see Fig. 62.7C)
V	Gross dilation and tortuosity of the ureter, pelvis, and calyces; the papillary impressions are no longer visible in the majority of calyces (see Fig. 62.2)

[a] According to the International Reflux Study in Children.
VUR, Vesicoureteral reflux.

damage compared with newborn males. Not all patients with antenatal hydronephrosis are investigated for the presence of VUR.

Reflux Identified After a Urinary Tract Infection

VUR is most commonly identified after UTI, particularly in a young child. The prevalence of VUR is higher in younger patients and decreases with age (Table 62.2). In neonates and toddlers, UTI may manifest as failure to thrive as opposed to typical symptoms of dysuria and frequency. VUR is more common in patients with complicated or upper tract UTI. Because VUR may potentiate the effect of UTI in children, the recommendations for evaluation of UTI have included ultrasound and VCU after resolution of symptoms. Current guidelines from the National Institute for Health and Care Excellence (NICE) and the American Academy of Pediatrics (AAP) do not recommend routine

Fig. 62.2 Gross Vesicoureteral Reflux (VUR) and Intrarenal Reflux. A voiding cystourethrogram shows grade V VUR with intrarenal reflux into several kidney lobes in an infant.

VCU in children after a first febrile UTI.9 The AAP guidelines, which are meant for children aged 2 to 24 months old, suggest limiting the use of VCU to children identified as having complex UTIs or that have any abnormalities on ultrasound. We recommend beginning with an ultrasound of the kidneys and bladder once a febrile UTI has been confirmed, proceeding to evaluation with VCU if the ultrasound is abnormal or after a second febrile infection (Fig. 62.4). Other factors that may be considered as indications for VCU after the first febrile UTI include atypical causative pathogen, complex clinical course, known kidney scarring, or other congenital anomalies of kidney and the urinary tract.

Most children diagnosed with VUR after a UTI are younger than 7 years. UTI in these patients may be associated with modifiable host

Mechanism of Vesicoureteral Reflux

Ureter

Bladder
wall
Nonrefluxing
vesicoureteral junction

Ureter

Bladder
wall
Refluxing
vesicoureteral junction

Prevalence of VUR in Patients
With Urinary Tract Infection, According to
Age

TABLE 62.2

Age

Percentage With VUR

2–3 days
3–6 days
2–6 months
7–12 months
1–4 years
5–9 years
10–14 years
14 years
Adult

57
51
60
35
50
35
14
10
5

VUR, Vesicoureteral reflux.
Normal ureteral orifice

Refluxing ureteral orifice

Fig. 62.3 Pathogenesis of Vesicoureteral Reflux. Competent (left)
and incompetent (right) vesicoureteral junctions and ureteral orifices.

Management of Children with
Urinary Tract Infection
Children 2–24 months of age identified
with first febrile UTI, based on urinalysis
and culture

Clinical Presentations of Vesicoureteral Reflux

BOX 62.1

- Complicated urinary tract infection: usually acute pyelonephritis in infants and children
- Asymptomatic
- Detected by fetal ultrasound
- Detected in the workup of members of an affected family
- Detected in pregnant persons with urinary tract infection
- Detected during workup of kidney stones in children
- Detected during assessment of other urologic congenital abnormalities

factors, such as bladder and bowel dysfunction (BBD). BBD is typically identified in toilet-trained children with urinary urgency, frequency, and/or incontinence in conjunction with constipation and is felt to be secondary to long-standing urine holding patterns. BBD is associated with development of UTIs that may be potentiated by the presence of VUR. Toilet-trained children with VUR identified after a UTI have a 43% incidence of dysfunctional voiding.10

Vesicoureteral Reflux in a Sibling

Approximately one-third of siblings of an index patient with VUR also have VUR.5 There is a slightly higher incidence of VUR in female siblings of female index patients; 75% of children with VUR identified by evaluating siblings are asymptomatic, and siblings diagnosed with reflux have a better prognosis compared with the index patient with VUR, with lower risk of infection and long-term kidney injury.5 11 The incidence of kidney damage is also lower in the siblings diagnosed with reflux compared with the index patient with VUR.11 UTI with progression of scar was noted in only 5% of siblings with VUR observed for 3 to 7 years, and most of those with grades I and II VUR had spontaneous resolution.11 The more benign course of sibling reflux compared with reflux identified after a UTI has led many to suggest limiting the testing of siblings. Currently, no routine testing for VUR is advised for siblings of a child with known VUR unless the sibling develops a UTI.

Other Presentations

An increased risk for kidney calculi has been reported in children with VUR. Recurrent infections with urease-splitting organisms can lead to

Normal
No further workup

Prevoid and postvoid renal and
bladder ultrasound

Abnormal: hydronephrosis or
other anatomic abnormality

Repeated febrile
UTI

Voiding cystourethrogram

No reflux detected
No further workup

Fig. 62.4 American Academy of Pediatrics algorithm for evaluation of young children with diagnosed urinary tract infection (UTI).

staghorn calculi. VUR or RN may also be discovered in adults after recurrent lower or upper UTI; indeed, about 5% of sexually active females with UTI have VUR. VUR may first present as an infection in a pregnant person. In pregnant persons with active reflux, the risk for pyelonephritis is increased. A meta-analysis of 434 females with 879 pregnancies with RN showed that there was an increased risk of pregnancy-induced hypertension and pulmonary embolism.12 Thus, it is likely that kidney scarring, not VUR itself, poses the greatest risk of morbidity in pregnant persons.13

Reflux Nephropathy

RN may occur in patients with VUR and can be seen in those with or without proven UTI.14 15 RN results from one of two processes (Table 62.3).16 Prenatal kidney injury has been postulated to be secondary to the “water-hammer” effect of high-grade reflux and occurs in the absence of infection. This typically causes kidney dysplasia. This form of kidney scarring, which is also called congenital RN, is more commonly noted in infants with high-grade VUR, with a greater predominance of males. The second mechanism for development of kidney injury is the combination of VUR and repeated UTI, which is also

TABLE 62.3

Types of Kidney Damage Associated With VUR

	Congenital	Acquired
Time of occurrence	Often prenatal	Postnatal, sometimes in adulthood
Previous urinary infection	Not usually	Usually
Sex	Usually males	Usually females (particularly after infancy)
Grade of VUR	Usually grades IV and V	Grades IV and V less common
Kidney scarring	Often present	Present in minority[a]
Associated bladder dysfunction	Hypercontractile bladder common	Less commonly, high-capacity bladder with incomplete voiding

[a] Depends on unilateral versus bilateral involvement and the severity of kidney involvement.

VUR, Vesicoureteral reflux.

Modified from Kenda RB, Zupancic Z, Fettich JJ, Meglic A. A follow-up study of vesico-ureteric reflux and renal scars in asymptomatic siblings of children with reflux. Nucl Med Commun. 1997;18:827.

BOX 62.2

Clinical Presentations of Reflux Nephropathy

- Complicated urinary infection: usually acute pyelonephritis in infants and children
- Hypertension: may be accelerated
- During pregnancy: urinary infection, hypertension, preeclampsia
- Proteinuria
- Chronic reduction in glomerular filtration rate
- Urinary calculi
- Asymptomatic
- Detected in the workup of members of an affected family
- Detected by fetal ultrasound
- Detected during assessment of other urologic congenital abnormalities

called acquired RN. In these children, who are more commonly female, the combination of upper tract infection and reflux leads to kidney inflammation and permanent scarring. In one study, kidney cortical defects were seen on dimercaptosuccinic acid radionuclide scan (DMSA) in 45% of children with febrile UTI and VUR compared with

24% with UTI without VUR.15 Scarring is more commonly located at the upper and lower poles of the kidney because of the anatomy of the kidney papillae in these regions.

The risk for kidney damage is greatest in the presence of highgrade VUR.17 The Randomized Intervention for Vesicoureteral Reflux (RIVUR) trial also documented that the risk for new kidney scarring is higher in relatively older children and not in younger children as reported in the literature previously.17 Other recent studies have also shown that older children may be at higher risk of kidney scarring.18 19 One possible explanation for the higher incidence of kidney scarring in younger children is a lower threshold for diagnosing and investigating younger children with UTI compared with older children. Other risk factors for RN include duration of fever of longer than 72 hours before antibiotic initiation, recurrent UTI, and organisms other than Escherichia coli.

RN is diagnosed by using technetium-99m (99mTc)-labeled DMSA kidney scanning that demonstrates defects in the kidney outline.20 As noted previously, high-grade prenatal reflux can lead to kidney injury in the absence of infection. Unfortunately, kidney scarring secondary to UTI is indistinguishable by DMSA kidney scan from that caused by prenatal kidney dysplasia. In addition, kidney injury can be noted after febrile UTI in the absence of identified VUR. Kidney scarring as shown by 99mTc DMSA scan correlates more closely with the severity of VUR than with a history of UTI.21 The clinical manifestations of RN are varied and may include complicated UTI, hypertension, proteinuria, and various manifestations of CKD (Box 62.2).

The process of kidney scarring may take several years; in one study, the mean time from discovery of VUR to the appearance of a kidney scar was 6.1 years.22 Injury is seen more at the kidney poles and is associated with clubbed calyces with medullary and cortical damage. The injury results from the local inflammatory response that may persist with chronic inflammation, tubular injury, local fibroblast activation, and interstitial collagen deposition (Fig. 62.5).23 The loss of nephrons is associated with hyperfiltration and hypertension that can result in proteinuria and progressive loss of kidney function. This also can lead to the development of FSGS (Fig. 62.6).

Hypertension

Hypertension occurs in 10% to 30% of children and young adults with RN,24 25 and according to one study, hypertension may take 8 years to develop from the time of diagnosis.22 The exact cause of hypertension resulting from kidney scarring is not known, but it is thought to be caused by impaired sodium excretion resulting from the kidney injury and loss of kidney function. Hypertension is relatively uncommon in children with VUR, with an estimated probability of 2%, 6%, and 15% at 10, 15, and 21 years of age, respectively. However, hypertension increases in proportion to the degree of kidney injury.26 Kidney scarring (noted by DMSA scans) was reported in 20% of newly diagnosed hypertension in children and adolescents.27

Proteinuria

Patients also may present with mild to moderate or (rarely) nephroticrange proteinuria. Severe or nephrotic range proteinuria may suggest a histologic diagnosis of secondary FSGS, which can be confirmed by kidney biopsy if kidney size is normal and diagnosis is uncertain (see Fig. 62.6).28 Proteinuria is commonly associated with hypertension and kidney dysfunction. CKD progression often occurs gradually over 5 to 10 years.

Chronic Kidney Disease

According to the North American Pediatric Renal Transplant Cooperative Study annual report of 2008, 3.5% of the 6491 children on dialysis had RN, which makes it the fourth most common cause of ESKD in children after FSGS; kidney aplasia, hypoplasia, or dysplasia; and obstructive uropathy.29 The number of children with RN who present with ESKD as adults is not clear. According to one study of 123 adults with VUR diagnosed in childhood, the estimated glomerular filtration rate (eGFR) in those with nondilating VUR averaged 75 mL/1.73 m2 and in the dilating group, the average was 72 mL/1.73 m2; four patients (9%) in the nondilating group and 13 (17%) in the dilating group had an eGFR of less than 60 mL/1.73 m2 30 In a study that evaluated the clinical course of 735 children with primary VUR between 1970 to 2004, the probability of CKD was reported as 5% at compatible with the diagnosis were reported in 20% to 69% by ultrasound compared with 40% to 92% by DMSA scintigraphy.32

Kidney ultrasound is not diagnostic for VUR and is not a sensitive method for diagnosis of kidney scars. Nonetheless, a kidney ultrasound is useful to diagnose congenital anomalies of kidney and urinary tract and to detect complications of acute pyelonephritis such as kidney abscess or pyonephrosis.

Voiding Cystourethrography

Fig. 62.5 Histologic Changes in Reflux Nephropathy. Sclerosed glomeruli (arrows), chronic inflammatory cell infiltration, and atrophic tubules with eosinophilic casts are present. (H&E stain; original magnification ×40.)

Fig. 62.6 Focal Segmental Glomerulosclerosis (FSGS) in Reflux Nephropathy. Light microscopy of a glomerulus from a patient with reflux nephropathy shows FSGS with the scarred area marked by an asterisk. (H&E stain; original magnification ×400.)

10 years after diagnosis of VUR. For children diagnosed after 1990, the probability of CKD was only 2%, indicating that the prognosis for patients diagnosed with VUR may be improving over time. Another study by the same group evaluated independent predictive factors of CKD in children with severe bilateral grades III to V VUR. The authors found that the probability of CKD for patients with bilateral severe reflux was 15% by 10 years after VUR diagnosis. The three variables that were independently associated with CKD were age at diagnosis of greater than 24 months, VUR grade V, and bilateral kidney damage.26

Diagnosis of Vesicoureteral Reflux and Reflux Nephropathy

An algorithm for diagnosis of VUR after the discovery of UTI is shown in Fig. 62.4. However, this is not followed by all practitioners, partly because of other published guidelines and the possible usefulness of antimicrobial prophylaxis in VUR, as reported by the RIVUR study.31 An example of the various tests in a child with UTI and VUR is shown in Fig. 62.7

Kidney Ultrasound

Ultrasound is the initial modality for the evaluation of postnatal hydronephrosis and UTI in children. Ultrasound is also used in siblings of children with VUR to determine whether kidney dilation suggestive of high-grade reflux is present. Although ultrasound can suggest the possibility of high-grade VUR, it is not sensitive for diagnosis of acute pyelonephritis. In patients with acute pyelonephritis, abnormalities

VCU is the primary diagnostic modality for identification of VUR. It requires catheterization. The grading of VUR is based on radiographic appearance by VCU (see Fig. 62.1). In children with UTI, VCU should be performed as soon as the child has completed antibiotic therapy. The results of VCU can be affected by size, type, and position of the catheter; rate of bladder filling; height of the column of contrast media; state of hydration of the patient; and volume, temperature, and concentration of the contrast medium. These parameters are not currently measured in the grading system. Durability of grade also appears to be hampered by the variability of a radiologist interpretation of VCU images. In an analysis comparing the interpretation of two blinded RIVUR radiologists with a local radiologist’s interpretation, all three radiologists agreed on VUR grade in only 59% of ureters.2 Ureteral dilation may be present without calyceal dilation, leading to discrepancies with grading.33

Nuclear cystography has been used to reduce the radiation exposure for children during follow-up of VUR. Nuclear cystography, although more sensitive, does not permit specific grading of VUR or reveal other anatomic defects, such as ureterocele and diverticulum. Therefore, nuclear cystography is typically not the primary study performed for identification of VUR, but it is useful in determining improvement or resolution of reflux during follow-up or after surgical correction.

DMSA Kidney Scintigraphy

DMSA scintigraphy is currently the gold standard for diagnosis of acute pyelonephritis and kidney scarring with a high rate of sensitivity. Single-photon emission computed tomography (SPECT) DMSA scintigraphy is superior to planar imaging for detection of kidney cortical damage.34 35 The sensitivity of DMSA scintigraphy in experimentally induced acute pyelonephritis in a pig model was reported to be 92% when correlated with histologic findings.35 By use of standardized criteria for its interpretation, high levels of intraobserver and interobserver agreement were reported.36 37

An abnormal DMSA scan during a febrile UTI allows for the identification of children with kidney inflammation who are at risk for development of kidney scars. For acute pyelonephritis, DMSA scintigraphy can be performed within 2 to 4 weeks after the onset of UTI symptoms; however, it is not encouraged because it usually does not change clinical management. Some have suggested the use of DMSA scanning as an initial modality to identify children with abnormalities that may suggest the need for evaluation for VUR. DMSA scintigraphy to identify kidney scarring should be performed 6 months after acute infection to allow reversible lesions to resolve.38

Dysplasia secondary to congenital reflux will appear similarly to kidney scarring after postnatal infections. In a child presenting with VUR, obtaining a baseline DMSA kidney scan allows identification of kidney dysplasia and scarring, which can then be observed over time.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be used for the diagnosis of kidney scars because it discriminates swelling from scarring, both of which would be interpreted by DMSA scintigraphy as kidney scarring.

R

A

L

B

C

Fig. 62.7 Investigation of Reflux Nephropathy in a 3-Year-Old Child With Urinary Tract Infection. (A) Intravenous urogram showing calyceal diverticulum in the upper pole of the right kidney and kidney scarring in the upper pole and, probably, the lower pole of the left kidney. (B) Dimercaptosuccinic acid scintigraphy (posterior view) demonstrating upper and lower pole scarring (arrows) in the left kidney and scarring of the right upper kidney in association with the calyceal diverticulum (arrowhead). (C) Voiding cystourethrogram showing grade IV vesicoureteral reflux on the left.

MRI may diagnose other coexisting conditions, such as nephrolithiasis,[39] which is not diagnosed by DMSA scintigraphy. Newer imaging methods that show promise in diagnosis of kidney scarring include dynamic contrast-enhanced MRI and MRI using a gadoliniumenhanced short tau inversion recovery (STIR) sequence. However, routine use of MRI is less practical because of limited availability, especially for infants, need for prolonged sedation, and high cost. Gadolinium must be used with caution in the presence of significantly reduced glomerular filtration rate (< 30 mL/min/1.73 m^2).

Proteinuria as a Marker for Reflux Nephropathy

Proteinuria predicts CKD progression because of RN.[40] Persistent albuminuria is helpful in diagnosis of glomerular damage at an early stage. Albuminuria increases with increasing severity of VUR and kidney scarring.[41] In children with bilateral VUR with kidney scarring and normal creatinine clearance, mild albuminuria was detected in 54% of cases.[42] Evaluation for albuminuria offers the possibility of early intervention, such as the use of angiotensin-converting enzyme (ACE) inhibitors, aimed at retarding CKD progression. Severe albuminuria is usually associated with FSGS.

NATURAL HISTORY OF VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Primary VUR, especially grades I to III, generally improves with time. This is likely the result of growth and lengthening of the submucosal segment of the ureter. Spontaneous resolution of VUR is more common with non-White race, lower grades of reflux, absence of kidney damage, and lack of voiding dysfunction. Primary VUR diagnosed before 1 year of age has a high likelihood of resolution[18,43]; however, after 1 year of age, the initial grade of reflux at presentation may be more useful to predict resolution. One retrospective study found spontaneous resolution rates to be 72% and 61% for grade I and II, compared with 32% for grade IV/V.[43] According to some studies, the resolution of VUR occurs more slowly in children with bilateral VUR compared with a unilateral VUR. The mean time until spontaneous resolution in Black children was 15 months versus 21 months in White children.[6] Increasing age at presentation and bilateral VUR decrease the probability of resolution, and bilateral grade IV or grade V VUR has a particularly low potential for spontaneous resolution.

The natural history of VUR in adults has been reported in few studies. In one study of adults (mean age of 24 years) with gross VUR diagnosed in infancy, proteinuria and CKD were present in 3 of the 13 patients with unilateral RN and 2 of the 4 patients with bilateral RN.44 In another study of 127 adults (mean age of 41 years) with VUR diagnosed during childhood, 35% had unilateral kidney scarring, 24% had bilateral kidney scarring, 24% had albuminuria, and 11% had hypertension. Of the patients with bilateral kidney scars, 83% had reduced GFR.45 In a study in VUR patients who were operated on, those with mild to moderate VUR and minimal kidney scarring were likely to maintain a normal GFR in adult life, whereas patients with high-grade VUR and severe scarring were likely to develop progressive CKD.46 This suggests that the degree of kidney scarring rather than VUR grade after surgical management had the greatest correlation to progressive CKD.

Males with RN have worse outcomes compared with females. This difference has previously been attributed to a delayed diagnosis in males because of an insidious onset of proteinuria and kidney failure. In contrast, the diagnosis may be discovered earlier in females because of recurrent UTI and pregnancy-related complications. However, it is quite possible that the sex differences in adults may be because males are more likely to have congenital RN with kidney dysplasia, which may lead to greater kidney damage than acquired RN, which is seen more in females.16

TREATMENT

The management of VUR is based on the premise that VUR predisposes children to the development of recurrent UTI and kidney parenchymal

TABLE 62.4

Reflux

American Urologic Association Guidelines for Management of Vesicoureteral

Grade of VUR

I

II

III

IV

V

<1 yr without UTI
<1 yr with UTI
>1 yr without BBD or
UTI
>1 yr without BBD and
UTI
>1 yr with BBD and
without UTI

Consider CAP
CAP
Consider CAP

Consider CAP
CAP
Consider CAP

CAP
CAP
Consider CAP

CAP
CAP
Possible surgery

CAP
CAP
Possible surgery

CAP/possible surgery

CAP/possible surgery

CAP/possible surgery

CAP/possible surgery

CAP/possible surgery

Treat BBD/CAP

Treat BBD/CAP

Treat BBD/CAP/change
CAP

Treat BBD/CAP/change
CAP

Treat BBD/CAP/possible
surgery when BBD
improved
Treat BBD/CAP/change
CAP/possible surgery
when BBD improved

Treat BBD/CAP/possible
surgery when BBD
improved
Treat BBD/CAP/change
CAP/possible surgery
when BBD improved

Treat BBD/CAP/possible
surgery when BBD
improved
Treat BBD/CAP/change
CAP/possible surgery
when BBD improved

>1 yr with BBD and UTI

BBD, Bladder/bowel dysfunction; CAP, continuous antibiotic prophylaxis; possible surgery, injectable materials or reimplantation for lower grades and reimplantation for higher grades.
Modified from American Urological Association. Vesicoureteral reflux. https://www.auanet.org/guidelines-and-quality/guidelines/vesicoureteral-refluxguideline.

injury but also has the potential for spontaneous resolution. Various treatment strategies have been used with the ultimate objective of preventing kidney injury. The two main treatment modalities are long-term antimicrobial prophylaxis and surgical correction. Surgical correction of VUR was common until antimicrobial prophylaxis for childhood UTI was introduced in 1975.47 The International Reflux Study in Children (n = 306 patients) showed no significant difference in outcome between medical and surgical management in terms of the development of new kidney lesions or the progression of established kidney scars, although there was a lower incidence of pyelonephritis in the surgical arm.48

Medical Management

Medical management involves prompt antibiotic treatment of UTI, long-term antimicrobial prophylaxis, appropriate management of BBD if present, and follow-up VCU to assess the resolution of VUR and the potential development of kidney injury.

Antimicrobial Prophylaxis

The RIVUR trial revealed that trimethoprim-sulfamethoxazole (TMP/SMZ) prophylaxis reduced the risk of UTI recurrence by 50%.31 Similar results were reported by another placebo-controlled double-blind (PRIVENT study) trial.49 However, some other randomized studies have shown no beneficial effect with prophylaxis. Systematic reviews and meta-analyses have also reported mixed results. These variations in results have been attributed to significant differences in study designs, including patient inclusion and exclusion criteria.50 No study has demonstrated any beneficial effect of antimicrobial prophylaxis for the prevention of kidney scarring. However, none of these studies were powered to evaluate kidney scarring as the primary outcome.

The antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole, trimethoprim alone, nitrofurantoin, and cephalexin. During the first 2 months of life, it is advisable to avoid TMP-SMZ because it may worsen hyperbilirubinemia and promote neurotoxicity.

Antibiotic resistance is a major risk of long-term prophylaxis and hence should be used selectively. In cases with febrile UTI and VUR, the American Urological Association (AUA) recommends continuous antibiotic prophylaxis in children less than 1 year of age and a selective approach in older children based on patient age, severity of VUR, recurrence of UTI, presence of BBD, and kidney cortical anomalies[51] (Table 62.4). The other factors that should be considered before initiating long-term antimicrobial prophylaxis include status of toilet training, risk of antibiotic resistance, anticipated compliance with daily medication administration, and the parental choice. In some cases, preemptive antimicrobial prophylaxis may be necessary to lower the risk of first UTI, such as in those with high-grade VUR diagnosed during workup for antenatal hydronephrosis.

Follow-up of patients with VUR and UTI requires rapid evaluation with stringent techniques for collection of urine specimens for culture (within 48 hours of the onset of fever) to allow early detection and prompt treatment of UTI. The timing of follow-up VCU is not well defined, but studies have suggested time intervals of 12 to 24 months.

Some studies have challenged the benefit of long-term antimicrobial prophylaxis in the prevention of recurrent infection and kidney injury in patients with VUR[52,53] and have alternatively suggested surveillance only. Concerns have also been raised regarding the potential risks for long-term antibiotic use, including the possibility of development of resistance or allergy. These studies have been used as the basis for the 2011 AAP recommendations, suggesting that evaluation for identification of VUR be limited.

The 2011 AAP guideline has affected the diagnosis and decreased surgical management of VUR by resulting in fewer VCUs ordered overall in patients 2 to 24 months old, with significant decline in VCU performed in patients with UTI.[54] The incidence of VUR has also paralleled the decrease in rate of VCU performance.[55] In a retrospective study of children age 0 to 24 months who were evaluated with both kidney ultrasound and VCU, 17% of patients in the cohort had grade IV reflux with a normal kidney ultrasound.[56] Use of the 2011 guideline may have resulted in high-grade reflux being missed in this cohort of patients.

Management of Bladder and Bowel Dysfunction

The management of bladder and bowel dysfunction may include the use of laxatives and timed frequent voiding every 2 to 3 hours. Pelvic floor exercises, behavioral modification, or anticholinergic medication have also been successfully used. A combined conservative medical and computer game–assisted pelvic floor muscle retraining decreases the incidence of breakthrough UTI and may facilitate VUR resolution in children with both BBD and VUR. Treatment of constipation by dietary measures, behavioral therapy, and laxatives helps to reduce UTI recurrence and may resolve enuresis and uninhibited bladder contractions.

TABLE 62.5

Surgical Techniques for Vesicoureteral Reflux

Technique	Success Rate (%)	Pros	Cons
Open reimplantation	95	High success rates Limited requirement for follow-up VCU Reduction in hospital stays	Surgical incision Hospitalization required Catheters needed during postoperative management Need for pain control Expensive
Endoscopic injection of dextranomer and hyaluronidase (Deflux)	70–80	Reasonable success rates Outpatient management Minimal pain	Lower success rates Need for repeated procedures Need for follow-up VCU
Laparoscopic or robotic reimplantation	70–90	Reasonable success rates Small incisions Less discomfort	Lower success rates Requires hospitalization Need for follow-up VCU Long procedure Expensive equipment Significant surgical learning curve

VCU, Voiding cystourethrography.

Surgical Management

Surgical management of VUR is now reserved for patients in whom medical management with antimicrobial prophylaxis has failed to prevent UTIs. Current indications for surgical management of VUR are recurrent infections despite compliance with a prophylactic antibiotic regimen, worsening of kidney scars as judged by DMSA scanning, and failure to comply with prophylaxis. The recent introduction of minimally invasive surgery for VUR management has made some clinicians reconsider the benefits of surgical correction as a potential first-line therapy: immediate correction could potentially avoid the need for antibiotic prophylaxis in children. Although most surgical techniques have high success rates for the correction of reflux and have been shown to reduce the risk of pyelonephritis, lower tract infections have been shown to occur in 20% of children that have had successful surgical management.57 A review of surgical techniques is presented in Table 62.5

Prevention of Kidney Injury

Although prevention of kidney injury remains the focus for the management of VUR, no modality has been shown to be able to consistently prevent scarring. Even the large multi-institutional studies were unable to show benefit of prophylactic regimens for prevention of

scarring17 53 because this was not a primary study endpoint and follow-up was short. Surgical ablation of VUR has also not been shown to impact the incidence of kidney scarring even with reduction in upper tract infection.

Hypertension and Proteinuria

Appropriate management of hypertension and proteinuria includes the use of ACE inhibitors or angiotensin receptor blockers (ARBs) as in other kidney diseases (see Chapter 82). Combinations of ACE inhibitors and ARBs may allow further reductions in proteinuria compared with monotherapy.58 However, although the blood pressure control has been shown to have a beneficial effect on slowing CKD progression, the role of antiproteinuric effect in doing so is not well established. Because of the side effects of ACE inhibitors and ARBs, particularly hyperkalemia in CKD patients, we recommend monotherapy with appropriate monitoring. Combination therapy may be considered in CKD patients with poorly controlled blood pressure on monotherapy and a low risk of hyperkalemia. Historically, some patients also occasionally had their poorly functioning scarred kidney removed to help control hypertension, provided the contralateral kidney was healthy. However, this is exceptionally rare in recent times because of the availability of many potent antihypertensive agents.

SELF-ASSESSMENT QUESTIONS

1. Which imaging modality is used to diagnose vesicoureteral reflux?
A. Ultrasound
B. Voiding cystourethrogram
C. DMSA kidney scan
D. Magnetic resonance imaging
E. Computed tomography scan
2. Which of the following patients diagnosed with VUR would have the least likelihood of spontaneous resolution?
A. 2-year-old female with grade II reflux
B. 2-year-old female with grade IV reflux
C. 2-year-old male with grade II reflux
D. 6-year-old female with grade IV reflux
E. None of the above

3. Which of the following antibiotics would be an appropriate choice of prophylaxis for a 1-month-old female diagnosed with grade IV reflux?
A. Trimethoprim-sulfamethoxazole
B. Trimethoprim and amoxicillin
C. Nitrofurantoin
D. Cefalexin
E. All of the above
4. Complications of reflux nephropathy include which of the following?

A. Hypertension
B. Proteinuria
C. Progressive kidney failure
D. Pregnancy-related complications
E. All the above

REFERENCES

1. Lebowitz RL, Olbing H, Parkkulainen KV, et al. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol. 1985;15:105.
2. Schaeffer AJ, Greenfield SP, Ivanova A, et al. Reliability of grading of vesicoureteral reflux and other findings on voiding cystourethrography. J Pediatr Urol. 2017;13:192.
3. Gargollo PC, Diamond DA. Therapy insight: what nephrologists need to know about primary vesicoureteral reflux. Nat Clin Pract Nephrol. 2007;3:551.
4. Arena F, Romeo C, Cruccetti A, et al. Fetal vesicoureteral reflux: neonatal findings and follow-up study. Pediatr Med e Chir. 2001;23:31.
5. Noe HN. The long-term results of prospective sibling reflux screening. J Urol. 1992;148:1739.
6. Skoog SJ, Belman AB. Primary vesicoureteral reflux in the black child. Pediatrics. 1991;87:538.
7. Shefelbine SE, Khorana S, Schultz PN, et al. Mutational analysis of the GDNF/RET-GDNFR alpha signaling complex in a kindred with vesicoureteral reflux. Hum Genet. 1998;102:474.
8. Papachristou F, Printza N, Kavaki D, Koliakos G. The characteristics and outcome of primary vesicoureteric reflux diagnosed in the first year of life. Int J Clin Pract. 2006;60:829.
9. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection:clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128(3):595–610.
10. Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol. 1998;160:1019.
11. Kenda RB, Zupancic Z, Fettich JJ, Meglic A. A follow-up study of vesicoureteric reflux and renal scars in asymptomatic siblings of children with reflux. Nucl Med Commun. 1997;18:827.
12. Attini R, Kooij I, Montersino B, et al. Reflux nephropathy and the risk of preeclampsia and of other adverse pregnancy-related outcomes: a systematic review and meta-analysis of case series and reports in the new millennium. Journal of nephrology. 2018;31:833.
13. Roihuvuo-Leskinen HM, Vainio MI, Niskanen KM, Lahdes-Vasama TT. Pregnancies in women with childhood vesicoureteral reflux. Acta Obstet Gynecol Scand. 2015;94:847.
14. Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol. 1973;1:132.
15. Ditchfield MR, de Campo JF, Nolan TM, et al. Risk factors in the development of early renal cortical defects in children with urinary tract infection. AJR Am J Roentgenol. 1994;162:1393.
16. Mattoo TK. Vesicoureteral reflux and reflux nephropathy. Adv Chronic Kidney Dis. 2011;18:348.
17. Mattoo TK, Chesney RW, Greenfield SP, et al. RIVUR trial Investigators. Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. Clin J Am Soc Nephrol. 2016;11(1):54–61.
18. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with Individual patient data. JAMA Pediatr. 2014;168(10):893–900.
19. Snodgrass WT, Shah A, Yang M, et al. Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. J Pediatr Urol. 2013;9(6 Pt A):856–863.
20. Wennerström M, Hansson S, Jodal U, Stokland E. Primary and acquired renal scarring in boys and girls with urinary tract infection. J Pediatr. 2000;136:30.
21. Pennesi M, Travan L, Peratoner L, et al. North East Italy Prophylaxis in

VUR study group: is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics. 2008;121:e1489.

22. Shindo S, Bernstein J, Arant Jr BS. Evolution of renal segmental atrophy (Ask-Upmark kidney) in children with vesicoureteric reflux: radiographic and morphologic studies. J Pediatr. 1983;102:847.
23. Eddy AA. Interstitial macrophages as mediators of renal fibrosis. Exp Nephrol. 1995;3:76.
24. Smellie JM, Prescod NP, Shaw PJ, et al. Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. Pediatr Nephrol. 1998;12:727.
25. Wallace DM, Rothwell DL, Williams DI. The long-term follow-up of surgically treated vesicoureteric reflux. Br J Urol. 1978;50:479.
26. Silva JM, Santos Diniz JS, Marino VS, et al. Clinical course of 735 children and adolescents with primary vesicoureteral reflux. Pediatr Nephrol. 2006;21:981.
27. Ahmed M, et al. Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children. Pediatr Nephrol. 2008;23(3):435.
28. Morita M, Yoshiara S, White RH, Raafat F. The glomerular changes in children with reflux nephropathy. J Pathol. 1990;162:245.
29. 2008 annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), p 8-5.
30. Roihuvuo-Leskinen H, Lahdes-Vasama T, Niskanen K, Ronnholm K. The association of adult kidney size with childhood vesicoureteral reflux. Pediatr Nephrol. 2013;28:77.
31. Hoberman A, Chesney RW, RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;371(11):1072.
32. Lavocat MP, Granjon D, Allard D, et al. Imaging of pyelonephritis. Pediatr Radiol. 1997;27:159.
33. Logvinenko T, Chow JS, Nelson CP. Predictive value of specific ultrasound findings when used as a screening test for abnormalities on VCUG. J Pediatr Urol. 2015;11:176.
34. Applegate KE, Connolly LP, Davis RT, et al. A prospective comparison of high-resolution planar, pinhole, and triple-detector SPECT for the detection of renal cortical defects. Clin Nucl Med. 1997;22:673.
35. Majd M, Nussbaum Blask AR, Markle BM, et al. Acute pyelonephritis: comparison of diagnosis with 99mTc-DMSA, SPECT, spiral CT, MR imaging, and power Doppler US in an experimental pig model. Radiology. 2001;218:101.
36. Patel K, Charron M, Hoberman A, et al. Intra- and interobserver variability in interpretation of DMSA scans using a set of standardized criteria. Pediatr Radiol. 1993;23:506.
37. Mattoo TK, Skoog SJ, Gravens-Mueller L, et al. Interobserver variability for interpretation of DMSA scans in the RIVUR trial. J Pediatr Urol. 2017;13(6):616.e1–e6.
38. Stokland E, Hellstrom M, Jakobsson B, et al. Imaging of renal scarring. Acta Paediatr suppl. 1999;88:13.
39. Kavanagh EC, Ryan S, Awan A, et al. Can MRI replace DMSA in the detection of renal parenchymal defects in children with urinary tract infections? Pediatr Radiol. 2005;35:275.
40. Torres VE, Velosa JA, Holley KE, et al. The progression of vesicoureteral reflux nephropathy. Ann Intern Med. 1980;92:776.
41. Bell FG, Wilkin TJ, Atwell JD. Microproteinuria in children with vesicoureteric reflux. Br J Urol. 1986;58:605.
42. Coppo R, Porcellini MG, Gianoglio B, et al. Glomerular permselectivity to macromolecules in reflux nephropathy: microalbuminuria during acute hyperfiltration due to amino acid infusion. Clin Nephrol. 1993;40:299.
43. Estrada Jr CR, Passerotti CC, Graham DA, et al. Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. J Urol. 2009;182:1535.
44. Bailey RR, Lynn KL, Smith AH. Long-term followup of infants with gross vesicoureteral reflux. J Urol. 1992;148:1709.

45. Lahdes-Vasama T, Niskanen K, Ronnholm K. Outcome of kidneys in patients treated for vesicoureteral reflux (VUR) during childhood. Nephrol Dial Transplant. 2006;21:2491.

46. Matsuoka H, Tanaka M, Yamaguchi T, et al. The long-term prognosis of nephropathy in operated reflux. J Pediatr Urol. 2019;15:605. e1.

47. Grüneberg RN, Leakey A, Bendall MJ, Smellie JM. Bowel flora in urinary tract infection: effect of chemotherapy with special reference to cotrimoxazole. Kidney Int suppl. 1975;4:S122.

References

48. Smellie JM, Tamminen-Mobius T, Olbing H, et al. Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings. The International Reflux Study in Children. Pediatr Nephrol. 1992;6:223.
49. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med. 2009;361:1748.
50. Mattoo TK, Carpenter MA, Moxey-Mims M, Chesney RW. The RIVUR trial: a factual interpretation of our data. Pediatr Nephrol. 2015.
51. Peters C, Skoog SJ, Arant BS, et al. Management and Screening of Primary Vesicoureteral Reflux in Children; 2010. amended 2017) https://www.auanet.org/guidelines/vesicoureteral-reflux-guideline 2017.
52. Roussey-Kesler G, Gadjos V, Idres N, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol. 2008;179:674.
53. Garin EH, Olavarria F, Garcia Nieto V, et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics. 2006;117:626.
54. Garcia-Roig M, Travers C, McCracken CE, Kirsch AJ. National Trends in the management of primary vesicoureteral reflux in children. J Urol. 2018;199:287.
55. Lee T, Ellimoottil C, Marchetti KA, et al. Impact of clinical guidelines on voiding cystourethrogram Use and vesicoureteral reflux incidence. J Urol. 2018;199:831.
56. Suson KD, Mathews R. Evaluation of children with urinary tract infectionimpact of the 2011 AAP guidelines on the diagnosis of vesicoureteral reflux using a historical series. J Pediatr Urol. 2014;10:182.
57. Yu TJ, Chen WF. Surgical management of grades III and IV primary vesicoureteral reflux in children with and without acute pyelonephritis as breakthrough infections: a comparative analysis. J Urol. 1997;157:1404.
58. Litwin M, Grenda R, Sladowska J, Antoniewicz J. Add-on therapy with angiotensin II receptor 1 blocker in children with chronic kidney disease already treated with angiotensin-converting enzyme inhibitors. Pediatr Nephrol. 2006;21:1716.

63

Urologic Issues for the Nephrologist

Ross M. Warner, J. Kilian Mellon

Medical management of nephrolithiasis is discussed in Chapter 60. The surgical management of urinary tract stones has been transformed by the introduction of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and ureteroscopy. These advances mean that open stone surgery is now a final resort when other modalities have been exhausted or are contraindicated. Table 63.1 details the use of different treatment modalities over time since the introduction of newer techniques.1 As familiarity with the available techniques and technology has developed, standardized treatment strategies have evolved and guidelines have been introduced.2 3 4 However, the optimal treatment for certain patients with kidney stones remains controversial, especially lower pole stones.

adequate analgesia, persistent obstruction with risk for impaired kidney function (e.g., with preexisting kidney impairment or in a single kidney), bilateral obstruction, or associated urinary tract sepsis. In the absence of an acute indication for surgical management, medical expulsive therapy (MET), such as tamsulosin (an alpha blocker) 400 µg once daily or nifedipine (calcium channel blocker) 30 mg once daily, is sometimes used to aid stone passage, particularly for distal ureteral stones, although the data on the efficacy of this are mixed. A recent U.K. study (the largest randomized controlled trial [RCT] of MET) demonstrated no significant benefit of this therapy.6 This was supported by the MIMIC study.5 In contrast, data from several meta-analyses of RCTs suggest that MET is beneficial for management of distal ureteral stones less than 10 mm.4 7 8 Therefore, MET for small distal ureteral stones is still recommended in most guidelines.2 3 4 Opinion among urologists remains divided. Another conservative approach is chemolysis because several stone types are, in principle, amenable to dissolution by oral medications or by direct instillation of chemical solutions. However, chemolysis is only effective for uric acid stones and some drug-induced calculi, which can be readily dissolved by alkalization of the urine, usually with oral potassium citrate, or with sodium bicarbonate solution instilled directly into the urinary tract via a percutaneous nephrostomy (PCN) tube.

Improvements in Imaging

Acute Surgical Intervention

Unenhanced computed tomography (CT) scanning of the abdomen and pelvis has replaced intravenous urography (IVU) as the standard imaging modality for stone diagnosis (Fig. 63.1). CT is readily available, quicker to perform, offers increased sensitivity compared with IVU (99% vs. 70%), and avoids the need for intravenous (IV) contrast. An additional advantage is that CT can demonstrate radiolucent stones (mainly uric acid and xanthine stones) and detect concomitant lesions and/or alternative diagnoses. CT requires an increased radiation dose, but this is less of an issue with modern equipment and newer radiation protocols. Comparative doses are 2.5 mSv for IVU, 5 mSv for standard non–contrast-enhanced CT, and 2 mSv for low-dose non–contrastenhanced CT.

The goals of acute surgical intervention are to relieve obstruction and, if feasible, to remove the calculus. If the patient is well enough for general anesthesia, ureteroscopic stone destruction using laser lithotripsy can be attempted. Alternatively, a double-J stent (a ureteral stent with two coiled ends) can be inserted to relieve obstruction until definitive treatment is performed (Fig. 63.2). Acute ESWL is increasingly being used for ureteral stones in stable patients with adequate pain relief and without superimposed infection. However, in the setting of uncontrolled urinary tract infection (UTI) resulting from an obstructing stone, decompression of the urinary tract and free drainage of urine are the priorities. Evidence suggests little difference in the outcomes whether an antegrade (i.e., PCN) or retrograde (i.e., double-J stent) is used.9 However, PCN is generally the preferred option (when not contraindicated) because it can be performed with local anesthesia and is less likely than endoscopic surgery to cause bacteremia (Fig. 63.3).

Close interaction between nephrologists and urologists is crucial to the optimal management of several common clinical problems. A proper understanding of urologic strategies helps the nephrologist to ensure that patients with these problems are given clear information and are optimally managed. Areas in which such coordinated work is most important include the management of stone disease, the surgical approach to urinary tract obstruction, the investigation of hematuria, and the management of urinary tract malignant neoplasms.

ADVANCES IN MANAGEMENT OF KIDNEY STONES

Conservative (Nonsurgical) Management

Spontaneous stone passage can be expected in up to 80% of patients with stones smaller than 4 mm. Conversely, for stones with a diameter of more than 7 mm, the chance of spontaneous stone passage is very low. Recent data from the MIMIC study, a multicenter retrospective cohort study of 4170 patients in 71 institutions across four countries, suggests a chance of just 29%.5 The location is also important; up to 70% of distal ureteral stones pass spontaneously, in contrast to only 45% of midureteral and 25% of proximal ureteral stones. Intervention is recommended when there is persistent pain (>72 hours) despite

Elective Surgical Intervention

Extracorporeal Shock Wave Lithotripsy

During ESWL, acoustic shock wave energy is delivered to a stone under fluoroscopic and/or ultrasound guidance. Treatment sessions typically last about 30 minutes, during which 1500 to 2500 shock waves are delivered. Treatment is given to outpatients under analgesia or IV sedation and can be repeated at intervals of 10 to 14 days. Stones up

TABLE 63.1 Changing Use of Techniques for Stone Removal

	1984	1990	1999
Location (%)			
Calyceal stones	35	43	46
Pelvic stones	42	20	13
Staghorn stones	8	3	1
Ureteral stones	15	34	40
Treatment Modality (%)			
ESWL	60	79	78
PCNL	20	5	2
Ureteroscopy	11	15	20
Open surgery	9	1	0.1

ESWL, Extracorporeal shock wave lithotripsy; PCNL, percutaneous nephrolithotomy.

Data from Rassweiler JJ, Renner C, Eisenberger F. The management of complex renal stones. BJU Int. 2000;86:919–928.

Fig. 63.3 Nephrostogram in Ureteral Obstruction Caused by a Stone. Contrast material is injected through a percutaneous nephrostomy tube placed in the lower pole calyx (arrow). The contrast material outlines a single large calculus (arrowheads) producing complete obstruction at the pelviureteral junction.

Fig. 63.1 Computed Tomography Scan Demonstrating a Ureteral Calculus. Non–contrast-enhanced scan showing a calculus (arrow) at the right vesicoureteral junction.

to 20 mm in size can be treated effectively, and stone-free rates of 60% to 98% have been reported. However, ESWL is operator dependent, and outcome is influenced by the size, composition, and location of the stone and the type of lithotripter used. Cystine and calcium oxalate monohydrate stones are especially resistant. Targeting of the stone may be impossible in the presence of obesity and skeletal deformities (increased skin-to-stone distance), and ESWL is contraindicated in patients with aortic or renal artery aneurysm, uncontrolled UTI, coagulation disorders/receiving anticoagulation treatment, pregnant persons, and obstruction distal to the stone being treated.

A double-J ureteral stent is sometimes placed endoscopically before ESWL treatment to prevent stone fragments from obstructing the distal ureter (Steinstrasse, literally “stone street”; Fig. 63.4). Other acute complications of ESWL include hemorrhage or hematoma, infection, and injury to adjacent organs. The risk for hypertension or reduced glomerular filtration rate (GFR) as sequelae of ESWL is controversial.

Percutaneous Nephrolithotomy

Fig. 63.2 Ureteral Stenting. Plain radiograph showing a double-J stent in the left ureter. Note that the curled ends of the stent remain in the pelvis despite ureteral peristalsis.

During PCNL, a tract through the kidney parenchyma is created between the skin and the collecting system of the kidney. A sheath within this tract is used as a working channel to remove stones under direct vision using a nephroscope. Preoperatively, CT imaging is used to localize calculi and neighboring organs (e.g., spleen, liver, large bowel, pleura, or lungs) and to plan access. The most frequently used access site is the dorsal calyx of the lower pole, and stone fragmentation is undertaken by ultrasound, pneumatic, or laser devices. With technologic advances, performing this procedure through smaller access sheaths (<18 Fr compared with standard 30 Fr sheaths) with fewer complications and equivalent stone clearance rates is becoming feasible.10 The PCNL technique is modified for special circumstances, usually by altering the site of puncture (e.g., directly into a calyceal diverticulum) or, if there are ureteral stones, by using a higher placed puncture to permit antegrade ureteroscopy. The percutaneous puncture may be facilitated by the preliminary placement of a retrograde ureteral catheter to dilate and opacify the collecting system, which is then punctured under fluoroscopy with or without ultrasound

Indications for Percutaneous Nephrolithotomy

TABLE 63.2

A

B

Fig. 63.4 Extracorporeal Shock Wave Lithotripsy (ESWL) Complicated by Stone Fragments Obstructing the Distal Ureter. (A) Preoperative plain radiograph showing stones in the left kidney pelvis. (B) After ESWL, note the disappearance of the pelvic stone, the string of stone fragments throughout the length of the ureter, and the double-J ureteral stent placed to facilitate their passage.

guidance. After completion of PCNL, there are a number of options to aid urinary drainage. These include ureteral stents (placed antegradely or retrogradely), “pig-tail” nephrostomy tubes, or a self-retaining balloon nephrostomy tube to tamponade the tract and provide further access if needed. Hemorrhage can complicate PCNL (from intrarenal or, rarely, intercostal/subcostal arteries) and usually can be treated conservatively or by selective angiographic embolization. Other complications include sepsis; fluid overload (similar to transurethral resection syndrome); injury to spleen, pleura, or colon; and extravasation.

PCNL usually results in minimal parenchymal injury, averaging only 0.15% of the total kidney cortex.11

Indications for PCNL are shown in Table 63.2. These continue to evolve and are being challenged by developments in ureteroscopic techniques, which are allowing more upper ureteral and renal pelvic stones to be dealt with by a retrograde approach.

ESWL is the first-line treatment for more than 75% of stone patients that require an intervention. Table 63.2 shows circumstances in which ESWL is less effective and PCNL becomes the preferred approach or a combination of the two modalities is used. For lower pole stones in particular, ESWL may not provide optimal clearance because of problems with the drainage of residual fragments. An RCT has shown that for lower pole stones greater than 10 mm, PCNL has much better clearance rates than ESWL (92% vs. 23%).12

Open Stone Surgery

Open surgery still has a place in the treatment of stone disease. Approximately 2% of stone patients are now treated with open surgery, mainly when anatomic factors preclude the use of minimally invasive methods or when these techniques have failed. Other indications include complex stone burden, the presence of intrarenal anatomic abnormalities (e.g., pelviureteral junction [PUJ] obstruction), and stones within a nonfunctioning kidney where nephrectomy may

Compositiona

Struvite stones

Stone position

Calcium oxalate
monohydrate stones
Cystine stones
Lower pole stones

Anatomic
abnormalities
Patient
characteristics

PUJ obstruction
Calyceal diverticula
Morbid obesity
Ureteral obstruction

Complete removal necessary
to eliminate infection and
minimize stone recurrence
Difficult to pulverize by ESWL
Difficult to pulverize by ESWL
Fragments less easily
evacuated from dependent
lower pole calyces,
especially if collecting
system dilated
Prevent passage of fragments
after ESWL
Stone cannot be placed in focal
point of ESWL machine

ESWL is the first choice for stone intervention, except in those circumstances that may favor PCNL.

[a] Stone composition can be defined with certainty only by direct stone analysis, but advances in imaging may ultimately provide a means to accurately assess stone composition in situ before treatment, thus allowing the urologist to select the treatment most likely to be successful.

ESWL, Extracorporeal shock wave lithotripsy; PCNL, percutaneous nephrolithotomy; PUJ, pelviureteral junction.

be more appropriate. During surgery the kidney pelvis and the parenchyma can be opened along avascular planes, and clamping of the kidney vessels and hypothermia of the kidney may be needed. In selected patients a laparoscopic or robot-assisted approach can be used for the treatment of stone disease.

Ureteroscopy

Continued advances in the design of endoscopes for ureteronephroscopy have rendered the entire urinary tract accessible to endoscopic examination and manipulation. Ureteroscopes may be semirigid or flexible, the latter allowing access to the renal pelvis and calyces. Stone fragmentation is achieved ideally by laser but also by ultrasound or pneumatic devices (lithoclast). Laser use is equally effective for all types of stones and has the additional advantages of a flexible fiber (allowing intrarenal stone fragmentation), low tissue penetration, and minimal stone displacement during use. Success rates for laser fragmentation of ureteral stones are approximately 80%. Fig. 63.5 highlights the increasing use of ureteroscopy in stone disease and also the increasing proportion of procedures in which a laser rather than ultrasound or a lithoclast is used to achieve stone fragmentation.

For lower pole kidney stones, although flexible ureteroscopes can access the lower pole to facilitate treatment, the stone-free rate in comparative studies is similar to that of ESWL.[13] [14] Furthermore, patients often prefer ESWL as the initial therapy compared with flexible ureterorenoscopy and lasertripsy. In the event of failed stone clearance after ureteroscopy, PCNL is commonly used next and is likely to remain an essential treatment for lower pole stones. Complications of ureteroscopy, particularly with use of graspers and baskets, include ureteral avulsion, perforation, extravasation, mucosal damage, hematuria, infection, and stricture. Advances in laser technology now enable stones to be reduced to dust-like particles, reducing the need for graspers and baskets and hence reducing complications.

A summary of the elective surgical management of nonobstructing kidney stones is shown in Table 63.3

100%

4,500

90%

4,000

80%

3,500

70%

3,000

60%
2,500
50%
2,000
40%
1,500

30%

1,000

20%

500

10%
0%

Total number of endoscopic procedures performed

Relative proportion of techniques used to fragment stones

Changing Use of Endoscopy to Achieve Stone Fragmentation

0
2001

2002

2003

2004

2005

2006

Endoscopic ultrasound procedures

2007

2008

2009

2010

2011

Endoscopic lithoclast procedures

Endoscopic laser treatment
Total endoscopic procedures

Fig. 63.5 Changing Use of Endoscopy to Achieve Stone Fragmentation. Chart showing the increasing use of endoscopy in stone surgery in addition to the increasing proportion of cases using lasers to achieve stone fragmentation. (Data from UK Hospital Episode Statistics dataset, http://www.hscic.gov.uk/hes.)

TABLE 63.3 Surgical Management of Intrarenal Stones

Stone Characteristic	First-Line Treatment Modality
Nonlower pole stone <20 mm	ESWL or URS
Nonlower pole stone >20 mm	PCNL
Lower pole stone <10 mm	ESWL or URS
Lower pole stone >10 mm	PCNL or URS

ESWL, Extracorporeal shockwave lithotripsy; PCNL, percutaneous nephrolithotomy; URS, ureteroscopy.

Data from Assimos D, Krambeck A, Miller N, et al. American Urological Association/Endourological Society Guideline: Surgical management of Stones, 2016. https://www.auanet.org/guidelines/kidney-stonessurgical-management-guideline.

Management of Staghorn Calculus

A staghorn calculus usually should be managed by intervention because reports of conservative therapy show a high rate of eventual nephrectomy (up to 50%) and an increase in associated morbidity (mainly kidney failure) and mortality (up to 28%). Patient age and GFR heavily influence treatment decision making. The primary treatment option for staghorn calculi in a patient with preserved kidney function is PCNL. For a staghorn calculus in a nonfunctioning kidney, partial or total nephrectomy may be indicated. ESWL or ureteroscopic stone removal alone are rarely effective for large staghorn calculi but can be used as an adjunct to PCNL to achieve total stone clearance. The advantage of a multimodal approach is the reduced need for additional access to the kidney and secondary PCNL. Consequently, endoscopic combined intrarenal surgery (ECIRS; i.e., retrograde flexible ureterorenoscopy and PCNL) is becoming more commonplace. Very rarely, open surgical removal of the stone may be indicated.

Stones in Transplanted Kidneys

The management of stone disease in a transplanted kidney is challenging because of the solitary kidney, the anatomic location within the pelvis, and the difficulty with retrograde access to the ureter and kidney. Early active intervention is indicated; prophylactic stenting, ureteroscopy, and PCNL are preferred to ESWL because stone targeting may not be possible. Open surgery may be needed in selected cases.

URINARY TRACT OBSTRUCTION

General Aspect

The causes of upper tract obstruction are listed in Chapter 61 (see Box 61.2), as is a summary of the management of obstruction (see Fig. 61.7). Upper tract obstruction caused by malignancy can be a result of direct tumor invasion, external compression by metastatic lymph node involvement or, rarely, true metastasis to the ureter. About 70% of tumors causing ureteral obstruction are genitourinary (cervical, bladder, prostate) in origin; breast and gastrointestinal carcinomas and lymphoma constitute the majority of the remainder.15 The presentation of a patient with obstruction may vary significantly, and hydronephrosis may develop progressively and insidiously and remain unrecognized until the patient develops anuria and uremia. Upper tract obstruction from malignancy rarely manifests with classic acute ureteral colic, which is typically seen with a benign cause such as a stone. Therefore, these patients often present first to a nephrologist because of an asymptomatic decline in GFR.

Bladder outflow obstruction may be acute and dramatic or chronic with few or no symptoms. To aid in understanding of the immediate needs and longer-term prognosis of these patients, the acute and the definitive management of the most common urologic diseases associated with obstruction and reduced GFR are outlined.

Acute Management

Relief of obstruction is crucial to reverse kidney impairment and preserve remaining kidney function. In cases of bladder outflow obstruction, a urethral or suprapubic catheter is indicated, whereas in upper tract obstruction, a double-J stent stent is preferable, when possible. The most straightforward approach is endoscopic retrograde placement under fluoroscopy, with PCN reserved for patients in whom the procedure fails. Bilateral stents should be placed if technically possible. However, tumor infiltration can distort trigonal anatomy, making identification of ureteral orifices for double-J stent insertion impossible at the time of cystoscopy. Furthermore, it has been suggested that stents fail to relieve obstruction in 40% to 50% of cases of external ureteral compression. Thus, these patients need to be closely monitored to ensure resolution of the obstruction. Alternatives include placing two stents within each obstructed ureter16 and a metallic, self-expanding stent, used alone or in conjunction with double-J stents, which has had good initial results in maintaining ureteral patency and avoiding PCN, in malignant ureteral obstruction.17

A stable patient with obstruction but without signs of sepsis is a candidate for attempted retrograde stent placement with use of general anesthesia. However, in a patient with sepsis, endoscopic manipulation can lead to bacteremia and septic shock. Furthermore, such patients may not be fit for general anesthesia, in which case the preferred initial approach is PCN, which can then be followed, after an interval, with antegrade ureteral stenting. The success rate of this combined approach is high (>90%).18 In patients with bilateral ureteral obstruction, it is not always necessary to insert bilateral PCN tubes. Significant palliation and return to nearly normal GFR can be accomplished by drainage of the kidney with the betterpreserved parenchyma as determined by CT scan or ultrasound.

Once they have been placed, PCN tubes or double-J stents need to be replaced every 3 to 6 months. If they are left for a longer period, they become increasingly brittle and encrusted and are liable to block or fracture under manipulation. Complications of ureteral stents include migration, obstruction with proteinaceous material, infection, fragmentation, and, rarely, erosion through the urinary tract.19 As many as 70% of patients with stents report lower urinary tract symptoms, mainly urgency, frequency, and nocturia, as well as pain along the urinary tract.

Morbidity after stenting or PCN is similar.20 The main problem with indwelling stents is the increased risk for recurrent obstruction (11% for stents vs. 1% for PCN). PCN may have an increased infection rate, and there may be psychological issues relating to the need for an external drainage bag. They are also more liable to displace. An alternative to attempt to offset this is the nephroureteral stent (otherwise referred to as a nephroureterostomy).21 Placed antegradely, a single stent with a coil in the bladder and further coil in the kidney pelvis then continues and exits percutaneously to drain into an external nephrostomy bag.

Fig. 63.6 Extraanatomic Stenting for Malignant Ureteral Obstruction. Plain radiograph showing placement of an extraanatomic stent for malignant obstruction of the right ureter. The upper end of the double-J stent has been placed in the right kidney pelvis (arrow). The stent then runs through a subcutaneous tunnel before the lower end enters the bladder (arrowhead).

Extra-anatomic stents are an alternative for patients in whom conventional stent insertion has failed or for whom permanent nephrostomy drainage is unacceptable. An extra-anatomic stent is placed by an initial percutaneous puncture and insertion of the upper end of a long (50-cm) double-J stent into the kidney. A subcutaneous tunnel is then created to bring the stent to the level of the iliac crest. Another tunnel is fashioned to bring the lower end of the stent out suprapubically, followed, finally, by suprapubic puncture of a full bladder and insertion of the lower end (Fig. 63.6).22 Extra-anatomic stents are usually changed at 6-month intervals, and preliminary experience confirms their value in maintaining ureteral patency and avoiding PCN. Because of the effectiveness of minimally invasive methods, open surgery today is rarely indicated in the acute setting.

SPECIFIC TYPES OF OBSTRUCTION

Pelviureteral Junction Obstruction

Surgical management of PUJ obstruction is aimed at obliterating the redundant (aperistaltic) portion of the ureter, allowing normalization of drainage from the affected kidney. The need for treatment is heralded by the onset of pain, infection, calculus formation, decline in GFR, or proven impaired excretion on mercaptoacetyltriglycine (MAG3) renography. The gold standard treatment is now laparoscopic or robotic pyeloplasty, although traditional open techniques are still used. Endoscopic (endopyelotomy) treatments are also performed in some centers. However, in treatment-naïve patients, endopyelotomy has inferior outcomes compared with pyeloplasty.23 24

Retroperitoneal Fibrosis

Retroperitoneal fibrosis can be treated medically or surgically. A causative factor should be excluded (see Chapter 61). There are reports of favorable outcomes after immunosuppression with high doses of corticosteroids or azathioprine/mycophenolate mofetil/rituximab. Alternatively, surgery, consisting of ureterolysis (freeing the ureters from the fibrotic plaques) and omentoplasty (transposition of the ureters into the peritoneal cavity in omental wraps), can have good longterm results.

Percutaneous Nephrostomy
for Malignant Obstructive Uropathy a

TABLE 63.4

Malignant Obstruction

For upper tract transitional cell carcinoma, acute obstruction is best treated by internal stenting. PCN is avoided because of the risk of tumor seeding. Upper tract transitional cell carcinoma is an aggressive tumor and necessitates prompt extirpative surgery.

Bladder cancer can lead to hydronephrosis by invading the ureteral orifices and intramural ureters. In the absence of metastatic disease, radical cystectomy is indicated, although temporary ureteral decompression may normalize GFR if neoadjuvant chemotherapy is planned.

In selected cases, bladder preservation strategies combining systemic chemotherapy and radiotherapy can offer long-term control of the disease.

Prostate cancer causes obstruction by occluding the urethra or invading the ureteral orifices. Hormonal treatment can shrink prostatic tissue and malignant deposits and offer long-term remission of symptoms. Limited resection of the prostate may sometimes be indicated.

The decision to offer ureteral decompression for upper tract obstruction caused by cancer is not straightforward and requires input not only from the urologist but also from colleagues in radiation and medical oncology and the palliative care team. There must also be careful discussion of the options with the patient and family.

Ureteral decompression is justified when radiotherapy and systemic chemotherapy remain therapeutic options after improvement in GFR but also may be justified for palliation of pain or ongoing renal tract sepsis.

A review of patients undergoing PCN for obstructive uropathy secondary to pelvic malignancy identified a subset with very poor survival in whom ureteral decompression is usually not justified (Table 63.4).25 Patients with gastric or pancreatic cancer survive a median of only 1.4 months after ureteral decompression.26 In another report, the average survival of patients with advanced malignant neoplasms undergoing endourologic diversion was only 5 months, half of which time was spent in the hospital.27 A more recent review suggests a median survival of 6.4 months for all-cause malignant ureteral obstruction and a complication rate as high as 41%.28

Benign Ureteral Strictures

These can be secondary to stone disease, iatrogenic, or caused by various benign diseases. The treatment of choice is endoscopic balloon dilation or ureterotomy. Open surgical repair or major reconstructive surgery may be needed in cases of recurrent strictures.

Hydronephrosis of Pregnancy

Hydronephrosis occurs in the majority of pregnant persons, typically seen from 6 to 10 weeks of gestation onward. It is caused by both mechanical obstruction from the gravid uterus and dilated ovarian venous plexus and a reduction in peristalsis caused by increasing levels of progesterone leading to smooth muscle relaxation. Resolution typically occurs within a few weeks of delivery but can take up to 3 months.

Females are usually asymptomatic with little or no impact on GFR, but they can provide a diagnostic dilemma if presenting with loin pain. Differentiating between a physiologic hydronephrosis and one caused by ureteral obstruction secondary to a stone can be a challenge because the use of ionizing radiation is to be avoided.

Bladder Outflow Obstruction

Bladder outflow obstruction in males is most frequently caused by either benign or malignant prostatic enlargement. Common presentations of

Group I: primary untreated malignancy
Group II: recurrent malignancy with further treatment
Group III: recurrent malignancy with no further treatment
Group IV: benign disease as a result of previous treatment
Overall

Median Survival (wk)

5-Year Survival Rate (%)

27

10

20

20

6.5
Not stated

None survived >1 year
64

26

22

[a]Outcome in 77 patients undergoing percutaneous nephrostomy for obstructive uropathy secondary to pelvic malignant disease.
Data from Lau MW, Temperley DE, Mehta S, et al. Urinary tract obstruction and nephrostomy drainage in pelvic malignant disease. Br J Urol. 1995;76:565–569.

both conditions include the onset of lower urinary tract symptoms and acute (painful) or chronic (painless) retention of urine.

Chronic retention can be considered as the maintenance of voiding with incomplete bladder emptying. It is further classified into low- and high-pressure chronic retention. Low-pressure chronic retention occurs in the absence of upper tract compromise, whereas high-pressure chronic retention is associated with hydronephrosis and kidney injury.

In acute retention, low-pressure chronic retention, and lower urinary tract symptoms caused by bladder outflow obstruction, treatment with 5α-reductase inhibitors (finasteride, dutasteride) or α-adrenergic receptor blockers (tamsulosin, alfuzosin) is usually indicated before surgery is offered.[29] Given the risk for worsening kidney failure if medical therapy fails, it is not a safe management option in high-pressure chronic retention. Surgical management is reserved for patients who either derive no benefit from or are not willing to pursue medical therapy, those with acute and low-pressure chronic retention, and those with high-pressure chronic retention. Before surgery, evaluation of likelihood of success is essential. Patients with very high postvoid residual volumes of urine (>1 L) are less likely to benefit from surgery because of the chronicity of their symptoms and consequent detrusor muscle weakness. These patients are often treated best with intermittent clean self-catheterization or a permanent urethral or suprapubic catheter.

The number of surgical management options available for bladder outflow obstruction is continually increasing. Although transurethral resection of the prostate (TURP) has been the gold standard procedure for decades, the development of laser technology is challenging this. Holmium laser enucleation of the prostate (HoLEP) and vaporization of prostatic tissue (Green light laser) are being increasingly performed in specialist centers with superior results with respect to reduced patient stay, bleeding, and duration of postoperative catheterization. Unlike standard TURP, laser prostatectomy also can be routinely performed safely in patients with large gland size (>100 mL) and on anticoagulation therapy. A recently published 7-year follow-up study comparing TURP with HoLEP reported no significant difference in quality of life, maximum urinary flow, incontinence, or erectile dysfunction, with a reduced need for reoperation in the HoLEP arm of the study.30 More novel techniques aimed at being less invasive and reducing the impact on sexual function and continence are becoming more commonplace. Examples include, but are not limited to, UroLift (urethrally placed implants that tack the occluding prostate out of the lumen),31 Aquablation (robot-assisted waterjet),32 and Rezum (water vapor treatment).33

Neurologic Diseases of the Lower Urinary Tract

Diseases of the central or peripheral nervous system can manifest with bladder underactivity, bladder overactivity, and/or detrusor-sphincter dyssynergia and lead to bilateral hydroureteronephrosis. Diabetes mellitus also can produce a flaccid denervated bladder through destruction of the peripheral nerves and can cause chronic retention and kidney failure. Of diabetics who develop peripheral neuropathy, 75% to 100% will develop some neurogenic lower urinary tract dysfunction.

The goal of treatment in patients with neurogenic bladder dysfunction is to maintain low intravesical pressures to protect the kidneys.

This can be achieved in a number of ways including clean intermittent self-catheterization, long-term suprapubic catheterization, anticholinergics, cystoscopic injection of intradetrusor onabotulinum toxin-A, or surgery, including augmentation cystoplasty.

INVESTIGATION OF HEMATURIA

Macrohematuria is perhaps the most important symptom in urologic practice, and apart from being alarming to the patient, it can be the first presenting sign of an underlying malignant urologic condition (most often a transitional cell tumor of the bladder). Studies show that 15% to 22% of patients with visible hematuria have an underlying genitourinary tract malignant neoplasm.

Patients with visible hematuria must be distinguished from those who have been found to have microhematuria (dipstick), in whom the risk for malignant change is significantly lower (2%–11%).

The outcome of full evaluation of a large group of patients attending a hematuria clinic is shown in Table 63.5 34 In addition to a small but important group of patients in whom malignant disease was identified, there was a significant pickup rate of parenchymal kidney disease (~10%) presenting with both visible and nonvisible hematuria. It is also important to note the sizable proportion of patients in whom a definitive diagnosis could not be reached.

Evaluation of Visible Hematuria

All adults with a single episode of visible hematuria require full urologic evaluation, including kidney imaging and cystoscopy. The only exception to this rule occurs when an adult younger than 40 years gives a history characteristic of glomerular hematuria, such as is typically seen in immunoglobulin A (IgA) nephropathy, in which dark brown hematuria lasting 24 to 48 hours coincides with intercurrent mucosal infection, usually of the upper respiratory tract. This hematuria may be painless, or there may be bilateral loin ache. These young adults should be referred first for nephrologic assessment.

Evaluation of Microhematuria

Perhaps the greatest degree of overlap in practice between urologists and nephrologists occurs in the initial assessment of patients with microhematuria. Concurrent UTI will cause microhematuria and should be treated before further evaluation. Furthermore, features such as menstruation, vigorous exercise, viral illness, and trauma can themselves account for microhematuria. In the presence of a transient or treatable underlying cause other than UTI, repeat urinalysis should be performed 2 days later. Further urinalysis should be deferred until 6 weeks after treatment of confirmed UTI. If microhematuria resolves, no further investigation is required.

The 2012 American Urological Association (AUA) guidelines on the assessment and management of asymptomatic microscopic

Outcome of Evaluation in a Hematuria Clinic: Cases Investigated

TABLE 63.5

Diagnoses Found	All (%)	Microscopic Hematuria (%)	Macroscopic Hematuria (%)
No diagnosis	63	69	53
Kidney cancer	0.6	0.3	0.9
Upper tract transitional cell carcinoma	0.1	0.1	0.1
Bladder cancer	12	5	19
Prostate cancer	0.4	0.2	0.6
Stone disease	4	4	3
Urinary tract infection	13	13	13
Kidney parenchymal disease	10	9	10

Likelihood of Finding Malignancy

Male, age >40 yr	8
Male, age <40 yr	2
Female, age >40 yr	5

0

Female, age <40 yr

24

7

19

0

Data from Khadra MH, Pickard RS, Charlton M, et al. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000;163:524–527.

(nonvisible) hematuria (AMH) defined AMH by the presence of three or more red blood cells (RBCs) per high-power field (HPF) on microscopic examination of one properly collected, noncontaminated urine sample. In addition to the benign causes listed, pyuria and bacteriuria also should be excluded with either dipstick or microscopy.

The most notable departure from previous guidance is the recommendation of urologic investigation after one episode of AMH, rather than waiting for two of three positive samples as previously suggested.

No studies directly compare the diagnostic yield of investigating the first episode of AMH rather than reserving investigation for patients with more than one episode. However, indirect comparison reveals a diagnostic yield of urinary tract malignancy of 1.8% and 3.6% in patients with one or more than one episode of AMH, respectively.[35]

Dipstick-positive hematuria may still herald significant disease in the absence of RBCs on microscopy because RBCs may lyse in alkaline or hypotonic urine before reaching the laboratory for analysis.[36]

Complete evaluation of microhematuria includes a history and physical examination, laboratory analysis, and radiologic imaging of the upper urinary tract, followed by cystoscopy (Fig. 63.7). The 2020 update to the AUA guidelines introduces risk stratification to the workup of patients with microhematuria. This provides guidance as to what imaging modality of the upper tract should be performed.[37]

In females, urethral and vaginal examinations should be performed to exclude local causes of microhematuria. In uncircumcised males, the foreskin should be retracted to expose the glans penis, if possible. If phimosis is present, a catheter specimen of urine may be required.

An assessment of GFR should be made (serum creatinine, estimated GFR [eGFR]) because intrinsic kidney disease may have implications for consequent imaging and treatment. The remaining laboratory investigations are guided by specific findings of the history, physical examination, and urinalysis. Multiphase CT urography, which allows evaluation of kidney parenchyma and also the collecting system, has been shown to have the highest sensitivity and specificity for imaging the upper tracts. If CT urography is unavailable, then ultrasound is an alternative imaging strategy. The 2020 guidelines recommend cystoscopy for all patients with AMH who are at least AUA intermediate risk

Evaluation of Asymptomatic Microscopic Hematuria

Initial evaluation of asymptomatic microhematuria

Exclude benign causes, including menstruation,
vigorous exercise, sexual activity, viral illness, trauma, and infection

Present
Nephrologic
evaluation

- Proteinuria
- Dysmorphic red blood cells
- Red cell casts
- Elevated serum creatinine

Absent

Isolated persistent
microhematuria

Urologic evaluation

Low-risk patient
Age <35 years
No smoking history
No chemical exposure
No macroscopic hematuria
No other urologic symptoms

High-risk patient
Age >35 years
History of smoking
Occupational exposure to
chemicals or dyes
(benzidine or aromatic amines)
History of macroscopic hematuria

Complete evaluation (upper tract
imaging, cytology, cystoscopy)

Upper tract imaging

Cystoscopy
(males)

Cytology

History of urologic disease
History of irritative voiding
symptoms
History of UTI
Analgesic abuse
History of pelvic irradiation

Positive

Negative

Treat
Negative

Positive
Urinalysis, blood pressure, and cytology
at 6, 12, 24, and 36 months
Treat

Positive,
atypical or
suspicious

Negative

Cystoscopy

Negative

Recommend

Negative for
3 years

No further urologic
monitoring

Persistent hematuria,
hypertension, proteinuria,
glomerular bleeding

Macrohematuria, abnormal
cytology, irritative voiding
symptoms without infection

Evaluate for primary renal
disease

Repeat complete evaluation

Positive

Treat

Glomerular bleeding
or proteinuria

Isolated hematuria

Renal biopsy

Renal biopsy controversial

Fig. 63.7 Evaluation of asymptomatic microscopic hematuria. UTI, Urinary tract infection.

for a urologic malignancy (i.e., females >50 years old, males >40 years old, those with a more than 10 pack per year smoking history, >11 RBCs per HPF, recurrent AMH, or with specific risk factors for urologic malignancy or clinical suspicion of malignancy) (Box 63.1). The

use of adjuncts to AMH workup such as urine cytologic examination and other urine biomarkers is no longer advocated.37
Significant proteinuria (>0.3 g/24 h), RBC casts, predominance of dysmorphic RBCs in the urine, or reduced GFR should prompt

Common Risk Factors for Urinary Tract Malignancy in Patients With Microhematuria

BOX 63.1

- Male sex
- Age (>35 years)
- Past or current smoking
- Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
- Analgesic abuse
- History of visible hematuria
- History of urologic disorder or disease
- History of irritative voiding symptoms
- History of pelvic irradiation
- History of chronic urinary tract infection
- History of exposure to known carcinogenic agents or chemotherapy such as alkylating agents
- History of chronic indwelling foreign body

referral to a nephrologist and evaluation for parenchymal kidney disease. When present, RBC casts are virtually pathognomonic of glomerular bleeding, but they are often absent in low-grade glomerular disease. Accurate determination of RBC morphology requires inverted phase-contrast microscopy. In general, glomerular bleeding is associated with more than 80% dysmorphic RBCs, and lower urinary tract bleeding is associated with more than 80% normal RBCs.38 This assessment is operator dependent (urine microscopy is further discussed in Chapter 4). An alternative is to assess urinary RBC size by Coulter counter analysis because dysmorphic RBCs are smaller than normal RBCs, but this method is not useful when RBC numbers in the urine are small. Even in the absence of features of glomerular bleeding, many patients with isolated microhematuria have glomerular disease, most commonly IgA nephropathy or thin basement membrane nephropathy.39 Because there is a low risk for progressive loss of GFR, kidney biopsy in this setting is not usually recommended. Nevertheless, one study showed that microhematuria unexplained by urologic evaluation carries a twofold risk for eventual development of kidney failure,40 so these patients should be observed for the development of hypertension, reduced GFR, or proteinuria.

Cyclophosphamide

Past treatment with cyclophosphamide increases the risk of bladder cancer up to ninefold, probably in a dose- and duration-dependent manner. Tumors have been reported 6 to 13 years after cyclophosphamide exposure and are often of high grade. Hematuria is also common after cyclophosphamide in the absence of cancer. If full evaluation does not identify a cause of hematuria, there is no agreed surveillance protocol; it is not clear whether routine follow-up by cystoscopy and urine cytology is valuable, although a high index of suspicion should be maintained.

INVESTIGATION AND MANAGEMENT OF A KIDNEY MASS

The incidence of renal cell carcinoma (RCC) has more than doubled in the last 30 years, now accounting for 3% of all cancers. It is the third most common tumor of the urinary tract but the most lethal. The apparent increased incidence is partly attributed to the widespread use of cross-sectional and ultrasound imaging; more than 50% of new cases are incidental findings on CT, magnetic resonance imaging (MRI), or ultrasound scan.

The primary goal in investigating a kidney mass is to diagnose or exclude malignancy. Ultrasound is 79% sensitive for the detection of kidney parenchymal masses but does not detect lesions that are less than 5 mm. Contrast enhancement with ultrasound also can identify malignancy and improve sensitivity. However, CT scanning before and after contrast administration is the most common modality used to characterize kidney masses. MRI, especially with T2-weighted and diffusion-weighted imaging, may be superior to CT in the correct characterization of benign lesions,41 but distinguishing an RCC from a benign lesion (i.e., oncocytoma, fat-free angiomyolipoma) is occasionally not feasible radiologically. The choice of imaging techniques and their interpretation are discussed further in Chapters 5 and 6

Because of the limitations of radiologic evaluation, percutaneous biopsy of a kidney mass is increasingly used to obtain a histologic diagnosis before treatment. Up to 30% of small kidney masses (<3 cm) are nonmalignant. Traditional fears regarding tumor seeding after percutaneous biopsy are not supported by recent studies. Biopsy of a kidney mass is recommended for diagnostic uncertainty despite imaging, before systemic therapy for metastatic RCC and in kidney tumors managed with surveillance or ablative modalities.42 Many clinicians also perform a biopsy before embarking on surgery in high-risk or elderly surgical candidates, those who will require technically challenging surgery, and patients with small kidney masses. In a recent systematic review evaluating 57 studies investigating more than 5000 patients, percutaneous biopsy was shown to have a high diagnostic yield, sensitivity (>98%), and specificity (>98%) for kidney cancers, with a low associated complication rate.43

The management of mixed cystic and solid masses is more problematic. Table 63.6 shows the Bosniak classification of cystic kidney masses.44 This classification, based on CT appearances, provides the basis for management according to risk for malignancy. The evaluation of multiple cystic lesions in the kidney is discussed further in Chapters 46 and 47

Tumor size is important; in a large retrospective study of 2935 patients with surgically treated solid kidney tumors, 46% of lesions that were less than 1 cm were benign compared with 22% and 10% of tumors 1 to 2 cm and 4 to 5 cm, respectively. Furthermore, only 2.3% of cancers smaller than 1 cm were of high grade, whereas for tumors greater than 7 cm, the percentage was 58%.45 Surveillance studies of small kidney tumors have shown a median growth rate of 0.28 cm per year; about 30% of these lesions will not increase in size.

Traditionally, radical nephrectomy was the gold standard treatment for localized kidney cancers. However, nephron-sparing surgery (NSS) is now recommended in all tumors that are less than 7 cm where technically feasible.42 Comparison of these two approaches for T1a (<4 cm) and T1b (4–7 cm) lesions has shown equivalent tumor clearance and a reduction in long-term kidney complications with partial nephrectomy.[46] Radical nephrectomy therefore should be reserved for larger kidney cancers (≥T2), those technically not amenable to partial nephrectomy, and for patients unlikely to benefit from NSS.[42]

The last two decades have also seen a shift from open to minimally invasive surgery. Laparoscopic radical nephrectomy and roboticassisted partial nephrectomy (particularly for small exophytic tumors) have now superseded open approaches for these techniques in most large centers. Minimally invasive treatment modalities give equivalent long-term cancer control, while reducing perioperative blood loss, postoperative analgesic requirement, and hospitalization.

Cryosurgery and radiofrequency ablation via laparoscopic or percutaneous approaches have emerged as treatment options for small localized kidney cancers. There is no consensus on the maximum size of lesions amenable to these techniques, but they are usually

TABLE 63.6

Bosniak Classification and Management of Cystic Kidney Masses[a]

Bosniak Class

Features on Imaging

Comment

Management

Class I: simple benign cyst

Round or oval
Uniform density <20 HU
Unilocular
No perceptible wall
No contrast enhancement
One or two nonenhancing septa
Calcifications in the wall or septum
Hyperdense lesions (50–90 HU, resulting from the
presence of blood, protein, or colloid) <3 cm
No contrast enhancement
Multiple hairline septa
“Perceived” enhancement
Nodular calcification
Hyperdense lesions >3 cm
One or more of the following:
Thick, irregular borders
Irregular calcifications
Thickened or enhancing septa
Multilocular form
Uniform wall thickening
Small nonenhancing nodules
Appear malignant
Heterogeneous cysts
Shaggy, thickened walls or enhancing nodules

Majority of asymptomatic cystic lesions

No further intervention
required

Class II: benign cyst

Class II F: probable benign cyst

Class III: indeterminate cystic
lesions

Class IV: presumed malignant
cystic masses

No further intervention
required

“Perceived” enhancement resulting from
contrast within capillaries of septa

Surveillance with CT scans
every 6–12 months

About 40% are neoplastic
Magnetic resonance imaging may improve
characterization

Surgical exploration

Appearances result from necrosis and
liquefaction of a solid tumor or a tumor
growing in the wall

Surgical exploration

All patients with symptomatic kidney masses should be referred for urologic assessment.
aApproach to kidney mass found incidentally by ultrasound or CT scanning.
CT, Computed tomography; HU, Hounsfield units.
Data from Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66:84–88.

reserved for tumors that are less than 4 cm. Such treatments offer the advantages of NSS, especially in patients with high surgical risk. Case series evaluating these modalities individually have reported promising results. However, there are no RCT data on either modality and nonrandomized studies have not shown any significant oncologic or survival benefit when comparing these modalities to partial nephrectomy, although several studies have reported reduced efficacy in terms of local recurrence, metastatic progression, and survival.47–49 Further disadvantages of both techniques include absence of histologic confirmation of complete tissue destruction and potential for more difficult salvage surgery for local recurrence.

Adjunctive Therapy for Kidney Cancer

The 5-year survival for patients diagnosed with localized RCC is approximately 80% to 90%. However, in the United States, up to 20% of patients with RCC present with metastasis. The 5-year survival falls to 60% and 10% in the presence of regional and distant metastasis, respectively. Metastatic RCC is resistant to commonly used chemotherapeutic agents, and cytokine therapy with either interleukin (IL)-2 or interferon-α (IFN-α) was standard treatment for metastatic RCC in the United States and Europe until 2005. Although more effective than traditional chemotherapy, it produced only modest response rates with significant toxicity.50 Identification of the molecular pathways implicated in the etiology of RCC has led to the development of targeted tyrosine kinase inhibitors and monoclonal antibodies directed against the vascular endothelial growth factor (VEGF) pathway (sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, cabozantinib) and mammalian target of rapamycin (mTOR)

(temsirolimus, everolimus). In randomized studies, many of these agents, compared with standard existing therapy, have improved both progression-free and overall survival when used as first- or secondline therapy.51–56 Further development of immune checkpoint inhibitors including nivolumab and pembrolizumab (IgG4 monoclonal antibodies blocking PD-1 [programmed cell death protein 1]) and ipilimumab (CTLA4 [cytotoxic T-lymphocyte-associated protein 4] inhibitor) within the last 5 years have developed treatment further. Landmark trials have demonstrated superior progression-free and overall survival with combination immune check point treatment compared with single VEGF-targeted therapy that had been the firstline treatment only a few years ago.57 58 The European Association of Urology has made recommendations on the sequence in which these agents should be used (Table 63.7).59 Nephrologic aspects of cancer therapy are further discussed in Chapter 67

Natural History of Reduced Glomerular Filtration Rate After Surgical Treatment of Kidney Cancer

Normal GFR is usually preserved in the long term after donor transplant nephrectomy. Donors are highly selected to minimize comorbidities and generally are younger than patients treated for kidney tumors. However, emerging long-term evidence suggests those undergoing donor nephrectomy do have increased long-term cardiovascular complications and reduced survival.60 Similarly, after surgery for kidney cancer, when the residual functioning kidney tissue is reduced, there is significant risk for late sequelae, including proteinuria, glomerulosclerosis, and progressive kidney failure resulting in increased cardiovascular complications and reduced survival. These risks are

Evidence-Based
Recommendations for Targeted Therapy in
Metastatic Renal Cell Carcinoma

TABLE 63.7

Prognosis
Risk Group[59] Standard of Care
Favorable

Pembrolizumab + axitinib

Intermediate/
poor

Pembrolizumab + axitinib
or
Ipilimumab + nivolumab

Alternative if Unable
to Receive/Tolerate
Standard of Care
Sunitinib
Pazopanib
Cabozantinib
Sunitinib
Pazopanib

Based on 2020 European Association of Urology Guidelines for renal cell carcinoma.
Data modified from Ljungberg B, Bensalah K, Bex A, et al. European Association of Urology guidelines on Renal Cell Carcinoma, 2020. www.uroweb.org/guideline/renal-cell-carcinoma/.

thought to be greater when radical rather than partial nephrectomy is performed. A recent systematic review of 21 nonrandomized comparative studies (11,204 patients) evaluating partial nephrectomy versus radical nephrectomy demonstrated superiority for NSS.[61] Partial nephrectomy was associated with greater perioperative blood loss and postoperative complications, affirming that it is a more challenging procedure. However, NSS was associated with a lower long-term decline in eGFR and reduced risk for chronic kidney disease. NSS also provided a more favorable cancer-specific survival. The one RCT to compare partial nephrectomy versus radical nephrectomy also has demonstrated that fewer patients undergoing NSS develop reduced GFR (<60 mL/min/$1.73m^2$), but survival and cancer outcomes are similar with either modality.[46]

Renal Cell Carcinoma in von Hippel–Lindau Disease

Von Hippel–Lindau disease (VHL) is a rare autosomal dominant condition with a predisposition to the development of RCC. The genetics, clinical manifestations, and general management of VHL are discussed in Chapter 47. The incidence of RCC in patients with VHL is about 45%. On histologic examination, the tumors are of the clear cell type, often multifocal and bilateral, and can be solid or cystic. The mean age at diagnosis is 39 years, and there is a 30% to 35% risk for tumor progression, metastasis, and death.

Longitudinal imaging studies have described the natural history of VHL kidney lesions. In one study, multifocal lesions were frequent[62] (on average, 8 per patient), of which 74% were classified as simple cysts, 8% as complex cysts with solid components, and 18% as solid masses. The solid components of VHL lesions almost always contain RCC. During a mean 2.4-year follow-up, most cysts remained the same size (71%) or enlarged (20%), and 9% became smaller. On the contrary, 95% of solid masses increased in size. Although it is generally thought that the cysts are premalignant, the transformation of a simple cyst to a solid lesion was observed in only two patients.

Patients with VHL require multidisciplinary management. Surgical intervention is not used for tumors that are less than 3 cm because metastasis is rare below this threshold. In addition, bilateral nephrectomy should be avoided, if possible, because of the substantial morbidity associated with kidney replacement therapy. The standard of care for these patients is partial nephrectomy, and a 10-year survival rate of 81% has been reported.

The results of NSS for VHL appear less satisfactory than for sporadic RCC because of a high risk for local tumor recurrence. Repeated surgery may be needed for new or growing lesions, and for this reason the use of minimally invasive methods is being investigated. Repeated ablation of tumors with radiofrequency and cryotherapy is possible with minimal morbidity; however, the long-term effectiveness of these methods has not yet been established.

SELF-ASSESSMENT QUESTIONS

1. A 50-year-old man presents with right-sided ureteral colic and on subsequent investigation is found to have a 4-mm distal ureteral calculus with no hydronephrosis. He has normal eGFR. In the absence of ongoing pain or sepsis, what is the most appropriate management option?
A. Acute endoscopic lasertripsy
B. Decompression with ureteric stenting
C. Trial of medical expulsive therapy
D. Discharge from care of urologist
E. Percutaneous nephrostomy

2. A 70-year-old man is seen in an outpatient clinic with a 2-month history of intermittent hematuria. He takes warfarin for atrial fibrillation but is otherwise healthy. His eGFR is in the normal range. What urologic investigations does he require?
A. Clotting screen to exclude overanticoagulation as the sole cause of his hematuria

B. Clotting screen; proceed to urologic workup only if INR is within therapeutic range
C. Clotting screen, flexible cystoscopy, and CT urogram
D. Clotting screen, serum creatinine (eGFR), flexible cystoscopy, and CT urogram

3. A 60-year-old man with diabetic nephropathy is referred with a 3-cm lower pole kidney lesion suspicious for malignancy on routine ultrasound scan. These findings are confirmed on CT scan. Despite his comorbidity, he is deemed fit for surgery. What is the most appropriate procedure to consider?
A. Open radical nephrectomy to achieve maximum oncologic benefit
B. Laparoscopic cryosurgery
C. Laparoscopic partial nephrectomy
D. Laparoscopic radiofrequency ablation

REFERENCES

1. Rassweiler JJ, Renner C, Eisenberger F. The management of complex renal stones. BJU Int. 2000;86:919–928.
2. Assimos D, Krambeck A, Miller N, et al. American Urological Association/ Endourological Society Guideline: Surgical Management of Stones; 2016. https://www.auanet.org/guidelines/kidney-stones-surgical-managementguideline.
3. Turk C (Chair), Neisius A, Petrik A, et al. European Association of Urology Guidelines on Urolithiasis; 2020. www.uroweb.org/guideline/urolithiasis.
4. National Institute for Health and Care Excellence. Renal and Ureteric Stones: Assessment and Management; 2019. NICE guideline [NG118] https://www.nice.org.uk/guidance/ng118.
5. Shah TT, Gao C, Peters M, et al. British Urology Researchers in Surgical Training (BURST) Collaborative MIMIC Study Group. Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: results from the Multi-centre cohort study evaluating the role of Inflammatory Markers in patients presenting with acute ureteric Colic (MIMIC) study. BJU Int. 2019;124(3):504–513.
6. Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. Lancet. 2015;386(9991):341–349.
7. Campschroer T, Zhu Y, Duijvesz D, et al. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2014;(4):CD008509.
8. Barrionuevo Moreno P, Asi N, Benkhadra K, et al. Surgical Management of Kidney Stones: A Systematic Review. Mayo clinic; 2015.
9. Pearle MS, Pierce HL, Miller GL, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. J Urol. 1998;160(4):1260–1264.
10. Mishra S, Sharma R, Garg C, et al. Prospective comparative study of miniperc and standard PNL for treatment of 1 to 2 cm size renal stone. BJU Int. 2011;108(6):896–899.
11. Webb DR, Fitzpatrick JM. Percutaneous nephrolithotripsy: a functional and morphological study. J Urol. 1985;134:587–591.
12. Albala DM, Assimos DG, Clayman RV, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis: initial results. J Urol. 2001;166:72–80.
13. Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. BJU Int. 2006;98:1283–1288.
14. Pearle MS, Lingeman JE, Leveillee R, et al. Prospective, randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole caliceal calculi 1 cm or less. J Urol. 2005;173:2005. –2009.
15. Zadra JA, Jewett MA, Keresteci AG, et al. Nonoperative urinary diversion for malignant ureteral obstruction. Cancer. 1987;60:1353–1357.
16. Fromer DL, Shabsigh A, Benson MC, et al. Simultaneous multiple double pigtail stents for malignant ureteral obstruction. Urology. 2002 Apr;59(4):594–596.
17. Wang HJ, Lee TY, Luo HL, et al. Application of resonance metallic stents for ureteral obstruction. BJU Int. 2011;108:428–432.
18. Chitale SV, Scott-Barrett S, Ho ET, Burgess NA. The management of ureteric obstruction secondary to malignant pelvic disease. Clin Radiol. 2002;57:118–121.
19. Saltzman B. Ureteral stents: indications, variations, and complications. Urol Clin North Am. 1988;15:481–491.
20. Ku JH, Lee SW, Jeon HG, et al. Percutaneous nephrostomy versus indwelling ureteral stents in the management of extrinsic ureteral obstruction in advanced malignancies: are there differences? Urology. 2004;64:95–99.
21. Khan M, Babar M, Tsampoukas G, et al. Nephroureterostomy as a treatment of obstructive uropathy: a single center experience. Arch Ital Urol Androl. 2020;92:248–252.
22. Minhas S, Irving HC, Lloyd SN, et al. Extra-anatomic stents in ureteric obstruction: experience and complications. BJU Int. 1999;84:762–764.
23. Emiliani E, Breda A. Laser endoureterotomy and endopyelotomy: an

update. World J Urol. 2015;33(4):583–587.

24. Siqueira Jr TM, Nadu A, Kuo RL, et al. Laparoscopic treatment for ureteropelvic junction obstruction. Urology. 2002;60:973–978.
25. Lau MW, Temperley DE, Mehta S, et al. Urinary tract obstruction and nephrostomy drainage in pelvic malignant disease. Br J Urol. 1995;76:565–569.
26. Donat SM, Russo P. Ureteral decompression in advanced non-urologic malignancies. Ann Surg Oncol. 1996;3:393–399.
27. Shekarriz B, Shekarriz H, Upadhyay J, et al. Outcome of palliative urinary diversion in the treatment of advanced malignancies. Cancer. 1999;85:998–1003.
28. Prentice J, Amer T, Tasleem A, et al. Malignant ureteric obstruction decompression: how much gain for how much pain? A narrative review. J R Soc Med. 2018;111(4):125–135.
29. Sarma AV, Wei JT. Benign prostatic hyperplasia and lower urinary tract symptoms. N Engl J Med. 2012;367:248–257.
30. Gilling PJ, Wilson LC, King CJ, et al. Long-term results of a randomized trial comparing holmium laser enucleation of the prostate and transurethral resection of the prostate: results at 7 years. BJU Int. 2012;109:408–411.
31. Roehrborn CG, Rukstalis DB, Barkin J, et al. Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol. 2017;24(3):8802–8813.
32. Gilling P, Barber N, Bidair M, et al. Three-year outcomes after Aquablation therapy compared to TURP: results from a blinded randomized trial. Can J Urol. 2020;27(1):10072–10079.
33. McVary KT, Rogers T, Roehrborn CG. Rezūm water vapor thermal therapy for lower urinary tract symptoms associated with benign prostatic hyperplasia: 4-year results from randomized controlled study. Urology. 2019;126:171–179.
34. Khadra MH, Pickard RS, Charlton M, et al. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000;163:524–527.
35. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and followup of asymptomatic microhematuria in adults: AUA guideline. J Urol. 2012;188(6 suppl):247324–247381.
36. Kincaid-Smith P. Haematuria and exercise-related haematuria. Br Med J (Clin Res Ed). 1982;285:1595.
37. Barocas D, Boorjian S, Alvarez R, et al. American Urological Association (AUA) / Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Guideline: Microhematuria; 2020. https://www.auanet.org/guidelines/microhematuria.
38. De Santo NG, Nuzzi F, Capodicasa G, et al. Phase contrast microscopy of the urine sediment for the diagnosis of glomerular and nonglomerular bleeding—data in children and adults with normal creatinine clearance. Nephron. 1987;45:35–39.
39. Topham PS, Harper SJ, Harris KPG, et al. Glomerular disease as a cause of isolated microscopic haematuria. Q J Med. 1994;87:329–336.
40. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49:800–805.
41. Curry NS, Bissada NK. Radiologic evaluation of small and indeterminate renal masses. Urol Clin North Am. 1997;24:493–505.
42. Ljungberg (Chair) B, Bensalah K, Bex A, et al. European Association of Urology guidelines on Renal Cell Carcinoma, 2020 www.uroweb.org/guideline/renal-cell-carcinoma/.
43. Marconi L, Dabestani S, Lam TB, et al. Systematic review and metaanalysis of diagnostic accuracy of percutaneous renal Tumour biopsy. Eur Urol. 2016;69(4):660–673.
44. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66:84–88.
45. Frank I, Blute ML, Cheville JC, et al. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170(Pt 1):2217–2220.

46. Van Poppel H, Becker F, Cadeddu JA, et al. Treatment of localized renal cell carcinoma. Eur Urol. 2011;60:662–672.
47. Guillotreau J, Haber GP, Autorino R, et al. Robotic partial nephrectomy versus laparoscopic cryoablation for the small renal mass. Eur Urol. 2012;59(5):899–904.

References

48. O’Malley RL, Berger AD, Kanofsky JA, et al. A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. BJU Int. 2007;99(2):395–398.
49. Olweny EO, Park SK, Tan YK, et al. Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. Eur Urol. 2012;59(6):1156–1159.
50. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renalcell carcinoma. Groupe Français d’Immunothérapie. N Engl J Med. 1998;338:1272–1278.
51. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009;27:3312–3318.
52. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27:3584–3590.
53. Escudier B, Bellmunt J, Négrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010;28:2144–2150.
54. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010;116:4256–4265.

55. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28:1059–1068.
56. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol. 2013;14(6):552–562.
57. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116–1127.
58. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378:1277–1290.
59. Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141–148.
60. Mjøen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. Kidney Int. 2014;86(1):162–167.
61. Mir MC, Derweesh I, Porpiglia F, et al. Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. Eur Urol. 2017;71(4):606–617.
62. Choyke PL, Glenn GM, Walther MM, et al. The natural history of renal lesions in von Hippel-Lindau disease: a serial CT study in 28 patients. AJR Am J Roentgenol. 1992;159(6):1229–1234.

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Acute Interstitial Nephritis

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DEFINITION

Acute interstitial nephritis (AIN) is an acute, often reversible disease characterized by inflammatory infiltrates within the kidney interstitium. AIN is a relatively rare cause of acute kidney injury (AKI), but it should not be overlooked because it usually requires specific therapeutic interventions.

PATHOGENESIS

Most studies suggest that AIN is an immunologically induced hypersensitivity reaction to an antigen that is classically a drug or an infectious agent. Evidence for a hypersensitivity reaction in drug-induced AIN includes the following: it occurs only in a small percentage of individuals; it is not dose dependent; it is often associated with extrarenal manifestations of hypersensitivity; it recurs after accidental reexposure to the same drug or to a closely related one; and it is sometimes associated with evidence of delayed-type hypersensitivity reaction (kidney granulomas). Similarly, AIN secondary to infections can be differentiated from pyelonephritis by the relative absence of neutrophils in the interstitial infiltrates and the failure to isolate the infective agent from the kidney parenchyma, again suggesting an immunologic basis to the disease.

Experimental models of AIN have identified three major types of antigens that induce the condition.1 Antigens may be tubular basement membrane (TBM) components (e.g., the glycoproteins 3M-1 and TIN-Ag/TIN1), secreted tubular proteins (e.g., uromodulin), or nonrenal proteins (e.g., from immune complexes).

Although human AIN may be secondary to an immune reaction directed against a kidney antigen, most cases of AIN are probably induced by extrarenal antigens, being produced in particular by drugs or infectious agents. These antigens may induce AIN by a variety of mechanisms, including binding to kidney structures (“planted antigen”); acting as haptens that modify the immunogenicity of native kidney proteins; mimicking kidney antigens, resulting in a cross-reactive immune reaction; and precipitating within the interstitium as circulating immune complexes.

Experimental models have identified both cell-mediated immunity and antibody-mediated immunity in the pathogenesis of AIN (Fig. 64.1). In humans, most forms of AIN are not associated with antibody deposition, which suggests that cell-mediated immunity plays a major role. This hypothesis is reinforced by the fact that interstitial infiltrates

usually contain numerous T cells, and these infiltrates sometimes form granulomas. Nevertheless, deposition of anti-TBM antibodies or of immune complexes can be observed occasionally in kidney biopsy specimens, and antibody-mediated immunity may play a role in the pathogenesis of the disease in these cases.

Formation of immune complexes within the interstitium, or interstitial infiltration with T cells, will result in an inflammatory reaction. This reaction is triggered by many events, including activation of the complement cascade by antibodies and release of inflammatory cytokines by T lymphocytes and phagocytes (see Fig. 64.1). Although the interstitial inflammatory reaction may resolve without sequelae, it sometimes induces interstitial fibroblast proliferation and extracellular matrix synthesis, leading to interstitial fibrosis and chronic kidney disease (CKD). Cytokines such as transforming growth factor-β appear to play a key role in the latter process.

EPIDEMIOLOGY

AIN is a relatively uncommon cause of AKI, although its incidence may be increasing.2 It accounts for 2% to 3% of all kidney biopsies, 10% to 15% of biopsies performed for unexplained AKI, and up to 25% of those performed for drug-induced AKI.2 Of kidney biopsies done in children with AKI, 3% to 7% show AIN.3

Before antibiotics were available, AIN was most commonly associated with infections such as scarlet fever and diphtheria. Drug-induced AIN now appears to account for about 70% to 90% of all cases.

DRUG-INDUCED ACUTE INTERSTITIAL NEPHRITIS

Clinical Manifestations

In the 1960s and 1970s, most cases of drug-induced AIN were caused by methicillin, and the clinical manifestations of methicillininduced AIN were considered the prototypical presentation of AIN.

Since then, many other drugs have been implicated in the induction of AIN (Box 64.1), of which antimicrobial agents (in particular, β-lactam antibiotics, sulfonamides, fluoroquinolones, and rifampin), nonsteroidal antiinflammatory drugs (NSAIDs) (especially fenoprofen), and proton pump inhibitors (PPIs) have been most commonly involved.4,5 In a large case series of biopsy-proven AIN, drug-induced AIN was because of antibiotics in 49% of cases, NSAIDs in 11%, and PPIs in 14%.4 There has been a rising incidence of AIN in the current decade. In a large single-center Spanish

Immune Mechanisms in Acute Interstitial Nephritis
Cell-mediated mechanisms

Antibody-mediated mechanisms

Blood vessel
Neutrophil

Blood vessel
Neutrophils

Monocyte

MHC
class II

(+)

(+)

(+)

Macrophage

(+)

Th1 lymphocyte
(+)

Cytotoxic
T lymphocyte
MHC class I

Natural
killer cell

Tubule

(+)

Processed antigen

Neutrophil
(+)

(+)

Macrophage

Th lymphocyte

(+)

Monocyte

MHC
class II

Th2 lymphocyte
(+)

B lymphocyte

Eosinophil
Natural
killer cell

Complement

(+)
Complement

Tubule

Fig. 64.1 Immune Mechanisms That Can Be Involved in Acute Interstitial Nephritis. Both cell-mediated and antibody-mediated mechanisms occur. The cell-mediated mechanism is primarily associated with macrophages and T cells. The antibody-mediated mechanism is frequently associated with neutrophil or eosinophil infiltration and with local complement activation. MHC, Major histocompatibility complex.

study of 182 patients, the most common offending drugs were NSAIDs (27%), antibiotics (22%), and PPIs (4%), but 30% of cases had no identified offending drug.6 Other antiulcer agents, diuretics, phenindione, phenytoin, allopurinol, highly active antiretroviral therapy (HAART), and anticancer agents such as tyrosine kinase inhibitors, pemetrexed, and ifosfamide also have been reported to cause AIN.7,8 In addition, AIN can be caused by immune checkpoint inhibitors (e.g., programmed death 1 [PD-1], PD ligand 1 [PD-L1], and cytotoxic T-lymphocyte–associated antigen 4 [CTLA4] inhibitors), as shown in meta-analysis and now confirmed by a large single-center study of 1016 patients to occur about 3% of the time.9,10 Most other drugs only rarely have been linked with AIN (see Box 64.1). AIN also has been reported after snake or wasp envenomation, and the pathogenic mechanism is likely to be similar to that in drug-induced AIN.

The clinical characteristics of drug-induced AIN are now recognized as much more varied and nonspecific than the spectrum seen in classic methicillin-induced AIN (Fig. 64.2).2,11,12

Kidney Manifestations

Symptoms of AIN usually develop a few days to a few weeks after the inciting drug is started, although cases have occurred months after initial exposure to the drug. In particular, AIN induced by NSAIDs or PPIs is often diagnosed several months after treatment initiation, and a recent paper suggests an average time of 4 months with immune checkpoint inhibitors.11 The typical presentation is sudden impairment in kidney function, associated with mild proteinuria (<1 g/day)

and abnormal urinalysis, in a patient with flank pain, normal blood pressure, and no edema. Clinical presentation is often incomplete (see Fig. 64.2), and AIN should be considered in any patient with unexplained AKI.2 Kidney dysfunction may be mild or severe, and dialysis is required in about one-third of patients. Hematuria and pyuria are present in a little more than half of the patients, and although leukocyte casts are common, hematuria is almost never associated with red blood cell casts. Flank pain (reflecting distention of the kidney capsule) is observed in about one-third of the patients and can be the main complaint on hospital admission. Some patients have low fractional sodium excretion.

Standard imaging procedures show kidneys normal in size or slightly enlarged. Ultrasound usually discloses an increased cortical echogenicity (comparable to or higher than that of the liver).

Extrarenal Manifestations

Extrarenal symptoms consistent with a hypersensitivity reaction are occasionally observed, including low-grade fever, maculopapular rash (Fig. 64.3), mild arthralgia, and eosinophilia. However, each of these symptoms is typically present in fewer than half of the patients (see Fig. 64.2), and these symptoms are all present in less than 10% of patients.2 With some drugs, other manifestations of hypersensitivity, such as hemolysis or hepatitis, can be present. Serum immunoglobulin E (IgE) levels also may be elevated.

The association of AKI with clinical signs suggestive of hypersensitivity or eosinophilia should lead to consideration of AIN. However, signs of hypersensitivity can be observed in patients with AKI that is

BOX 64.1

Drugs Responsible for Acute Interstitial Nephritis

Antimicrobial Agents
Penicillins
Amoxicillin
Ampicillina
Aztreonam
Carbenicillin
Cloxacillin
Flucloxacillin
Methicillina
Mezlocillin
Nafcillin
Oxacillina
Benzylpenicillina
Piperacillin
Cephalosporins
Cefaclor
Cefazolin
Cefotaxime
Cefotetan
Cefoxitin
Ceftriaxone
Cephalexin
Cephaloridine
Cephalothin
Cephradine
Quinolones
Ciprofloxacina
Levofloxacina
Moxifloxacin
Norfloxacin
Other
Acyclovir
Azithromycin
Clarithromycin
Colistin
Cotrimoxazolea
Erythromycina
Ethambutol
Flurithromycin
Foscarnet
Gentamicin
Indinavir
Interferon
Isoniazid
Lincomycin
Linezolid

Minocycline
Nitrofurantoina
Piromidic acid
Polymyxin Ba
Quinine
Rifampina (rifampicina)
Spiramycina
Sulfonamidesa
Teicoplanin

Telithromycin
Tetracycline
Vancomycina
NSAIDs, Including Salicylates
Salicylates and Derivatives
Acetylsalicylic acid (aspirin)
Diflunisala
Propionic Acid Derivatives
Benoxaprofen
Fenbufen
Fenoprofena
Flurbiprofen
Ibuprofena
Ketoprofen
Naproxen
Acetic Acid Derivatives
Indometacina (indomethacina)
Alclofenac
Diclofenac
Fenclofenac
Sulindac
Zomepirac
Enolic Acid Derivatives
Meloxicam
Piroxicama
Fenamic Acid Derivatives
Mefenamic acid
Coxibs
Celecoxib
Rofecoxib
Other
Azapropazone
Mesalamine (mesalazine, 5-ASA)
Phenazone

Phenylbutazone
Sulfasalazine
Tolmetin
Antalgics
Aminopyrine
Antipyrine
Anticonvulsants
Carbamazepinea
Diazepam
Lamotriginea
Levetiracetam
Phenobarbital (phenobarbitone)
Phenytoina
Valproic acid (valproate sodium)
Diuretics
Chlorthalidone
Etacrynic acid (ethacrynic acid)
Furosemidea (frusemidea)
Hydrochlorothiazidea
Indapamide
Triamterenea
Antiulcer Agents
Histamine-2 Receptor
Antagonists
Cimetidinea
Famotidine
Ranitidine
Proton Pump Inhibitors
Esomeprazole

Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
Immune Checkpoint
Inhibitors
Ipilimumaba
Nivolumab
Pembrolizumab
Other Anticancer Agents
Adriamycin
Bevacizumab
Bortezomib
Carboplatin

Cytosine arabinoside
Gemcitabine
Ifosfamide
Interleukin-2
Lenalidomide
Methotrexate
Pemetrexed
Sorafenib
Sunitinib
Others
Allopurinola
α-Methyldopa
Amlodipine
Azathioprine
Betanidine (bethanidine)a
Bismuth salts
Captoprila
Carbimazole
Cetirizine
Chlorpropamidea
Clofibrate
Clozapine
Cyclosporine
Deferasirox
Diltiazem
d-Penicillamine
Etanercept
Exenatide
Fenofibratea
Fluindione
Gold salts
Griseofulvin
Interferon
Isotretinoin
Liraglutide
Nifedipinea
Phenindionea
Phenothiazine
Phenylpropanolamine
Probenecid
Propranolol
Propylthiouracil
Sirolimus
Streptokinase
Sulfinpyrazone
Warfarin
Zopiclone

Drugs most commonly involved are in bold.

a Drugs that can cause granulomatous AIN.
AIN, Acute interstitial nephritis; NSAIDs, nonsteroidal antiinflammatory drugs.

not related to AIN, including patients with drug-induced acute tubular necrosis.

Specific Drug Associations

The clinical and biologic manifestations of AIN may have some specificity, depending on the drug involved.

As outlined earlier, methicillin-induced AIN was characterized by a high frequency of abnormal urinalysis and extrarenal symptoms and by well-preserved kidney function. Kidney failure was reported in only about 50% of patients (see Fig. 64.2).[2]

More than 200 cases of rifampin-induced AKI have been reported.[12] Prior exposure is common; most cases occurred after readministration

Clinical Manifestations of Drug-Induced Acute Interstitial Nephritis
Eosinophilia
Extrarenal symptoms
Mild proteinuria
Pyuria
Hematuria
Macroscopic hematuria
Oliguria
Renal failure
40%
50%
60%
70%
80%
90%
100%
Percentage of patients

Fig. 64.2 Clinical Manifestations of Drug-Induced Acute Interstitial Nephritis (AIN). Data were pooled from different case reports, including more than 200 patients with drug-induced AIN. Patients with AIN associated with methicillin therapy or with a nephrotic syndrome are not included.

0%

10%

20%

30%

Fig. 64.3 Maculopapular Rash in a Patient With Drug-Induced Acute Interstitial Nephritis (AIN). Such cutaneous lesions occur in about 40% of patients with drug-induced AIN, but they can also be seen in patients with drug-induced acute tubular necrosis.

of rifampin or several months after intermittent administration of the drug had begun. Kidney failure is usually associated with the sudden onset of fever, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), and myalgias. It also may be associated with hemolysis, thrombocytopenia, and, less frequently, hepatitis. Kidney biopsy usually shows tubular injury and interstitial inflammatory infiltrates. Although circulating antirifampin antibodies are often found, immunofluorescence (IF) staining of kidney biopsy specimens for immunoglobulin and complement is negative in most cases, suggesting that cell-mediated immunity plays a key role in the induction of the nephritis. In a few cases, AIN developed after continuous treatment with rifampin for 1 to 10 weeks in which extrarenal symptoms or antirifampin antibodies were absent, and kidney biopsy specimens showed severe interstitial infiltrates but few tubular lesions.

Phenindione-induced AIN is generally associated with the development of hepatitis, which can be fatal.

Allopurinol-induced AIN appears to occur more often in patients with CKD and is usually seen in association with rash and liver dysfunction and sometimes with full manifestations of Stevens-Johnson syndrome.13 This severe allergic reaction is primarily observed in patients with the human leukocyte antigen B58 genotype.

AIN caused by NSAIDs is associated with nephrotic syndrome in about 75% of cases. Patients are usually older than 50 years, and although it has been observed with all NSAIDs, including cyclooxygenase 2–

selective inhibitors, half of the cases have been reported with fenoprofen. Most occurrences develop after the patient has taken NSAIDs for months (6 months on average), but AIN can occur within days or after more than a year. With the exception of the heavy proteinuria and associated edema, the presentation of these patients is similar to that of patients with other forms of drug-induced AIN (Fig. 64.4), although extrarenal symptoms are present in only about 10% of patients. Kidney disease caused by NSAIDs must be differentiated from other NSAID kidney manifestations, including hemodynamically mediated AKI, papillary necrosis, and NSAID-induced membranous nephropathy. Drugs other than NSAIDs can rarely induce AIN associated with the nephrotic syndrome; a few cases have been reported after administration of ampicillin, rifampin, lithium, interferon, phenytoin, pamidronate, and d-penicillamine.

Clinical Presentation of AIN and Nephrotic
Syndrome Associated With NSAID Use

Eosinophilia
Extrarenal
symptoms
Pyuria
Macroscopic
hematuria
Hematuria
Hypertension
Edema
0%

20%

40%

60%

80%

100%

Fig. 64.5 Drug-Induced Acute Interstitial Nephritis. On light microscopy, the characteristic feature is interstitial infiltration with mononuclear cells, with normal glomeruli. It is usually associated with interstitial edema and tubular lesions. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

Proportion of patients

Fig. 64.4 Clinical Presentation of Acute Interstitial Nephritis (AIN) and Nephrotic Syndrome Associated With Nonsteroidal Antiinflammatory Drug (NSAID) Use. Data were pooled from different case reports including more than 60 patients.

PPIs, such as omeprazole or pantoprazole, are commonly recognized as a cause of AIN. Symptoms are nonspecific, although approximately 10% of subjects present with fever, chills, and anorexia.

Consistent with the fact that drug-induced AIN can lead to permanent kidney damage, large observational studies have shown that the use of PPIs is associated with an increased risk for development or progression of CKD, and development of AIN is viewed as being the likely underlying mechanism.14

Target immune therapies have transformed the treatment and outcomes of many cancers in the last few years but not without multiple immune-mediated adverse side effects, including AKI.15 In one large study, immune checkpoint inhibitor–associated AKI usually occurred at an average of 14 weeks (range, 6–37 weeks), and the majority had other drugs known to cause AIN (69%) and often with multiple checkpoint inhibitors used on patients at the same time, with the majority recovering (85%). A small biopsy series demonstrated that 92% of patients had tubulointerstitial nephritis as the cause of the AKI, which was associated with persistent mild kidney impairment at 12 months.11

The use of kidney biopsy versus just an empiric steroid pulse when any AKI occurs associated with checkpoint inhibitor use is controversial, but biopsy may aid decision making about whether to continue giving a checkpoint inhibitor and/or prescribe corticosteroids.16

Pathology

The hallmark of AIN is the presence of inflammatory infiltrates in the kidney interstitium (Fig. 64.5). These infiltrative lesions are often patchy, predominating in the deep cortex and outer medulla, but they can be diffuse in severe cases. They are composed mostly of T cells and monocytes-macrophages, but plasma cells, eosinophils, and a few neutrophilic granulocytes also may be present. The relative number of CD4+ T cells and CD8+ T cells is variable from one patient to another. In some cases, T lymphocytes infiltrate across the TBM and between tubular cells, mainly in distal tubules, and the resulting lesion is referred to as tubulitis.

In some cases of drug-induced AIN, kidney biopsy shows interstitial granulomas (Fig. 64.6). These granulomas are usually sparse and nonnecrotic, with few giant cells, and are associated with nongranulomatous interstitial infiltrates. Granulomas are also found in AIN related to infection (Box 64.2), sarcoidosis, Sjögren syndrome, and granulomatous polyangiitis.

Fig. 64.6 Drug-induced granulomatous acute interstitial nephritis (AIN). The patient was taking omeprazole over the counter and presented with fever, chills, malaise, and cough. Workup showed a serum creatinine of 4.5 mg/dL (400 µmol/L) and 15.5-cm enlarged kidneys that were pushing up on the diaphragm, causing the cough. Biopsy shows AIN with eosinophils (red arrows), lymphocytes, and early granuloma formation (demarcated by black arrows). (Courtesy R.J. Johnson, University of Colorado, Denver.)

Interstitial infiltrates are always associated with interstitial edema, which is responsible for separating the tubules (see Fig. 64.5). They can also be associated with focal tubular lesions, which range from mild cellular alterations to extensive necrosis of epithelial cells, and are sometimes associated with a disruption of the TBM. These tubular lesions usually predominate where the inflammatory infiltrates are most extensive.

Tubulointerstitial lesions are not associated with vascular or glomerular lesions. Even in AIN associated with a nephrotic syndrome, glomeruli appear normal on light microscopy; glomerular lesions are similar to those seen in minimal change disease (see Chapter 18).

In most patients with AIN, kidney biopsy specimens do not show immune deposits, and both IF and electron microscopy are negative. Nevertheless, staining of the tubular or capsular basement membrane

Infections That Can Be Associated With Acute Interstitial Nephritis

BOX 64.2

Bacteria
Brucella spp.
Campylobacter jejuni
Corynebacterium diphtheriae
Escherichia coli
Legionella spp.
Leptospira spp.
Mycobacterium tuberculosis[a]
Salmonella spp.[a]
Staphylococcus spp.
Streptococcus spp.
Yersinia pseudotuberculosis

Hantavirus
Hepatitis A virus
Hepatitis B virus
Herpes simplex virus
Human immunodeficiency virus
Measles virus
Polyomavirus
Rickettsia

Viruses
Adenovirus
Cytomegalovirus
Epstein-Barr virus[a]

Other
Chlamydia spp.
Mycoplasma spp.

[a] Infections

Parasites
Toxoplasma spp.[a]
Leishmania donovani

that can induce granulomatous acute interstitial nephritis.

Fig. 64.7 Linear Deposits of Immunoglobulin G in Drug-Induced Acute Interstitial Nephritis. Deposits along the tubular basement membrane (TBM) are shown on immunofluorescence microscopy. These antibodies recognize either a component of the TBM or a drug metabolite bound to the TBM. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

Identification of the Causative Drug

for IgG or complement may occasionally be seen by IF; the staining pattern is either granular or linear (Fig. 64.7). Linear fixation of IgG along the TBM indicates the presence of antibodies directed against membrane antigens or against drug metabolites bound to the TBM, and circulating anti-TBM antibodies have been detected in some cases. These linear deposits are seen mostly in patients taking NSAIDs, phenytoin, or allopurinol.

Identification of the causative drug is relatively easy when AIN occurs in a patient taking only one drug. However, patients are often taking more than one drug capable of inducing AIN and in a recent study,6 30% of cases had no offending drug clearly implicated. Two biologic tests have been used, primarily in research laboratories, to help identify the causative drug: the lymphocyte stimulation test and the identification of circulating antidrug antibodies. However, neither test appears to be clinically useful at this time because of issues with sensitivity and specificity.

Diagnosis

Natural History

The most accurate way to diagnose AIN is by kidney biopsy. However, both eosinophiluria and gallium scanning have been suggested as helpful in making the diagnosis.

Eosinophils can be detected in urine and, although eosinophiluria is frequently used to corroborate the diagnosis of drug-induced AIN, review of published series shows that this test has rather poor sensitivity and a low positive predictive value, even when only patients with AKI are considered. In the largest and most recent series, only 36% (26 of 73) of patients with drug-induced AIN had eosinophiluria, and 28% (20 of 69) of patients with acute tubular necrosis also had eosinophiluria (Fig. 64.8).17 Eosinophiluria may also occur in patients with diseases such as proliferative or crescentic glomerulonephritis (GN), atheroembolic kidney disease, urinary tract infection, urinary schistosomiasis, and even prerenal AKI.18 Thus, eosinophiluria should be abandoned as a test for AIN. Firm diagnosis requires kidney biopsy and/or a clinical response on withdrawal of the drug of concern.

An increased kidney uptake of gallium-67 (67Ga) has been reported in AIN.19 Analysis of available series shows that in 53 patients with AIN, 83% had an abnormal kidney scan (maximum after 48 hours), whereas it was normal in 17 of 18 patients with acute tubular necrosis. However, these studies were small and retrospective, and 67Ga kidney scanning is not specific for AIN and may be abnormal in patients with pyelonephritis, cancer, or glomerular diseases. We do not recommend use of gallium scanning as a diagnostic tool.

Because the clinical presentation of AIN is variable and because noninvasive diagnostic procedures have limitations, kidney biopsy is often essential for the diagnosis of AIN. Several studies have shown that prebiopsy diagnosis may be incorrect in a substantial number of patients.

Drug-induced AIN was long considered benign, with complete recovery of kidney function if the inciting agent was removed. However, recent studies show that the course of AIN is not always benign, and serum creatinine does not return to baseline in about 40% to 50% of patients.4 20 Even in those with kidney recovery, an increase in serum creatinine can persist for several weeks. Unfortunately, there are few known prognostic predictors. The severity of kidney failure does not appear to be linked with the prognosis.4 It has been suggested that the presence on kidney biopsy of diffuse neutrophil- or macrophage-rich infiltrates, interstitial granulomas, or tubular atrophy is associated with a poor prognosis, but this has not been consistently found in all series. The best prognostic predictors may actually be the duration of AKI and the severity of interstitial fibrosis.

Treatment

In addition to removal of the inciting agent, which is essential and should be done as soon as possible, corticosteroids have been used to treat AIN. Most commonly, patients received high-dose oral corticosteroids sometimes associated with pulses of intravenous methylprednisolone. In the recent decade, properly controlled trials still suggest that corticosteroids improve outcomes, particularly in idiopathic AIN.20 The largest recent study6 confirmed shortcourse therapy (3 weeks) was as effective as a prolonged course (8 weeks).

In different series, corticosteroids rapidly induced a reduction in serum creatinine in patients whose kidney function did not improve within about 1 week after discontinuation of the inciting agent. It is interesting that in patients with NSAID-induced AIN, corticosteroids do not seem to modify the course of the nephrotic syndrome.

Eosinophiluria in the Diagnosis of Drug-Induced
Acute Interstitial Nephritis
Acute tubular necrosis
with eosinophiluria

Acute tubular necrosis
without eosinophiluria

Drug-induced AIN
without eosinophiluria

Drug-induced AIN
with eosinophiluria

Non–drug-induced AIN Non–drug-induced AIN
with eosinophiluria
without eosinophiluria

Fig. 64.8 Eosinophiluria in the Diagnosis of Drug-Induced Acute Interstitial Nephritis (AIN). Data from a recent and large retrospective series confirm that eosinophiluria (defined by the presence of 1% or more eosinophils in urine) lacks sensitivity and specificity for the diagnosis of drug-induced AIN in patients with acute kidney injury. (From Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176[2]:238–246.)

On the basis of anecdotal case reports, some authors have advocated use of mycophenolate mofetil in patients resistant to corticosteroids.21 We recommend administration of a 3-week course of prednisolone in patients whose kidney function fails to improve within 1 week after discontinuation of the inciting drug and rapidly return to baseline values, provided the diagnosis of AIN has been confirmed by kidney biopsy.6 We initiate treatment with a dose of prednisone of 1 mg/kg/day and not higher than 60 mg/day, and after 1 to 2 weeks, we progressively taper the dose so that the total duration of treatment is 4 to 6 weeks.

ACUTE INTERSTITIAL NEPHRITIS SECONDARY TO INFECTIOUS DISEASES

Infections were once the most common cause of AIN, but the frequency of AIN induced by an infection has decreased with the widespread use of antibiotics. Nevertheless, the diagnosis of infectious AIN should not be overlooked, and AIN occurring in patients treated with antibiotics should not always be attributed to the drug.

Infectious agents can cause kidney parenchymal inflammation by direct infection, resulting in acute pyelonephritis (see Chapter 53). However, many infectious agents may induce an immunologically mediated AIN in the absence of direct invasion (see Box 64.2). In this case the clinical presentation depends mostly on the underlying infection. On histologic examination, lesions are identical to those described for drug-induced AIN, and they also can occasionally result in granulomas (see Box 64.2). Infection-associated AIN usually resolves with the treatment of the underlying infection, and corticosteroid therapy is not recommended.

An important cause of infection-associated AIN is hantavirus.22 Hantavirus infections occur worldwide and are responsible for a disease that has been known as hemorrhagic fever with renal syndrome, epidemic hemorrhagic fever, and nephropathia epidemica. Rodents are the main reservoir of the virus, and humans are probably infected by the airborne route. Besides fever, fatigue, and muscle aches (sever lumbar pain that is sometime interpreted as nephrolithiasis), which are

Fig. 64.9 Acute Interstitial Nephritis Secondary to Hantavirus Infection. Vascular congestion and foci of medullary hemorrhage are suggestive of the diagnosis. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

observed in all patients, extrarenal symptoms often include headache, lightheadedness, abdominal pain, nausea and vomiting, and thrombocytopenia; the last can be responsible for hemorrhagic complications. AKI is almost always associated with proteinuria, sometimes in the nephrotic range, and with hematuria. Kidney biopsy is usually not required for the diagnosis but if performed reveals not only interstitial inflammatory infiltrates, which predominate in the medulla, but also vascular congestion and interstitial bleeding (Fig. 64.9). In 50% of patients, IF studies show granular immune deposits along the TBM and within glomeruli. Kidney function usually improves after a few days, and complete recovery is the rule. Nevertheless, in severe cases, recovery can be complicated by the occurrence of hemorrhagic complications or severe shock. The diagnosis is based on serologic test results, which become positive early (within weeks) in the course of the disease.

Tubulointerstitial lesions are common in human immunodeficiency virus (HIV)-positive patients who undergo a kidney biopsy for

AKI. Interstitial infiltrates are often associated with glomerular lesions, but they can be isolated. These forms of AIN have been observed in both White and Black patients, and they might be related not only to drugs and opportunistic infections but also to the HIV infection itself.23 24

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH SYSTEMIC DISEASES

Sarcoidosis

In sarcoidosis, reductions in the glomerular filtration rate (GFR) usually occur as a complication of hypercalciuria and hypercalcemia, but granulomatous AIN associated with sarcoidosis also may occur (Fig. 64.10).25 26 The presentation is usually that of AKI, which can be isolated or associated with mild proteinuria and sterile leukocyturia. It is associated with extrarenal symptoms of sarcoidosis in about 90% of patients, most frequently with lymphadenopathy and lung, eye, or liver involvement. Nevertheless, only slightly more than half of the patients have hilar lymphadenopathy or pulmonary interstitial fibrosis at the time of diagnosis.26 Treatment with high-dose corticosteroids quickly improves kidney function, but most patients do not recover completely. The starting dose should be prednisone 1 mg/kg/day and not higher than 60 mg/day, and corticosteroid therapy should be tapered slowly and not withdrawn before at least 1 year to prevent relapses. Whereas some authors advocate long-term maintenance therapy with low-dose corticosteroids, we usually stop corticosteroids after 2 to 3 years. Because of the risk for late relapse, these patients should be observed for a prolonged time.

Sjögren Syndrome

Clinically significant interstitial nephritis is rare in Sjögren syndrome and usually results in chronic tubular dysfunction.27 Some patients may present with severe symptomatic hypokalemia with distal renal tubular acidosis. Rarely, Sjögren syndrome presents with AKI because of AIN, which is often responsive to treatment with high-dose corticosteroids.

Systemic Lupus Erythematosus

About two-thirds of kidney biopsy samples in patients with systemic lupus show tubulointerstitial involvement, but significant tubulointerstitial injury in the setting of minimal glomerular abnormalities is rare, with only about 10 cases reported in the literature.28 In these cases, kidney biopsy shows typical features of AIN on light microscopy and IF staining always discloses immune deposits along the TBM, usually with a granular pattern. Kidney function improves after high-dose corticosteroids, and additional immunosuppressive drugs are not usually required. Azathioprine also has been used as a corticosteroid-sparing agent.

Immunoglobulin G4–Related Disease

IgG4-related disease is a newly recognized systemic autoimmune disease that predominantly affects men older than 50 years (see Chapter 65). In the kidney, it is most commonly responsible for AIN characterized by the presence of interstitial infiltrates rich in IgG4-positive plasma cells and immune deposits along the TBM.29 30 This interstitial nephritis can be associated with membranous nephropathy, with kidney inflammatory masses visible on imaging, or with ureteral obstruction. It usually responds rapidly to treatment with corticosteroids.

Other Systemic Diseases

Among patients with cryoglobulinemia and AKI, a few exhibit significant interstitial inflammatory infiltrates associated with granular immune deposits in the interstitium and along the TBM. This

Fig. 64.10 Granulomatous acute interstitial nephritis in a patient with sarcoidosis. (Courtesy Dr. B. Mougenot, Paris VI University, Paris.)

AIN is usually associated with characteristic glomerular lesions and, rarely, lesions of the arterioles, and treatment is the same as for cryoglobulinemia-induced GN (see Chapter 26).

Most kidney lesions associated with small-vessel vasculitis consist of both extracapillary GN and tubulointerstitial nephritis (see Chapter 26). Nevertheless, a few patients with AIN and minimal glomerular lesions have been described.

ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH MALIGNANCY

Infiltration of kidney parenchyma by malignant cells is common in patients with leukemia or lymphoma. Most of the time, this infiltration is clinically silent (or causes enlarged kidneys), but a few patients with AKI have been described.31 Chemotherapy or radiotherapy may rapidly improve kidney function in these patients, but before these treatments are started, it is important to exclude more common causes of AKI associated with cancer (see Chapter 67).

IDIOPATHIC ACUTE INTERSTITIAL NEPHRITIS

More than 50 cases of idiopathic AIN with anterior uveitis have been reported (tubulointerstitial nephritis and uveitis [TINU] syndrome).32 This syndrome is found most commonly in females of pubertal age but also can occur in pubertal males and in adults. Initial symptoms may be ocular, with ocular pain and visual impairment, or pseudoviral, with fever, myalgia, and asthenia. AIN is responsible for AKI, ranging from mild to severe, that may be associated with abnormal urinalysis. Kidney biopsy shows diffuse interstitial inflammatory infiltrates, almost always without granulomas and without immune deposits. In children, kidney prognosis is excellent, and serum creatinine usually returns to baseline values within a few weeks, with or without corticosteroid therapy. In adults the kidney prognosis seems to be less favorable, and corticosteroid therapy might be useful in preventing evolution to chronic kidney impairment. Uveitis, which can occur at any time in respect to AIN, is usually responsive to topical corticosteroids, but it may relapse without any recurrence of AIN.

Cases of idiopathic AIN without uveitis have been reported. IF studies of kidney biopsy specimens can show linear deposits of IgG along the TBM, granular deposits of IgG along the TBM, or no immune deposits, suggesting this entity is heterogeneous. The treatment of patients with idiopathic AIN is still controversial. Patients who receive corticosteroids usually show a dramatic improvement of kidney function, but others have recovered normal kidney function without any treatment.

ACUTE INTERSTITIAL NEPHRITIS IN KIDNEY TRANSPLANTS

Acute rejection is by far the most common cause of AIN in kidney allograft recipients (see Chapter 109). Nevertheless, AIN can be induced by drugs or infections. Cases of drug-induced AIN have been reported even in the first weeks after transplantation, when immunosuppression is maximal.33 Among patients with infectious AIN, the frequency of polyomavirus-induced AIN appears to be increasing, and it should be suspected in patients with acute deterioration of kidney function and so-called decoy cells in urine (see Chapter 110).34

SELF-ASSESSMENT QUESTIONS

1. A 65-year-old man presents with unexplained AKI. A kidney biopsy shows the presence of diffuse inflammatory infiltrates within the interstitium, leading to the conclusion that the AKI is a result of AIN. He has a recent history of treatment with an NSAID and a PPI for osteoarthritis. Which one of the following statements is correct?
A. Both NSAIDs and PPIs are among the classes of drugs most commonly responsible for AIN.
B. Only very few cases of AIN have been attributed to treatment with a PPI, and the AIN was most likely induced by treatment with an NSAID.
C. Only very few cases of AIN have been attributed to treatment with an NSAID, and the AIN was most likely induced by treatment with a PPI.
D. Only very few cases of AIN have been attributed to treatment with a PPI or an NSAID, and the AIN is unlikely to have been induced by treatment with an NSAID or a PPI.
2. A 75-year-old woman presents with AKI associated with mild proteinuria (albumin-to-creatinine ratio 500 mg/g), microscopic hematuria, and pyuria. AKI developed while she was being treated with a fluoroquinolone, and her treating physician suspects that it was caused by AIN induced by the fluoroquinolone. Which one of the following statements is correct?
A. The patient should be tested for eosinophiluria. If less than 1% of urinary white blood cells are eosinophils, the diagnosis of AIN can almost certainly be ruled out.
B. The patient should undergo a kidney gallium scan. If there is no kidney uptake, the diagnosis of AIN can almost certainly be ruled out.
C. The presence of an elevated ratio of albumin to creatinine is sufficient to rule out the diagnosis of drug-induced AIN in a patient who previously did not have albuminuria and who has not been treated with an NSAID.
D. A kidney biopsy is the only test that can be performed to reliably rule out or confirm the diagnosis of AIN.
3. A 30-year-old woman develops AKI while being treated with penicillin. A kidney biopsy shows diffuse interstitial infiltrates, confirming the diagnosis of AIN. Her serum creatinine has been stable at 3.0 mg/dL for the last 5 days. Which one of the following statements is correct?
A. The prognosis for drug-induced AIN is excellent, and full recovery should be expected within 6 weeks after removal of the inciting agent.
B. The prognosis for drug-induced AIN is excellent in patients who do not have granulomas on renal biopsy, and full recovery should be expected.
C. The prognosis for drug-induced AIN is excellent in patients who do not require dialysis, and full recovery should be expected if serum creatinine does not continue to rise.

D. The course of drug-induced AIN is not always benign, and it leads to chronic kidney disease in at least 40% of cases.

REFERENCES

1. Neilson EG. Pathogenesis and therapy of interstitial nephritis. Kidney Int. 1989;35(5):1257–1270.
2. Goicoechea M, Rivera F, Lopez-Gomez JM. Increased prevalence of acute tubulointerstitial nephritis. Nephrol Dial Transplant. 2013;28(1):112–115.
3. Ulinski T, Sellier-Leclerc AL, Tudorache E, et al. Acute tubulointerstitial nephritis. Pediatr Nephrol. 2012;27(7):1051–1057.
4. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis. 2014;64(4):558–566.
5. Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. Kidney Int. 2014;86(4):837–844.
6. Fernandz-Juarez G, Perez JV, Caravaca- Fontan F, et al. Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. Clin J Am Soc Nephrol. 2018;13(12):1851–1858.
7. Schmid S, Opravil M, Moddel M, et al. Acute interstitial nephritis of HIVpositive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. Virchows Arch. 2007;450(6):665–670.
8. Airy M, Raghavan R, Truong LD, Eknoyan G. Tubulointerstitial nephritis and cancer chemotherapy: update on a neglected clinical entity. Nephrol Dial Transplant. 2013;28(10):2502–2509.
9. Xu C, Chen Y-P., Du X-J., et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network metaanalysis. BMJ. 2018;363:k4226.
10. Seethapathy H, Zhao S, Chute D, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol. 2019;14(12):1692–1700.
11. Hultin S, Nahar K, Menzies AM, et al. Histological diagnosis of immune checkpoint inhibitor induced acute renal injury in patients with metastatic melanoma: a retrospective case series report. BMC Nephrol. 2020;21:391.
12. Covic A, Goldsmith DJ, Segall L, et al. Rifampicin-induced acute renal failure: a series of 60 patients. Nephrol Dial Transplant. 1998;13(4):924–929.
13. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother. 1993;27(3):337–343.
14. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176(2):238–246.
15. Gupta S, Cortazar FB, Riella L, Leaf DE. Immune checkpoint inhibitor nephrotoxicity: update 2020. Kidney360. 2020;1:130–140.
16. Perazella MA. Kidney biopsy should be performed to document the cause of immune checkpoint inhibitor – associated acute kidney injury: commentary. Kidney. 2020;360(1):166–168.
17. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. Clin J Am Soc Nephrol. 2013;8(11):1857–1862.

18. Corwin HL, Bray RA, Haber MH. The detection and interpretation of urinary eosinophils. Arch Pathol Lab Med. 1989;113(11):1256–1258.
19. Graham F, Lord M, Froment D, et al. The use of gallium-67 scintigraphy in the diagnosis of acute interstitial nephritis. Clin Kidney J. 2016;9(1):76–81.
20. Gonzalez E, Gutierrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int. 2008;73(8):940–946.
21. Preddie DC, Markowitz GS, Radhakrishnan J, et al. Mycophenolate mofetil for the treatment of interstitial nephritis. Clin J Am Soc Nephrol. 2006;1(4):718–722.
22. Krautkramer E, Zeier M, Plyusnin A. Hantavirus infection: an emerging infectious disease causing acute renal failure. Kidney Int. 2013;83(1):23–27.
23. Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. Curr Opin Crit Care. 2008;14(6):647–653.
24. Hamzah L, Booth JW, Jose S, et al. Renal tubular disease in the era of

combination antiretroviral therapy. AIDS. 2015;29(14):1831–1836.
25. Rajakariar R, Sharples EJ, Raftery MJ, et al. Sarcoid tubulo-interstitial nephritis: long-term outcome and response to corticosteroid therapy. Kidney Int. 2006;70(1):165–169.
26. Hannedouche T, Grateau G, Noel LH, et al. Renal granulomatous sarcoidosis: report of six cases. Nephrol Dial Transplant. 1990;5(1):18–24.
27. Francois H, Mariette X. Renal involvement in primary Sjögren syndrome. Nat Rev Nephrol. 2016;12(2):82–93.
28. Mori Y, Kishimoto N, Yamahara H, et al. Predominant tubulointerstitial nephritis in a patient with systemic lupus nephritis. Clin Exp Nephrol. 2005;9(1):79–84.
29. Raissian Y, Nasr SH, Larsen CP, et al. Diagnosis of IgG4-related tubulointerstitial nephritis. J Am Soc Nephrol. 2011;22(7):1343–1352.
30. Saeki T, Kawano M. IgG4-related kidney disease. Kidney Int. 2014;85(2):251–257.
31. Tornroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. Am J Kidney Dis. 2003;42(5):960–971.
32. Liakopoulos V, Ioannidis I, Zengos N, et al. Tubulointerstitial nephritis and uveitis (TINU) syndrome in a 52-year-old female: a case report and review of the literature. Ren Fail. 2006;28(4):355–359.
33. Josephson MA, Chiu MY, Woodle ES, et al. Drug-induced acute interstitial nephritis in renal allografts: histopathologic features and clinical course in six patients. Am J Kidney Dis. 1999;34(3):540–548.
34. Hariharan S. BK virus nephritis after renal transplantation. Kidney Int. 2006;69(4):655–662.

65

Chronic Interstitial Nephritis

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DEFINITION

Chronic interstitial nephritis is a histologic entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, macrophage and lymphocytic infiltration, and interstitial fibrosis. Because the degree of tubular damage accompanying interstitial nephritis is variable, the term tubulointerstitial nephritis is used interchangeably with interstitial nephritis. Tubulitis refers to infiltration of the tubular epithelium by leukocytes, usually lymphocytes.

There are many primary and secondary causes of chronic interstitial nephritis (Box 65.1). Tubulointerstitial injury is clinically important because it is a better predictor than the degree of glomerular injury of present and future renal function. Although any glomerular disease can cause secondary injury to the tubulointerstitium through the effects of proteinuria and ischemia, in this chapter we discuss only primary chronic interstitial nephritis.

PATHOGENESIS

The tubulointerstitium can be injured by toxins (e.g., heavy metals), drugs (e.g., analgesics), crystals (e.g., calcium phosphate, uric acid), infections, obstruction, immunologic mechanisms, and ischemia.

Regardless of the initiating mechanism, the tubulointerstitial response shows little variation. Tubular injury results in the release of chemotactic substances and the expression of leukocyte adhesion molecules that attract inflammatory cells into the interstitium. Tubular cells express human leukocyte antigens, serve as antigen-presenting cells, and secrete complement components and vasoactive mediators, all of which may further stimulate or attract macrophages and T cells.

Growth factors released by tubular cells and macrophages, such as platelet-derived growth factor and transforming growth factor β, may stimulate fibroblast proliferation and activation, leading to matrix accumulation.1 The source of fibroblasts in renal interstitial fibrosis remains controversial but may include an intrinsic fibroblast (perivascular Gli1-positive progenitors) population, migration of circulating fibrocytes from perivascular areas, and phenotypic transition of pericytes into fibroblasts.2 Over time, a loss of peritubular capillaries and decreased oxygen diffusion caused by expansion of the interstitium render the kidney hypoxic, and progressive apoptosis leads to local hypocellularity and fibrosis.2 Kidney function can become severely decreased, and kidney replacement therapy may be required.

EPIDEMIOLOGY

Whereas chronic interstitial nephritis occurs with progressive kidney disease of all causes, primary chronic interstitial nephritis is not a common cause of end-stage kidney disease (ESKD); reports range from 42% in Scotland to 3% to 4% in China and the United States.3–5 This

variability in reported incidence may relate to differences in how diagnoses are made, exposure to causal factors, and treatment modalities, such as the choice of antibiotics and the indication for pain killers.

Marked increases in the incidence of chronic interstitial nephritis have been reported in certain areas. Chronic kidney disease of unknown etiology/uncertain cause (CKDu) is a type of CKD that mainly affects agricultural communities in specific areas of the world. These regional nephropathies include Sri Lanka and India, some coastal areas of Central America, and the Balkan region in Europe (see Chapters 66 and 79).

PATHOLOGY

The pathologic features of chronic interstitial nephritis are nonspecific. They include tubular cell atrophy or dilation; interstitial fibrosis that

is composed of interstitial (types I and II) collagens; and mononuclear cell infiltration with macrophages, T cells, and occasionally other cell types (neutrophils, eosinophils, and plasma cells). Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts producing a thyroid-like appearance, hence the term thyroidization.
Some forms of chronic interstitial nephritis are associated with granulomatous lesions. Whereas a noncaseating granulomatous pattern is typical of sarcoidosis, interstitial granulomatous reactions also occur in response to infection of the kidney by mycobacteria (Fig. 65.1), fungi, or bacteria; certain drugs (including rifampin, sulfonamides, proton pump inhibitors [PPIs], and narcotics); and oxalate or uric acid crystal deposition.6 Interstitial granulomatous reactions have been noted in renal malacoplakia (Chapter 53), granulomatous polyangiitis, heroin abuse, and after jejunoileal bypass surgery. The etiology for granulomatous interstitial nephritis remains obscure in 10% of cases.

CLINICAL MANIFESTATIONS

The impaired kidney function is often insidious, and the early manifestations of the disease are those of tubular dysfunction, which may go undetected (Box 65.2).7 Diagnosis is often made incidentally on routine laboratory screening or during evaluation of hypertension, in association with reduced glomerular filtration rate (GFR). Proteinuria is commonly less than 1 g/day. Urinalysis may show only occasional white blood cells (WBCs) and, rarely, WBC casts. Hematuria is uncommon. Anemia may occur relatively early because of dysfunction or loss of renal erythropoietin-producing cells in the interstitium.
The tubular dysfunction is often generalized, but some conditions may manifest with proximal tubular defects, including aminoaciduria, phosphaturia, proximal renal tubular acidosis (RTA), or, rarely, complete Fanconi syndrome (see Chapter 50). Distal tubular defects can be associated with distal RTA (type 1 or type 4; see Chapter 13).

BOX 65.1

Major Causes of Chronic Interstitial Nephritis[a]

BOX 65.2

Diseases in Which the Kidneys Are Macroscopically Normal

- Drugs and toxins (e.g., aristolochic acid, lithium, cyclosporine, tacrolimus, indinavir, cisplatin, proton pump inhibitors)
- Metabolic (hyperuricemia, hypokalemia, hypercalcemia, hyperoxaluria, cystinosis)
- Heavy metals (lead, cadmium, arsenic, mercury, gold, uranium)
- Radiation
- Balkan nephropathy
- Mesoamerican nephropathy
- Immune-mediated conditions (systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, granulomatous polyangiitis, other vasculitides)
- Vascular diseases (atherosclerotic kidney disease) (see Chapter 43)
- Transplantation (chronic transplant rejection)
- Hematologic disturbances (multiple myeloma, light-chain deposition disease, lymphoma, sickle cell disease, paroxysmal nocturnal hemoglobinuria) (see Chapters 51 and 68)
- Progressive glomerular disease of any cause (glomerulonephritides, diabetes, hypertension)
- Idiopathic

- Deterioration of glomerular filtration rate with insidious onset
- Tubular proteinuria mainly composed of low-molecular-weight protein (generally <1 g/day)
- Inactive urinary sediment
- Anemia of chronic kidney disease at a relatively early stage
- Proximal tubular dysfunction (aminoaciduria, phosphaturia, proximal renal tubular acidosis, Fanconi syndrome)
- Distal tubular dysfunction (type IV renal tubular acidosis)
- Medullary dysfunction (concentrating defects)
- Salt-wasting syndrome
- Salt-sensitive hypertension

Diseases in Which the Kidneys Are Macroscopically Abnormal

- Analgesic nephropathy
- Chronic obstruction (see Chapter 61)
- Hereditary (nephronophthisis, medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease)
- Infection (chronic pyelonephritis, malacoplakia, xanthogranulomatous pyelonephritis; see Chapter 53)

[a] Kidneys of any clinical entity can be shrunken at end-stage. Some diseases categorized as macroscopically normal can, in later stages, result in macroscopically abnormal kidneys. For example, kidneys of sickle cell nephropathy are macroscopically normal unless papillary necrosis is present.

Functional Manifestations of Chronic Interstitial Nephritis

Concentrating defects (increased urinary frequency and nocturia) can be a sign of medullary dysfunction and may be severe enough to result in nephrogenic diabetes insipidus. Some patients develop a saltwasting syndrome. Others, particularly with microvascular disease, may have a relative inability to excrete salt with resultant salt-sensitive hypertension.[8]

Clues to the causes of tubulointerstitial nephritis by history and physical examination are shown in Table 65.1[9]

TREATMENT

Treatment includes identification and elimination of any exogenous agents (drugs, heavy metals), metabolic causes (hypercalcemia), or conditions (obstruction, infection) potentially causing the chronic interstitial lesion. In addition to classic drugs and toxins, a growing list of medications (e.g., PPIs) is now being linked to the risk for developing CKD, which emphasizes the need to consider the risk and benefit of any drug carefully, particularly in patients with a progressive course. Specific treatments may be required for an underlying cause of chronic interstitial nephritis, such as corticosteroids for sarcoidosis. General measures include control of blood pressure. Most clinicians favor the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which reduce glomerular and systemic pressures, decrease proteinuria, and increase renal blood flow. However, the role of ACE inhibitors and ARBs is less clear when blood pressure is normal or when there are excessive solute losses (such as salt-wasting). Specific therapies for each clinical entity are discussed later.

DRUG-INDUCED CHRONIC INTERSTITIAL NEPHRITIS

Several drugs and herbs can cause chronic interstitial nephritis. Cyclosporine- and tacrolimus-induced nephropathy are discussed in Chapter 106; aristolochic acid as a cause of aristolochic acid–associated nephropathy (formerly known as Chinese herbs nephropathy and Balkan nephropathy) is discussed in Chapter 79

Lithium Nephropathy

Definition and Epidemiology

Fig. 65.1 Renal Tuberculosis. Noncaseating granulomas with epithelioid cells in miliary tuberculosis (arrows show the peripheries of the granulomas). Although the typical pathologic change is granuloma with caseous necrosis with Langerhans-type giant cells, these atypical granulomas can be observed in tuberculosis and should be differentiated from sarcoidosis. (H&E stain.) (Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)

Lithium is commonly used in the treatment of bipolar disorder. Complications of lithium treatment include nephrogenic diabetes insipidus, acute lithium intoxication, and chronic lithium nephrotoxicity. A meta-analysis of the data of 14 studies involving 1172 patients receiving chronic lithium therapy showed that the prevalence of reduced GFR was 15%.[10]

TABLE 65.1

Examination

Clues to Causes of Tubulointerstitial Nephritis by History and Physical

Feature

Symptom, Sign, or Historical Clue

Potential Diagnosis

Occupational history
Alcohol
Social history
Past history

Exposure to heavy metals (e.g., batteries, alloys)
History of moonshine ingestion
Country of origin
Systemic lupus erythematosus
Sjögren syndrome
Sarcoidosis
Inflammatory bowel disease
Autoimmune pancreatitis
Chronic pain syndrome
Gouty attack
Prescribed
OTC (NSAIDs, PPIs)
Herbal
Indinavir
Dry eyes
Uveitis
Hyperuricemia
Hypokalemia
Hypercalcemia
High serum IgG4 levels
Decreased volume, bumpy contours, and papillary calcification on CT
Microcysts on MRI or ultrasound
Nephrocalcinosis on CT

Lead or cadmium nephropathy
Lead nephropathy
Balkan nephropathy
Disease-associated chronic interstitial nephritis

Medication

Physical examination
Laboratory examination

Radiologic examination

Analgesic nephropathy
Lead nephropathy
Drug-induced chronic interstitial nephritis
Analgesic
Aristolochic acid-associated nephropathy
Crystal nephropathy
Sjögren syndrome

TINU syndrome
Chronic uric acid nephropathy
Hypokalemic nephropathy
Hypercalcemic nephropathy
IgG4-related sclerosing disease
Analgesic nephropathy
Lithium nephropathy
Hypercalcemic nephropathy

CT, Computed tomography; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs; OTC, over the counter; PPIs, proton pump inhibitors; TINU, tubulointerstitial nephritis and uveitis.

Modified from Beck LH Jr, Salant DJ. Glomerular and tubulointerstitial diseases. Prim Care. 2008;35:265–296.

Pathogenesis

Diabetes insipidus results from accumulation of lithium in the collecting tubular cells after entry into these cells through sodium channels in the luminal membrane. Lithium blocks vasopressin-induced reabsorption by inhibiting adenylate cyclase activity, and hence cyclic adenosine monophosphate production, and also by decreasing the apical membrane expression of aquaporin 2, the collecting tubule water channel.

Chronic lithium-induced interstitial nephritis may occur, possibly because of inositol depletion and inhibition of cell proliferation.

Pathology

Biopsies show focal chronic interstitial nephritis with interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Although similar histologic changes have been reported in psychiatric patients without a history of lithium therapy, patients with lithium exposure often show microcystic changes in the distal tubule; interstitial inflammation and vascular changes are relatively minor. The degree of interstitial fibrosis is related to the duration of administration and cumulative dose.

Clinical Manifestations

Lithium-associated diabetes insipidus. The most common presentation of lithium-induced nephrotoxicity is nephrogenic diabetes insipidus, characterized by resistance to vasopressin, polyuria, and polydipsia. Impaired urinary concentrating ability is found in about 50% of patients, and polyuria resulting from nephrogenic diabetes insipidus occurs in about 20% of patients chronically treated with lithium. Lithium is also rarely a cause of hypercalcemia, which could potentially exaggerate the tubular concentrating defect and contribute to the development of chronic interstitial nephritis in lithium-treated patients. Nephrogenic diabetes insipidus in lithium treatment may be associated with distal RTA, although this partial functional defect is virtually never of clinical importance.

Chronic lithium nephropathy. In a retrospective analysis of data from the United Kingdom, the presence of lithium in serum was associated with an increased risk for stage 3 CKD (hazard ratio 1.93), with females aged younger than 60 years and those with lithium concentrations higher than median at increased risk.11 Nephrogenic diabetes insipidus induced by lithium may persist despite the cessation of treatment, indicating irreversible renal damage.

In one study, the mean serum creatinine concentration of patients with biopsy-proven chronic lithium nephrotoxicity was 2.8 mg/dL (247 µmol/L) at the time of biopsy, and 42% of patients had proteinuria greater than 1 g/day.12 After kidney biopsy, all but one patient discontinued treatment with lithium, but seven patients nevertheless progressed to ESKD. A study of 74 lithium-treated patients in France showed that lithium-induced nephropathy developed slowly over several decades, with an average latency between the start of therapy and

ESKD of 20 years.11

Magnetic resonance imaging, in particular the half-Fourier acquisition single-short turbo spin-echo T2-weighted sequence, without the use of gadolinium, or ultrasound may help in detection of the characteristic microcysts in the kidney.13

Treatment

After other potential causes of polyuria and polydipsia have been excluded, particularly psychogenic polydipsia, the first step to consider is a reduction in lithium dosage. The potassium-sparing diuretic amiloride improves the polyuria and also blocks lithium uptake through sodium channels in the collecting duct. Thiazide diuretics should be avoided because they increase the risk for acute lithium intoxication because of the resultant volume contraction and an increase in sodium and lithium reabsorption in the proximal tubule. ACE inhibitors are generally not used because of the risk for hypotension and worsening GFR in the setting of volume depletion.

Patients undergoing long-term lithium treatment should have kidney function (serum creatinine and estimated GFR) and 24-hour urine volume measured yearly. Lithium has a narrow therapeutic index, so levels should be monitored and maintained between 0.6 and 1.25 mmol/L. The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5–2.0 mmol/L), moderate (2.0–2.5 mmol/L), or severe (>2.5 mmol/L). Once-daily regimens are less toxic than multiple daily administration schedules, perhaps because of the possibility of renal tubular regeneration with a once-daily administration schedule.14 Prevention of volume depletion is also important.

Because progressive kidney injury with reduced GFR in patients without prior acute lithium intoxication is relatively unusual, reductions in GFR initially should be treated by decreasing the dose of lithium. If GFR is persistently reduced, a kidney biopsy should be considered, although the findings rarely mandate the cessation of lithium treatment. At all times, the risk for discontinuation in a patient with a severe unipolar or bipolar affective disorder needs to be balanced against the relatively low risk for progressive kidney injury.

A

Analgesic Nephropathy

Definition and Epidemiology

Analgesic nephropathy resulted from the abuse of analgesics, commonly mixtures containing phenacetin, aspirin, and caffeine, that were available as over-the-counter preparations in Europe and Australia. It is now extremely rare; indeed, some doubt that new cases are still presenting, after restrictions in compound analgesic sales.15 A large study in the United States showed no association between use of current analgesic preparations and increased risk for chronic kidney dysfunction,16 although it does increase the risk for acute kidney injury (see Chapter 70).

Pathogenesis and Pathology

The primary injury in analgesic nephropathy is medullary ischemia caused by toxic concentrations of phenacetin metabolites combined with relative medullary hypoxia, aggravated by inhibition of vasodilatory prostaglandin synthesis and glutathione (an antioxidant) levels. The main pathologic consequence is papillary necrosis, with secondary tubular atrophy, interstitial fibrosis, and a mononuclear cellular infiltrate (Fig. 65.2).

Clinical Manifestations

Analgesic nephropathy is five to seven times more common in females than in males. Kidney manifestations are nonspecific and consist of slowly progressive CKD with impaired urine concentrating ability, urinary acidification defects, and impaired sodium conservation. Patients may present with hypertension, reflecting the use of nonsteroidal antiinflammatory drugs (NSAIDs), and degree of kidney parenchymal injury. Urinalysis shows sterile pyuria and mild proteinuria. Patients with analgesic nephropathy are at increased risk for transitional cell carcinoma of the uroepithelium. A recent prospective analysis of the Nurses' Health Study and the Health Professionals Follow-up Study also showed an association of regular use of nonaspirin NSAIDs with an increased risk of renal cell carcinoma, but aspirin and acetaminophen use were not implicated.17

B

Fig. 65.2 Histologic Changes in Analgesic Nephropathy. (A) Interstitial nephritis in a patient with analgesic nephropathy associated with marked mononuclear cellular infiltrate including eosinophils (arrows). (H&E stain; original magnification ×600.) (B) Analgesic nephropathy with interstitial fibrosis and inflammatory cell infiltration. (Masson trichrome stain; original magnification ×400.) (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Diagnosis

Papillary necrosis is present histologically in almost all patients, but it can be detected radiologically only if part or all of the papilla has sloughed. Papillary necrosis is not pathognomonic of analgesic nephropathy; it is also seen in diabetic nephropathy (particularly during an episode of acute pyelonephritis), sickle cell nephropathy, urinary tract obstruction, and renal tuberculosis. Non–contrastenhanced computed tomography (CT) demonstrates a decrease in renal mass with either bumpy contours or papillary calcifications (Fig. 65.3; see also Chapter 51).18

Treatment

Management consists of stopping or at least reducing the intake of analgesic medications. Because of the increased incidence of uroepithelial tumors, close follow-up, including regular urinalysis, is necessary. New hematuria requires early referral for urologic evaluation, which includes urinary cytology, cystoscopy, and CT scan. It would be prudent to perform yearly urinary cytologic examination at least several years after cessation of analgesics.

Analgesic nephropathy associated with over-the-counter medicines is also discussed in Chapter 79

A

Fig. 65.3 Papillary Calcifications in Analgesic Nephropathy. Non–contrast-enhanced computed tomography scan of a patient with longtime analgesic abuse shows thinning of the renal parenchyma and typical papillary calcifications (arrows). (Courtesy Dr. Yoshifumi Ubara, Toranomon Hospital, Tokyo.)

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY METABOLIC DISORDERS

Metabolic disorders that cause interstitial nephritis are discussed here. Hyperoxaluria is described in Chapter 60 and cystinosis in Chapter 50

Chronic Uric Acid Nephropathy

Definition and Epidemiology

Nearly half of patients with gout have reduced GFR, and most have evidence for CKD at autopsy. An elevated serum uric acid has also been consistently shown to predict the development of CKD.[19] This has led many investigators to propose that hyperuricemia and/or gout may be a cause of CKD,[20] either from the deposition of urate crystals in the kidney or from effects of soluble uric acid to active inflammatory processes. Nevertheless, two recent clinical trials of urate-lowering therapy in subjects with CKD were negative, challenging whether chronic uric acid nephropathy exists.[21,22]

Pathogenesis

Chronic gout and severe hyperuricemia can be associated with the deposition of uric acid crystals in the renal medulla (Fig. 65.4). A recent study suggests this may be present in as many as a third of subjects with gout and that it can be diagnosed by ultrasound findings of a hyperechoic renal medulla.[23] The deposition of urate crystals can cause injury to the tubules and rupture into the interstitium where they cause inflammasome activation with inflammation and fibrosis. Experimental studies also suggest that high levels of soluble uric acid may also cause chronic kidney injury by activating the renin-angiotensin system and inducing oxidative stress, resulting in microvascular disease, glomerular hypertension, and impaired renal autoregulation.[24]

Pathology

Renal functional abnormalities are observed in 30% to 50% of patients who have had gout for many years, and histologic changes are observed in more than 90%.[25] The most consistent histologic findings are arteriolosclerosis, focal or global glomerulosclerosis, and chronic tubulointerstitial disease. Uric acid crystals also can be occasionally found within tubules and in the interstitium (see Fig. 65.4), especially in the outer medulla, and, on rare occasions, medullary kidney tophi can be found on gross anatomic dissection.

B

Fig. 65.4 Chronic Uric Acid Nephropathy. (A) Large collections of elongated or fragmented uric acid crystals are present in association with atrophic tubules. (H&E stain; original magnification ×400.) (B) The crystalline masses are refractile under polarized light. (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Clinical Manifestations

Patients with gout often present with hypertension with mildly impaired kidney function, mild proteinuria, unremarkable urinary sediment, and minor tubular dysfunction (usually impairment of urine-concentrating ability manifested as isosthenuria). Approximately one-third of subjects with CKD also have a history of gout, and nearly 50% have hyperuricemia. A role for uric acid in CKD should particularly be considered if there is a disproportionate elevation in serum uric acid in relation to the degree of GFR reduction (Table 65.2).26

Diagnosis

The most important differential diagnosis for chronic uric acid nephropathy is chronic lead nephropathy. Familial juvenile hyperuricemic nephropathy is a rare autosomal dominant disease that mimics chronic gouty nephropathy but manifests in adolescence or during early childhood (see Chapter 50).

Treatment

It remains controversial whether lowering uric acid can improve kidney disease in patients with gout or hyperuricemia. One randomized trial

TABLE 65.2 Serum Creatinine and Uric Acid Levels in Chronic Kidney Disease

SERUM CREATININE		SERUM URIC ACID	
mg/dL	µmol/L	mg/dL	µmol/L
<1.5	<132	9	536
1.5–2.0	132–176	10	595
>2.0	>176	12	714

Serum uric acid levels are increased with decreased glomerular filtration rate, but if uric acid levels are especially high for the level of creatinine, then chronic urate nephropathy should be considered. Shown are threshold levels of uric acid for which higher levels should increase the suspicion for chronic urate nephropathy.

Modified from Badve SV, Pascoe EM, Tiku A, et al.; CKD-FIX Study Investigators. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382:2504–2513.

demonstrated that allopurinol therapy is associated with preservation of eGFR in CKD, although the treatment did not show any effects on the defined study endpoint, which was ESKD.27 Withdrawal of allopurinol from patients with stable CKD has resulted in worsening of hypertension and acceleration of kidney dysfunction, especially in patients who were not on ACE inhibitors.28 Lowering uric acid in patients with asymptomatic hyperuricemia is also associated with an increase in eGFR.29 There also have been reports that lowering uric acid may reduce the risk for cardiovascular disease in patients with CKD.27 30 Recently, two placebocontrolled randomized trials did not find lowering uric acid to be of benefit in subjects with type 1 diabetes and CKD (the PERL study)21 and in subjects with CKD (CKD-Fix Trial).22 However, both studies recruited subjects with normal uric acid levels in which benefit was not expected, and both excluded subjects with a history of gout, which was the group most expected to benefit.

We still recommend lowering uric acid in subjects with CKD who have markedly elevated serum uric acid levels (>8–9 mg/dL) or a history of gout with evidence of active progression of CKD. To reduce the risk for a hypersensitivity reaction (Stevens-Johnson–like syndrome), allopurinol should be initiated at a dose of 50 to 100 mg/day, increasing to 200 or 300 mg/day after several weeks as tolerated. The allopurinol hypersensitivity syndrome is more common in subjects who carry HLA-*B58:01, and typing subjects before initiation of treatment may be of benefit in subjects who are Han Chinese or Korean that are more likely to carry this HLA antigen.

The newer xanthine oxidase inhibitor febuxostat does not require modification of dose at lower eGFR and appears to be less frequently associated with hypersensitivity or nephrotoxicity, but there are some studies that suggest that its use may be associated with greater cardiovascular mortality than that observed with allopurinol.31

Hypokalemic Nephropathy

Fig. 65.5 Hypokalemic Nephropathy. Vacuolization of the renal tubules is observed in association with interstitial fibrosis in a patient with hypokalemic nephropathy. (Masson trichrome stain; original magnification ×400.) (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

(Fig. 65.5). This abnormality generally requires at least 1 month to develop and is reversible with potassium supplementation. More prolonged hypokalemia can lead to more severe changes, predominantly in the kidney medulla, including interstitial fibrosis, tubular atrophy, and cyst formation. There is experimental evidence that hypokalemic injury may be caused by hypokalemia-induced renal vasoconstriction with ischemia. Local ammonia production stimulated by hypokalemia also may lead to intrarenal complement activation that may contribute to the kidney injury. Furthermore, the associated intracellular acidosis can stimulate cell proliferation, which may account for the occasional development of cysts in hypokalemic patients.

Clinical Manifestations

Impaired urinary concentration, manifesting with nocturia, polyuria, and polydipsia, may occur, particularly when serum potassium concentration is consistently below 3.0 mmol/L for months or years. The average duration of hypokalemia reported in patients with chronic hypokalemic nephropathy is 3.5 to 9 years. The renal defect is associated with decreased collecting tubule responsiveness to vasopressin, possibly because of decreased expression of aquaporin 2.

Diagnosis

Although degenerative changes in proximal tubular cells are a consistent but nonspecific finding in hypokalemic nephropathy, a particularly characteristic finding is vacuolar changes in the proximal tubules (see Fig. 65.5). Similar vacuolization of the convoluted tubules is observed in ethylene glycol poisoning.

Definition and Epidemiology

Treatment

Hypokalemia, if persistent for prolonged periods, can induce kidney cysts, chronic interstitial nephritis, and progressive loss of kidney function, known as hypokalemic nephropathy, which can be inherited or acquired. Hypokalemic nephropathy occurs in 15% to 20% of individuals with anorexia nervosa.32

Hypokalemia usually can be treated with oral potassium supplements. The treatment of hypokalemia is discussed in Chapter 10. Coarse cytoplasmic vacuoles may persist for some time after normalization of serum potassium values.

Pathology

Definition and Epidemiology

The characteristic finding is vacuolation of the kidney tubules as a result of dilation of cisternae of the endoplasmic reticulum and basal folding, which is usually limited to the proximal tubular segments

Hypercalcemic Nephropathy

Hypercalcemia can cause transient and reversible kidney vasoconstriction with a decrement in kidney function and chronic interstitial nephritis secondary to tubular cell necrosis and intratubular

A

B

C

Fig. 65.6 Hypercalcemic Nephropathy Caused by Sarcoidosis. (A) Marked tubular atrophy and interstitial fibrosis with mild lymphocytic infiltrate. (B) Dense calcium deposits are seen in the thickened basement membrane of the atrophic tubules and in the fibrotic area of interstitium (serial section of A). (C) Intraluminal calcium plaque in the atrophic tubules. Granular calcium deposits are observed in the arterial wall (arrow). (A, PAS stain. B–C, von Kossa stain.) (Courtesy Dr. Noriko Uesugi, Ibaraki, Japan.)

obstruction. In addition, hypoparathyroidism (especially after surgical treatment of hyperparathyroidism) can result in marked hypercalciuria and a similar syndrome in the absence of hypercalcemia.

blood flow. Irreversible, advanced CKD is a rare consequence of longstanding hypercalcemia and is almost invariably associated with calcium crystal deposition in the interstitium of the kidney.

Pathology

CHRONIC INTERSTITIAL NEPHRITIS CAUSED BY HEREDITARY DISEASES OF THE KIDNEY

Focal degeneration and necrosis of the tubular epithelium, primarily in the medulla, where calcium is concentrated, develop soon with persistent hypercalcemia. Although focal degenerative and necrotic lesions of the tubular epithelium can be observed with acute hypercalcemia, the most distinctive histologic feature of long-standing hypercalcemia is calcific deposits in the interstitium (nephrocalcinosis; Fig. 65.6). Deposition begins in the medullary tubules, followed by deposition in the cortical proximal and distal tubules and within the interstitial space and secondarily leads to mononuclear cell infiltration and tubular necrosis.

Clinical Manifestations

Macroscopic nephrocalcinosis is often detected on radiography or ultrasound. A defect in urinary concentration is the most notable tubular dysfunction and manifests as polyuria and polydipsia. The mechanism is incompletely understood, but the impairment relates both to a reduction in medullary solute content and to interference with the cellular response to vasopressin. Reversible impairment of eGFR can result from either acute or chronic hypercalcemia by decreased renal

Nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD), or autosomal dominant tubulointerstitial kidney disease (ADTKD) (or the NPHP-MCKD complex) are hereditary diseases associated with renal cysts at the corticomedullary junction.

Karyomegalic interstitial nephritis is a hereditary form of chronic tubulointerstitial nephritis histologically characterized by nuclear enlargement with irregular outlines, hyperchromatic aspect, and prominent nucleoli. These disorders are described in detail in Chapters 47 and 50

CHRONIC INTERSTITIAL NEPHRITIS ASSOCIATED WITH HEAVY METAL EXPOSURE

Lead Nephropathy

Definition and Epidemiology

Acute lead intoxication is rare but may manifest with abdominal pain, encephalopathy, hemolytic anemia, peripheral neuropathy, and proximal tubular dysfunction (Fanconi syndrome). In contrast, chronic low-level exposure to lead is associated with CKD, often with hyperuricemia. Because lead has a biologic half-life of several decades, both intermittent acute poisoning and low-level environmental exposure result in chronic cumulative lead poisoning.

Although some epidemiologic studies have suggested that low-level exposure may be associated with CKD or hypertension,33–35 data indicating that lead causes CKD and ESKD are relatively sparse,36 although there may be regional differences in the observed risk because of geographic variation in exposure. The pathogenesis of the kidney disease may be related to the accumulation of reabsorbed lead in the proximal tubule cells, effects of chronic lead exposure on the vasculature, or lead-induced hyperuricemia. Additional well-controlled longitudinal studies with adequate exposure and effect variables are awaited to confirm that lead exposure causes deterioration of renal function and eventual ESKD.

Pathology

The kidneys are granular and contracted. The characteristic morphology is chronic interstitial nephritis demonstrating nonspecific tubular atrophy, interstitial fibrosis, and a paucity of inflammatory cells. The earliest histologic finding is proximal tubular injury, with intranuclear inclusion bodies composed of a lead-protein complex. Glomerular scarring can be observed as a secondary event, and arteries and arterioles demonstrate medial thickening and luminal narrowing, probably related to hypertension. Immunofluorescence (IF) studies are noncontributory.

Clinical Manifestations

Chronic lead nephropathy is usually identified when a source of high exposure is known (occupational hazard or consumption of illicitly distilled spirits [moonshine]). Hyperuricemia is common because of impaired uric acid excretion. Urine sediment is benign, and urinary protein excretion is less than 2 g/day. Hypertension is almost always present, and in the absence of appropriate testing or a careful exposure history, lead nephropathy is often misdiagnosed as hypertensive kidney disease. Gouty arthritis (“saturnine gout”) affects about half of patients. Patients with chronic lead intoxication may occasionally manifest other signs, including peripheral motor neuropathy, anemia with basophilic stippling, and perivascular cerebellar calcification.

Diagnosis

Lead nephropathy may be underdiagnosed because no simple diagnostic blood test is available. Lead nephropathy is easily confused with chronic uric acid nephropathy, in which uric acid deposits (tophi) may form in the renal interstitium. All patients with hyperuricemia and reduced eGFR should have a history of occupational lead exposure excluded. The blood lead concentration is an insensitive measure of cumulative body stores. A clinical diagnosis of lead nephropathy is based on a history of exposure, evidence of kidney dysfunction, and an abnormal calcium disodium edetate ($CaNa_2$ EDTA) lead chelation test. The association with gout and CKD is strong enough to merit lead chelation testing in patients with CKD who have gout and risk for lead exposure. $CaNa_2$ EDTA is administered (2 doses of 0.5 g in 250 mL 5% dextrose given 12 hours apart), and urine is collected for 3 days because urinary excretion is slower when eGFR is reduced. Normal urinary lead levels are less than 650 μg/3 days. x-Ray fluorescence, which provokes the emission of fluorescent photons from the target area, is an alternative method that detects increased bone lead levels, which are also a reflection of cumulative lead exposure. Although x-ray fluorescence measurements allow a rapid, noninvasive estimation of lead in bone, detection equipment is available at only a small number of centers.

Treatment

Treatment involves infusions of $CaNa_2$ EDTA together with removal of the source of lead. The likelihood of a satisfactory response to $CaNa_2$ EDTA is influenced by the degree of interstitial fibrosis that has already occurred.

In industrial and occupational settings, such as in foundry workers and individuals working with lead-based paints and glazes, preventive measures to minimize exposure and low-level absorption are essential. Some studies in children show success with the oral chelating agent succimer (Chemet). Chelation therapy may slow progressive CKD, even in patients with mild lead intoxication.[37] However, chelation therapy has not been widely used because of adverse drug effects and concerns about the effects of remobilized lead. It is generally not indicated for adults with blood lead concentrations of less than 45 µg/dL. Because of a lack of clinical trials demonstrating the efficacy and safety of chelation, recommendations for treatment with chelating agents are empiric and may be controversial.

Other Heavy Metal–Induced Nephropathies

Cadmium is a metal with a wide variety of industrial uses, including the manufacture of glass, metal alloys, and electrical equipment. Cadmium is preferentially concentrated in the kidney, principally in the proximal tubule, in the form of a cadmium-metallothionein complex that has a biologic half-life of about 10 years. Cadmium contamination may be an important contributor to the high risk for chronic interstitial nephritis in some agricultural communities in the developing world. A major outbreak of cadmium toxicity occurred in Japan as a result of industrial contamination. The disease was called itai-itai, or “ouch-ouch,” because bone pain was the major clinical manifestation. Other manifestations included proximal tubular dysfunction (Fanconi syndrome), hyperphosphaturia, and vitamin D–resistant rickets with osteomalacia. The mechanism by which cadmium elicits chronic inflammation and fibrosis in the kidney is relatively unstudied. The diagnosis is suggested by a history of occupational exposure, increased urinary β_2-microglobulin, and increased urinary cadmium levels (>7 µg of cadmium per 1 gram of creatinine). Once manifested, kidney injury tends to be progressive, even if exposure is discontinued. Chelation is not effective in humans, and prevention is the only effective treatment.

Arsenic, used as a poison gas in World War I, is present in insecticides, weed killers, wallpaper, and paints. Chronic arsenic toxicity from inorganic arsenic most commonly manifests as sensory and motor neuropathies, distal extremity hyperkeratosis, palmar desquamation, diarrhea and nausea, Aldrich-Mees lines (white bands on the nails), and anemia. In rare cases, it may cause kidney disease, manifested by proximal RTA and chronic interstitial fibrosis. Diagnosis is made by demonstration of an elevated urinary inorganic arsenic level.[38]

Mercury is found in alloy plants, mirror plants, and some batteries, and mercury intoxication usually occurs as a result of accidental exposure to mercury vapor. Mercury has been shown to induce membranous nephropathy (MN) in experimental animals and has been reported with the use of mercury-containing skin-lightening creams.[39] Neither elemental mercury nor the mercurous salt (Hg_2Cl_2) produces sustained renal tubular injury, but mercury dichloride ($HgCl_2$) may produce acute tubular necrosis and subsequent chronic interstitial nephritis in laboratory animals. However, a report of endemic methyl mercury poisoning in Japan (Minamata disease) revealed a clinical picture dominated by neurologic sequelae; kidney disease in these patients was surprisingly benign, consisting only of tubular proteinuria without changes in serum creatinine.

RADIATION NEPHRITIS

Definition and Epidemiology

Although radiation nephritis was relatively common decades ago, the incidence has decreased considerably because recognition of radiationinduced renal damage has altered protocols for the administration of therapeutic radiation. In general, direct exposure of the kidney to 20 to 30 Gy (1 Gy = 100 rad) over 5 weeks or less will produce radiation nephritis.

Pathology

In general, vascular and glomerular lesions of thrombotic microangiopathy may predominate. The initial target of ionizing radiation within the kidney appears to be endothelial cells, leading to endothelial cell swelling. Electron microscopy (EM) reveals a split appearance of the capillary wall caused by the mesangial interposition and widening of the subendothelial space by a nondescript fluffy material. These features are shared by hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, suggesting a common pathogenic mechanism originating from endothelial injury. However, tubulointerstitial changes are also usually present. Vascular occlusion leads to tubular atrophy, and severe disease is characterized by progressive interstitial fibrosis and the presence of interstitial inflammatory cells.

with a bland urine sediment and abnormalities in tubular function, including Fanconi syndrome, distal RTA, hypokalemia, and nephrogenic diabetes insipidus. Sjögren syndrome is one of the most common causes of acquired distal (type 1) RTA in adults, and the hypokalemia may be marked, resulting in a clinical presentation of severe weakness. Hypokalemia may occur in the absence of RTA, resulting from salt wasting and secondary hyperaldosteronism.

Treatment

Treatment with corticosteroids at the stage of cellular infiltration is frequently beneficial for protecting kidney function. Although CKD tends to slowly progress over time, ESKD is relatively rare.

Sarcoidosis

Definition and Epidemiology

Histologic evidence of interstitial nephritis with noncaseating granulomas is common in patients with sarcoidosis, but the frequency of clinically significant disease is low.41 It may manifest as either acute interstitial nephritis or chronic interstitial nephritis.

Pathogenesis and Pathology

Hypertension is commonly observed. Progression to a chronic form of radiation nephritis may occur if resolution of acute radiation nephritis is incomplete. These patients present with proteinuria, progressive CKD, and eventual development of ESKD several years after irradiation in the absence of an acute phase.

Kidney biopsy reveals normal glomeruli; interstitial infiltration, mostly with mononuclear cells; tubular injury; and, with more chronic disease, interstitial fibrosis. Whereas the classic finding is noncaseating granulomas in the interstitium, they are uncommon and nonspecific. An analysis of 18 patients with granulomatous interstitial nephritis showed that in 5 the disorder was associated with sarcoidosis; in 2, tubulointerstitial nephritis and uveitis; in 2, medication; and in 9, the condition was idiopathic.42 IF and EM studies typically show no immune deposits.

Treatment

Clinical Manifestations

Prevention is the best approach; risk can be minimized by shielding the kidneys or fractioning the total-body irradiation into several small doses over several days. No specific treatment is available for established radiation nephritis. The general approach is control of hypertension and supportive treatment of CKD.

Most affected patients have clear evidence of diffuse active sarcoidosis, although some present with an isolated elevation in serum creatinine and only minimal extrarenal manifestations. The urinalysis may be normal or show only sterile pyuria or mild proteinuria.

In addition, hypercalcemia induced by increased production of calcitriol (1,25-dihydroxyvitamin D3) by activated mononuclear cells (particularly macrophages) in the lung and lymph nodes occasionally results in renal problems (see the previous discussion of hypercalcemic nephropathy).

The serum ACE level is used best not as a primary diagnostic tool but as a marker of disease activity and response to therapy. A normal serum ACE level does not exclude sarcoidosis of the kidney.

Clinical Manifestations

INTERSTITIAL NEPHRITIS MEDIATED BY IMMUNOLOGIC MECHANISMS

Sjögren Syndrome

Definition and Epidemiology

Sjögren syndrome may be associated with chronic interstitial nephritis. The reported prevalence of kidney involvement in Sjögren syndrome varies from 2% to 67%, principally because of different definitions between studies. Recent analysis of 130 patients with primary Sjögren syndrome in China showed an 80% incidence of biopsy-proven chronic interstitial nephritis.[40]

Pathology

The lesion is characterized histologically by infiltration of lymphocytes and plasma cells in the interstitium with tubular cell injury and, rarely, granuloma formation. This progresses to tubular atrophy and interstitial fibrosis over time. IF reveals granular deposits of immunoglobulin G (IgG) and C3 along the tubular basement membrane (TBM).

Clinical Manifestations

The clinical and biochemical manifestations of interstitial nephritis may be the presenting or only features of Sjögren syndrome. Serum creatinine concentration is generally only mildly elevated in association

Treatment

Corticosteroid therapy tends to improve kidney function, although recovery is often incomplete. Limited data are available concerning the optimal protocol for corticosteroid therapy, but initial dose is usually prednis(ol)one 0.5 to 1 mg/kg/day, which is followed by a slow taper. Rapid tapering of corticosteroids can result in relapse.

Systemic Lupus Erythematosus

Definition and Epidemiology

Interstitial nephritis with immune complexes is defined by granular deposits of immunoglobulins and complement in the TBM, interstitium, or both. Systemic lupus erythematosus is the most common reason for this type of interstitial nephritis (Fig. 65.7), and interstitial involvement is present in half of kidney biopsy specimens in lupus. Tubulitis serves as an independent predictive factor for eGFR decline in lupus nephritis.[43] Rarely, tubulointerstitial immune complex disease may be the only manifestation of lupus nephritis.

nephrotoxicity of these agents is very uncommon (mean rate only 0.3% per patient-year).44 The median time for development of kidney injury after commencing aminosalicylates is 3 years.45 There is no clear relationship between aminosalicylate dose and the risk for nephrotoxicity, suggesting that this is an idiosyncratic response. Some patients have been reported to have biopsy-proven interstitial nephritis before the diagnosis of Crohn disease.

Aminosalicylates should be withdrawn when reduced eGFR develops in a patient with inflammatory bowel disease; if this does not result in a fall in serum creatinine, renal biopsy should be considered. Only one-third of cases recover completely after drug withdrawal.45 Corticosteroids are recommended when kidney function does not respond to drug withdrawal.

A

Immunoglobulin G4-Related Kidney Disease

Definition and Epidemiology

On the basis of histologic and immunohistochemical examination of various organs of patients with autoimmune pancreatitis, a novel clinicopathologic entity of immunoglobulin (Ig) G4-related sclerosing disease has been proposed.46 This systemic disease is characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs (Fig. 65.8). Initial reports of IgG4related sclerosing disease came from Japan, but it has now been described in Europe and the United States and is considered to be a worldwide entity.

Pathogenesis

B

Fig. 65.7 Chronic Interstitial Nephritis in Systemic Lupus Erythematosus. (A) Interstitial nephritis observed in patients with systemic lupus erythematosus. (PAS stain; original magnification ×400.) B, Immunofluorescence study of the same patient revealed deposition of immunoglobulin G in the interstitium, in tubular cells, and along the tubular basement membrane. (Courtesy Drs. Akira Shimizu and Hideki Takano, Nippon Medical School, Tokyo.)

Whether IgG4 is pathogenic or is a “bystander” remains unknown. IgG4 does not activate the classical complement pathway effectively. However, immune complex formation may play a pathogenic role, raising the possibility of complement fixation via the lectin pathway or activation of the classical pathway of complement by some unknown mechanism.

Pathology

Treatment

The most common pattern of involvement by IgG4-related kidney disease is tubulointerstitial nephritis with dense infiltration of IgG4positive mononuclear cells. Distinctive features of the tubulointerstitial nephritis include: (1) well-demarcated borders between involved and uninvolved areas; (2) involvement of the cortex and deep medulla, often extending beyond the renal capsule; (3) interstitial inflammatory cells made up predominantly of plasma cells and lymphocytes, with a high prevalence of IgG4-positive cells often admixed with fibrosis; (4) peculiar features of interstitial fibrosis called storiform fibrosis or bird’s-eye pattern; and (5) deposits visible by light microscopy and IF in the TBM, Bowman’s capsule, and interstitium.47 Recent pathologic analysis revealed perivascular inflammation or fibrosis of mediumand small-sized vessels as a newly identified pathologic feature of IgG4related kidney disease and proposed the term interstitial fibrosclerosis because storiform fibrosis contains mainly nonfibrillar collagens.48 IF shows granular TBM staining for IgG accompanied by C3 of lesser staining intensity. MN also has been described as a manifestation of IgG4-related kidney disease.49

Corticosteroid therapy is usually effective in suppressing tubular dysfunction and preserving renal function.

Clinical Manifestations

Clinical Manifestations

The presentation may be as acute or chronic interstitial nephritis. The possibility of interstitial involvement (without glomerular disease) is suggested by a rising serum creatinine concentration and a bland urine sediment. Interstitial involvement may be accompanied by signs of tubular dysfunction, such as distal RTA (type 1 or type 4); by isolated hyperkalemia resulting from impaired distal potassium secretion; or by hypokalemia resulting from salt wasting. The potentiating effects of sodium wasting on potassium secretion include an increase in sodium delivery to the potassium secretory site in the collecting tubules and associated volume depletion with subsequent stimulation of aldosterone secretion.

Inflammatory Bowel Disease

Although the most frequent kidney-related complications of Crohn disease are calcium oxalate stones and renal amyloidosis, interstitial nephritis has been reported in patients treated for chronic inflammatory bowel disease. Aminosalicylates (5-aminosalicylic acid, mesalazine, and sulfasalazine) are responsible for most of these cases, but

Clinical manifestations are observed in various organs, with presentations including sclerosing cholangitis, cholecystitis, sialadenitis, and retroperitoneal fibrosis. IgG4-related tubulointerstitial nephritis can be mass forming, similar to IgG4-related inflammatory lesions in other organs. Of patients with IgG4-related disease, 80% are reported to have had radiographic abnormalities of the kidneys: bilateral and multiple small low-attenuation lesions, a mass, or bilateral kidney enlargement.50

A

B

C

Fig. 65.8 Chronic Interstitial Nephritis in Immunoglobulin (Ig) G4-Related Sclerosing Disease. (A) Interstitial nephritis with numerous mononuclear cell infiltrates observed in a patient with autoimmune pancreatitis. Many of these cells are positive for IgG4 in typical cases. (PAS stain; original magnification ×200.) (B) Small nests of swollen plasma cells or individual plasma cells are encircled by collagenous tissue. The features resemble a maple wood grain pattern called "bird's eye." Plasma cells look like birds' eyes in the wood, whereas fibrotic tissues correspond to branches of the wood. (C) Computed tomography scan of the patient revealed pancreatic swelling (arrows). (A and C, Courtesy Dr. Hiroshi Nishi, University of Tokyo, Tokyo. B, From Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. Clin J Am Soc Nephrol. 2007;2:222–230.)

Although most IgG4-related sclerosing disease is associated with autoimmune pancreatitis, cases without pancreatic involvement have been described. The disease occurs predominantly in older males. Serum IgG4 levels are raised, and IgG4-positive cells are found in the interstitium. According to a recent meta-analysis, a cut-off value of serum IgG4 ranging from 135 to 144 mg/dL confers a sensitivity of 87% and a specificity of 83%.51 However, the finding of an elevated serum IgG4 is not specific because this may occur in 5% of the normal population. The patients often show hypocomplementemia and eosinophilia. Recently proposed diagnostic criteria are shown in Table 65.3

Treatment

The response to corticosteroids is generally favorable, but reappearance of clinical manifestations is common. The protocol has not been established, but a starting dose of approximately 40 mg/day may be prudent. There is no correlation between histologic pattern and response to therapy, and even patients with extensive fibrosis on biopsy have shown a response to corticosteroid therapy. Rituximab may be an alternative treatment for IgG4-related kidney disease. In a recent openlabel pilot trial of 30 patients, two doses of rituximab (1000 mg each) achieved the primary outcome composed of improvement of disease

activity and damage, no disease flares before month 6, and no steroid use between months 2 and 6, in 77% of participants.52

Other Forms of Immune-Mediated Interstitial Nephritis

Primary anti-TBM nephritis is an extremely rare form of interstitial nephritis that usually is acute and characterized by linear deposits of immunoglobulins, commonly IgG, and complement in the TBM, together with tubular interstitial inflammation and anti-TBM antibodies in the serum. Anti-TBM antibodies, usually IgG, may be found in 50% to 70% of patients with anti–glomerular basement membrane nephritis and occasionally in patients with MN, systemic lupus, IgA nephropathy, minimal change disease, and malignant hypertension. The antibodies are directed against a protein that is found in the proximal TBM and regulates tubulogenesis.

OBSTRUCTIVE UROPATHY

Complete or partial urinary tract obstruction is accompanied by pathologic changes in both the tubulointerstitium and glomeruli consisting of interstitial fibrosis, tubular atrophy, and occasionally focal glomerular sclerosis. Details are discussed in Chapter 61

TABLE 65.3 Diagnostic Criteria for IgG4Related Tubulointerstitial Nephritis

Histology	Plasma cell–rich tubulointerstitial nephritis with >10 IgG4positive plasma cells per high-power field in the most concentrated field[a] Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy[b]
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis

Diagnostic criteria for IgG4-related TIN. Diagnosis of IgG4 TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4positive plasma cells and at least one other feature from the categories of imaging, serology, or other organ involvement.

[a] Mandatory criterion.

[b] Supportive criterion, present in >80% of cases.

IgG, Immunoglobulin G; TIN, tubulointerstitial nephritis.

From Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. J Crohns Colitis. 2016;10:149–158.

VASCULAR DISEASES

Ischemia resulting from intrarenal vascular involvement causes tubular atrophy, interstitial fibrosis, and cellular infiltration. This is further discussed in Chapter 43. Chronic ischemia in the tubulointerstitial compartment also plays a crucial role in the progression of a variety of glomerular and tubulointerstitial diseases.[2]

INFECTION-ASSOCIATED CHRONIC INTERSTITIAL NEPHRITIS

Although a variety of bacterial and viral infections can be associated with acute interstitial nephritis (see Chapter 64), chronic interstitial nephritis secondary to infectious agents appears to be rare. Insidious Mycobacterium tuberculosis infection can cause chronic granulomatous tubulointerstitial nephritis.[53] Chronic bacterial infections can result in xanthogranulomatous pyelonephritis or renal malacoplakia (see Chapter 53). In mice, an atypical virus termed mouse kidney parvovirus is capable of driving a stepwise progression of pathology ranging from sporadic tubular inclusions to tubular degeneration and interstitial fibrosis.[54]

SELF-ASSESSMENT QUESTIONS

1. A 29-year-old woman was admitted to the hospital because of anorexia, binge eating, and self-induced vomiting. On admission, her body mass index was 12.2 and she presented with nocturia and polyuria. The serum potassium level was 2.8 mEq/L. Which one of the following do you expect as the pathologic change of the kidney biopsy specimen of this patient?

A. Calcific deposits in the interstitium

B. Vacuolation of the kidney tubules

C. Noncaseating granulomas
D. Infiltration of IgG4-positive mononuclear cells
E. Acellular interstitial nephritis with intranuclear inclusion bodies in the proximal tubules

2. IgG4-related tubulointerstitial nephritis is an emerging clinicopathologic entity that is a part of the systemic disease characterized by infiltration of IgG4-positive plasma cells in various organs.
Which one of the following is most likely to be associated with this disease?

A. Uroepithelial carcinoma
B. Inflammatory bowel disease
C. Cerebral aneurysm
D. Autoimmune pancreatitis
E. Angiokeratoma

3. A 58-year-old woman with a 30-year history of bipolar affective illness was admitted to hospital because of thirst, polyuria, and weight loss. Lithium had been prescribed for the preceding 18 years. On admission, she presented with hypernatremic dehydration. Which one of the following represents the best next step to diagnose the characteristic morphologic changes in the kidney?
A. Non–contrast-enhanced MRI
B. Blood oxygen level–dependent MRI
C. Non–contrast-enhanced computed tomography
D. Scintigraphy
E. Intravenous urography

REFERENCES

1. Boor P, Sebeková K, Ostendorf T, Floege J. Treatment targets in renal fibrosis. Nephrol Dial Transplant. 2007;22:3391–3407.
2. Kramann R, Schneider RK, DiRocco DP, et al. Perivascular gli1 + progenitors are key contributors to injury-induced organ fibrosis. Cell Stem Cell. 2015;16:51–66.
3. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17:17–25.
4. Rastegar A, Kashgarian M. The clinical spectrum of tubulointerstitial nephritis. Kidney Int. 1998;54:313–327.
5. Rychlík I, Jancová E, Tesar V, et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000. Nephrol Dial Transplant. 2004;19:3040–3049.
6. Chen H, Tang Z, Zeng C, et al. Pathological demography of native patients in a nephrology center in China. Chin Med J. 2003;116:1377–1381.
7. Shah S, Carter-Monroe N, Atta MG. Granulomatous interstitial nephritis. Clin Kidney J. 2015;8:516–523.
8. Braden GL, O’Shea MH, Mulhern JG. Tubulointerstitial diseases. Am J Kidney Dis. 2005;3:560–572.
9. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodríguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Engl J Med. 2002;346:913–923.
10. Beck Jr LH, Salant DJ. Glomerular and tubulointerstitial diseases. Prim Care. 2008;35:265–296.
11. Shine B, McKnight RF, Leaver L, et al. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet. 2015;386:461–468.
12. Boton R, Gaviria M, Batlle DC. Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis. 1987;10:329–345.
13. Markowitz GS, Radhakrishnan J, Kambham N, et al. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol. 2000;11:1439–1448.
14. Presne C, Fakhouri F, Noël LH, et al. Lithium-induced nephropathy: rate of progression and prognostic factors. Kidney Int. 2003;64:585–592.
15. Karaosmanoglu AD, Butros SR, Arellano R. Imaging findings of renal toxicity in patients on chronic lithium therapy. Diagn Interv Radiol. 2013;19:299.
16. Rexrode KM, Buring JE, Glynn RJ, et al. Analgesic use and renal function in men. JAMA. 2001;286:315–321.
17. Cho E, Curhan G, Hankinson SE, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. Arch Intern Med. 2011;171:1487–1493.
18. Elseviers MM, De Schepper A, Corthouts R, et al. High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure. Kidney Int. 1995;48:1316–1323.
19. Obermayr RP, Temml C, Gutjahr G, et al. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol. 2008;19:2407–2413.
20. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant. 2013;28:2221–2228.
21. Doria A, Galecki AT, Spino C, PERL Study Group, et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382:2493–2503.
22. Badve SV, Pascoe EM, Tiku A, CKD-FIX Study Investigators, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382:2504–2513.
23. Bardin T, Nguyen QD, Tran KM, et al. A cross-sectional study of 502 patients found a diffuse hyperechoic kidney medulla pattern in patients with severe gout. Kidney Int. 2021;99:218–226.
24. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359:1811–1821.
25. Johnson RJ, Kivlighn SD, Kim YG, et al. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular

disease, and renal disease. Am J Kidney Dis. 1999;33:225–234.
26. Murray T, Goldberg M. Chronic interstitial nephritis: etiologic factors. Ann Intern Med. 1975;82:453–459.

27. Goicoechea M, de Vinuesa SG, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5:1388–1393.
28. Talaat KM, el Sheikh AR. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. Am J Nephrol. 2007;27:435–440.
29. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomerular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol. 2011;6:1887–1894.
30. Terawaki H, Nakayama N, Miyazawa E, et al. Effect of allopurinol on cardiovascular incidence among hypertensive nephropathy patients: the Gonryo study. Clin Exp Nephrol. 2013;17:549–553.
31. White WB, Saag KG, Becker MA, et al. CARES investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378:1200–1210.
32. Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. Anorexia nervosa and the kidney. Am J Kidney Dis. 2012;60:299–307.
33. Inglis JA, Henderson DA, Emmerson BT. The pathology and pathogenesis of chronic lead nephropathy occurring in Queensland. J Pathol. 1978;124:65–76.
34. Muntner P, He J, Vupputuri S, et al. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. Kidney Int. 2003;63:1044–1050.
35. Yu CC, Lin JL, Lin-Tan DT. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. J Am Soc Nephrol. 2004;15:1016–1022.
36. Evans M, Elinder CG. Chronic renal failure from lead: myth or evidencebased fact? Kidney Int. 2011;79:272–279.
37. Lin JL, Lin-Tan DT, Hsu KH, Yu CC. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. N Engl J Med. 2003;348:277–286.
38. Tonelli M, Wiebe N, Bello A, et al. Alberta kidney disease network. Concentrations of trace elements in hemodialysis patients: a prospective cohort study. Am J Kidney Dis. 2017;70:696–704.
39. Chakera A, Lasserson D, Beck Jr LH, et al. Membranous nephropathy after use of UK-manufactured skin creams containing mercury. QJM. 2011;104:893–896.
40. Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjögren’s syndrome. J Rheumatol. 2008;35:278–284.
41. Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist’s perspective. Am J Kidney Dis. 2006;48:856–870.
42. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. Clin J Am Soc Nephrol. 2007;2:222–230.
43. Pagni F, Galimberti S, Galbiati E, et al. Tubulointerstitial lesions in lupus nephritis: International multicentre study in a large cohort of patients with repeat biopsy. Nephrology (Carlton). 2016;21:35–45.
44. Gisbert JP, González-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. Inflamm Bowel Dis. 2007;13:659. 638.
45. Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. J Crohns Colitis. 2016;10:149–158.
46. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385:1460–1471.
47. Yamaguchi Y, Kanetsuna Y, Honda K, et al. Characteristic tubulointerstitial nephritis in IgG4-related disease. Hum Pathol. 2012;43:536–549.
48. Hara S, Kawano M, Mizushima I, et al. Distribution and components of interstitial inflammation and fibrosis in IgG4-related kidney disease:

analysis of autopsy specimens. Hum Pathol. 2016;55:164–173.
49. Alexander MP, Larsen CP, Gibson IW, et al. Membranous glomerulonephritis is a manifestation of IgG4-related disease. Kidney Int. 2013;83:455–465.
50. Raissian Y, Nasr SH, Larsen CP, et al. Diagnosis of IgG4-related tubulointerstitial nephritis. J Am Soc Nephrol. 2011;22:1343–1352.
51. Hao M, Liu M, Fan G, et al. Diagnostic value of serum IgG4 for IgG4related disease: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltim). 2016;95:e3785.

References

52. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015;74:1171–1177.
53. Chapagain A, Dobbie H, Sheaff M, Yaqoob MM. Presentation, diagnosis, and treatment outcome of tuberculous-mediated tubulointerstitial nephritis. Kidney Int. 2011;79:671–677.

54. Roediger B, Lee Q, Tikoo S, et al. An atypical parvovirus drives chronic tubulointerstitial nephropathy and kidney fibrosis. Cell. 2018;175:530–543.

66

Endemic Nephropathies

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Localized epidemics of chronic kidney disease (CKD) have been reported in various parts of the world and are known as endemic nephropathies. The word endemic is used in a lay rather than epidemiologic sense, to emphasize their regionally confined nature. By definition, these nephropathies are distinct from CKD of standard causes and tend to manifest insidiously. Although aging and the metabolic syndrome are also associated with reductions in estimated glomerular filtration rate (eGFR), endemic nephropathies are distinguished by earlier onset, absence of classic risk factors, and more rapid progression to kidney failure.

There have been remarkable examples in which the cause of endemic nephropathies have been identified. In the 1920s, an increased frequency of CKD in children and young adults in Queensland, Australia, was shown to be due to lead poisoning, such as from exposure to paints. Patients presented with either Fanconi syndrome from acute lead intoxication or CKD and hypertension associated with chronic intoxication. Likewise, an epidemic of CKD resulting from chronic interstitial nephritis and associated with Fanconi syndrome with hypophosphatemia and osteomalacia was observed in the 1950s and 1960s in the Toyama prefecture, Japan, and was shown to be caused by cadmium poisoning; a factory was dumping cadmium into the Jinzu River leading to contamination of the rice and soybeans. The disease was called itai-itai (“ouch-ouch”) by the locals due to the severe joint pains, and manifested over decades, especially among older women. For more information on nephropathies associated with heavy metals, see Chapter 65. Finally, Balkan endemic nephropathy is another example in which the cause, the herb Aristolochia clematis contaminating wheat, has been identified. It is now considered to be an aristolochic acid–induced nephropathy, along with the Chinese herb nephropathy, a chronic tubulointerstitial disease observed in individuals taking these herbs for weight loss in the early 1980s. Diseases caused by Aristolochia (Aristolochia-associated nephropathy) are discussed in Chapter 79

MESOAMERICAN NEPHROPATHY

In 2002, physicians from the Hospital Rosales in San Salvador, El Salvador, reported a large number of patients presenting to the emergency room with kidney failure of undetermined etiology and a distinct epidemiologic pattern: most were Hispanic men between ages 20 and 60 performing manual work in the Pacific coast fields.[1] Subsequently, similar epidemic clusters were described along the Pacific coast of Guatemala, Nicaragua, and Costa Rica (Fig. 66.1). Sugarcane cutters have been the most studied, although the disease may be found among all types of farmers, miners, and construction and transportation workers, among others. Review of historical records suggest the phenomenon has been present since the 1970s, but diagnosis and registry has only been performed during recent decades (Fig. 66.2).[2] In some areas, such as in Chichigalpa, Nicaragua, the prevalence of CKD (defined as eGFR <60 mL/min/1.73 m^2) approaches 40% of men between ages 20 and 40 years.[3] This contrasts with an overall prevalence of 8.3% for all adults and with less than 0.4% for men ages 20 to 40 years in the United States.

Pathogenesis

Although rare reports link Mesoamerican nephropathy with exposure to carbamate pesticides or methyl parathion, no confirmatory data exist.[4,5] However, lag between exposure and disease, the variability in environmental fate and stability of agrochemicals, and changes in compounds over time, added to their seasonal use, make the contribution from agrochemicals difficult to evaluate. Heavy metals have been investigated as well, along with silica and nickel,[6-8] but definitive evidence has not yet emerged.

One common risk factor is heat stress and recurrent dehydration, leading some to suggest this might be a type of heat stress nephropathy. Heat stress is known to cause acute kidney injury (AKI) from a variety of mechanisms, including heat stroke and rhabdomyolysis, but the concept of CKD occurring from heat exposure is new. Consistent with this possibility is the observation that Mesoamerican nephropathy is much more common in people who work at low altitudes, where it is warmer than at higher altitudes, despite similar working conditions and pesticide exposure.9 Experimentally, recurrent heat stress and dehydration have been shown to induce CKD in animals through hyperosmolarity-induced activation of the polyol-fructose and vasopressin pathways, and the kidney injury is amplified if animals are rehydrated with fructose-containing beverages as opposed to water. Kidney injury is also worse if body temperatures are higher in response to heat. Heat stress also may result in subclinical rhabdomyolysis, uric acid overproduction, and supersaturation of urine leading to intermittent uric acid crystalluria.10 Some infectious diseases, such as leptospirosis, have also been proposed as a causal or potentiating factor, although supporting evidence is limited.7

Pathology

The primary finding in patients with advanced CKD is chronic tubulointerstitial fibrosis with variable degrees of glomerulosclerosis (Fig. 66.3).11 Whether the glomerular changes are secondary to chronic disease or represent a primary glomerular injury is unclear. Immune deposits are absent. A subset of patients may present with AKI and acute tubulointerstitial disease on biopsy.12 Hyperuricemia, a common feature, has been found experimentally to cause glomerular hypertension, and vasopressin induces hyperfiltration in addition to the effects on tubular injury; however, uric acid crystals are not present in biopsies.

Clinical Manifestations

In early stages, some patients present with AKI or with muscle weakness related to hypokalemia or with aseptic dysuria, possibly related to uric acid crystalluria. Other asymptomatic patients are identified during

Mesoamerican Nephropathy Is
Common in Hotter Areas of Central America
Average Tmax 1951-2010
18N
17N
16N
33

15N

32
31
Degrees Celsius

14N
13N
12N
Sites of
epidemic

11N

30
29
28
27
26

10N

25

9N

23

24
22

8N
7N
6N

84W
82W
80W
78W
92W
90W
88W
86W

Fig. 66.1 Mesoamerican Nephropathy. Major areas where Mesoamerican nephropathy has been observed are along the Pacific Coast, especially involving the Guanacaste region of Costa Rica, the Bajo Lempa region of El Salvador, and the Chinandega region of Nicaragua. These are also the hottest areas in Central America. (From Glaser J, Lemery J, Rajagopalan B, et al. Climate change and the emergent epidemic of chronic kidney disease from heat stress in rural communities: the case for heat stress nephropathy. Clin J Am Soc Nephrol. 2016;11[8]:1472–1483.)

40
35
1970-1982

30

2003-2012

25
20
15
10

Guanacaste

5

2
01

7

Guanacaste
Women

20

08

-2

00

2
-2

7

00

03
20

-2

99

98

2

Rest of
Costa Rican
Men

19

-1

7

99

93
19

-1

2

98

88
19

-1

98

83

7
Guanacaste
Men

19

-1

97

78
19

-1
73

19

70

-1

97

2

0

19

Age-adjusted chronic kidney disease mortality rates per 100,000

Epidemiology of Mesoamerican Nephropathy in Costa Rica

Rest of
Costa Rican
Women

Smoothed relative risk
0-0.89

1.30-2.99

0.90-1.29
3.00+
Fig. 66.2 Mortality of Chronic Kidney Disease in Guanacaste, Costa Rica.

Mesoamerican nephropathy has been suspected since the 1970s in the Guanacaste region of Costa Rica. Shown is the increasing mortality of chronic kidney disease in the Guanacaste region of Costa Rica in men compared with the rest of Costa Rica. (From Wesseling C, van Wendel de Joode B, Crowe J, et al. Mesoamerican nephropathy: geographic distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. Occup Environ Med. 2015;72[10]:714–721.)

A

B

Fig. 66.3 Renal Pathology in Endemic Nephropathy. (A) Mesoamerican nephropathy is characterized by chronic tubulointerstitial fibrosis with localized inflammation (arrows). Other findings include glomerular ischemia and variable glomerulosclerosis. Renal vascular disease is usually mild. (B) Sri Lankan nephropathy also has a similar histologic appearance with the tubulointerstitial fibrosis with some pockets of inflammatory cells. (×40 magnification. B, H&E stain.) (A, Courtesy Dr. Annika Wernerson, Karolinska Institute Sweden. B, From Wijetunge S, Ratnatunga NV, Abeysekera TD, et al. Endemic chronic kidney disease of unknown etiology in Sri Lanka: correlation of pathology with clinical stages. Indian J Nephrol. 2015;25[5]:274–280.)

TABLE 66.1 Characteristics of Patients With Mesoamerican Nephropathy

No evidence for common causes of CKD	Absence of diabetes (blood glucose <125 mg/dL or 7 mmol/L)
	BP normal or only slightly high
	Minimal evidence for GN (no RBC casts, urine protein <2 g/d)
	No evidence for obstruction (ultrasound)
	No evidence for polycystic kidney disease (ultrasound)
Clinical presentation	Asymptomatic rise in serum creatinine
	Minimal albuminuria
	Frequent hyperuricemia
	Serum potassium level often lower than expected
	Biopsy usually shows chronic tubulointerstitial disease and variable glomerulosclerosis (often performed late in disease)

BP, Blood pressure; CKD, chronic kidney disease; GN, glomerulonephritis, RBC, red blood cell.

health screening through elevated serum creatinine (Table 66.1). Blood pressure is normal or only slightly elevated, and urine sediment shows low-grade (<1 g/d) or no proteinuria with occasional red cells and leukocytes. Serum sodium and potassium are often low and appear to be associated with increased urinary losses[7]; similarly, elevated magnesium and phosphate losses in the urine are also common, supporting a tubular defect.[13] Serum uric acid is generally elevated, typically 2 mg/dL higher than expected for the eGFR.[14]

Diagnosis, Treatment, and Prognosis

Diagnosis is made on clinical grounds, based on living in an endemic area and presenting with CKD without clear cause (Fig. 66.4). The presence of hypokalemia and hyperuricemia and the absence of relevant proteinuria aids diagnosis. Kidney biopsies are rarely performed. Empiric treatment includes counseling on hydration and prevention of heat stress and avoidance of nonsteroidal antiinflammatory drugs. Given experimental data that rehydration with sugary beverages could worsen kidney injury, avoidance of soft drinks or sugary beverages as hydration drinks is recommended. Local nephrologists treat subjects empirically with low-dose angiotensin-converting enzyme

inhibitors (especially if they are no longer at risk for dehydration and hypokalemia is present) and with allopurinol and bicarbonate when hyperuricemia is present to reduce the formation of urine urate crystals and improve the aseptic dysuria. Dialysis is infrequently available because of social determinants; prognosis is guarded, and mortality is high.7 15

SRI LANKAN NEPHROPATHY

Reports of an epidemic of CKD in the North Central Province of Sri Lanka began in the late 1980s. Regionally, this disease is simply labeled CKDu (chronic kidney disease of uncertain etiology). There are over 100,000 individuals affected, with an ongoing mortality of 5000 per year.16 Typically, affected individuals are men between the ages of 30 and 60 years who are working in the rice paddies under hot conditions. Women also may develop the disease. The clinical presentation is similar to that of Mesoamerican nephropathy, with low-grade to no proteinuria and an asymptomatic elevation in serum creatinine, although biopsy data indicate concomitant CKDu among people with prior diagnoses of diabetes and hypertension as well17 (see Table 66.1). Hyperuricemia is also common.10 Kidney biopsies early in the disease show acute inflammation and/or chronic tubulointerstitial fibrosis, whereas later biopsies also show increasing glomerulosclerosis (see Fig. 66.3).17 18 Many patients are poor and have little access to medical care, although the government has organized screening camps to detect disease earlier and is increasing dialysis capacity.16 19

The primary hypothesis has been that Sri Lankan nephropathy is caused by an agrochemical toxin or heavy metal exposure such as cadmium or arsenic. Nevertheless, levels of heavy metals in the drinking water are within acceptable ranges,20 and it has been difficult to incriminate any specific agrochemical such as glyphosate.16 For example, in an analysis of hair and nail samples of persons with biopsy-proven CKDu, concentrations of trace elements matched those measured in controls.5 A genome-wide analysis identified potential loci for susceptibility that map to tubular function.21

Preliminary data also suggest those who drink local well water are at higher risk for CKD, suggesting the presence of an unidentified toxin.21 Importantly, the risk for CKD was also increased in those highly exposed to the sun, those who worked more than 6 hours per day, and those who drank less than 3 L of liquids per day.22 Noteworthy,

Diagnosis and Management of Mesoamerican Nephropathy
Early stages of CKD (stage 1 and stage 2)

Later stages of CKD (stages 3 to 5)

Subject from endemic area presents with muscle weakness
or cramps (hypokalemia), hyponatremia, or aseptic dysuria

Subject from endemic area presents with elevated
serum creatinine

Epidemiology Correct?
Working or spending a lot of time outside
History of heat exposure
Age 15 to 65
No
Look for other
causes

Include

Yes
Presentation Consistent?

Exclude

Elevated blood glucose (glucose >125 mg/dL)
BP >150/100 mm Hg or history of poorly
controlled BP
Nephrotic proteinuria or RBC casts
Ultrasound with obstruction or polycystic kidneys
Age > 65 with serum creatinine 1.2 2.0 mg/dL

Proteinuria usually <1 g/d
BP normal or slightly high
History of dysuria (common)
Hyperuricemia (common)
Hypokalemia (common)

Treatment (empirically based)
Keep well hydrated
Avoid extreme heat exposure
Avoid sugary beverages
(>6% sugar)
Avoid NSAIDs
Empiric therapy (see text)

Usual causes of CKD

Likely MeN
Rule out AKI (such as rhabdomyolysis or
acute NSAID use)
Fever and myalgias (look for leptospirosis
or rhabdomyolysis)

Diabetes
Hypertension
Glomerulonephritis/nephrotic syndrome
Obstruction
Polycystic kidney disease

Fig. 66.4 Diagnosis and management of Mesoamerican nephropathy (MeN). AKI, Acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; NSAID, nonsteroidal antiinflammatory drug; RBC, red blood cell.

because many workers believe the well water contains toxins, it seems likely that those who drink well water might be the same subjects who were limiting their water intake. Thus, these studies also raise the question whether heat stress and recurrent dehydration may be involved in this disease as well.[10]

Although a specific cause has not been identified, a publication from the Ministry of Health in Sri Lanka suggests that the incidence of CKD may be declining.[23]

OTHER ENDEMIC NEPHROPATHIES

An epidemic of CKD has been reported in the Uddanam region of Andhra Pradesh, southern India, and may have been present since the early 1990s.[24] Uddanam nephropathy is observed primarily in men working in the agricultural fields where the primary crops are cashews, coconuts, and rice. Similar to the other epidemics, patients present with minimal proteinuria and elevated serum creatinine and have chronic tubulointerstitial disease on kidney biopsy.[25] Hyperuricemia is also common. Large-scale prospective efforts to investigate disease incidence and risk factors are underway.

Other similar epidemics are also emerging elsewhere. This includes an epidemic among agricultural workers within Tierra Blanca in the Veracruz region of Mexico, where heat stress also has been mentioned as a risk factor, and agricultural work was associated with low eGFR.[26] [27] Similarly, the Central Valley of California and Rio Grande Valley in Texas have among the highest incidence of end-stage kidney disease (ESKD) in the United States,[28] and these “hot spots” have also been linked to agricultural activity.[29] There are also early reports that similar epidemics may be manifesting in northeastern Thailand, Egypt, and Sudan. Indeed, to date there are no distinguishing features among the various epidemics, and many believe the disease may have similar etiologies worldwide.

POTENTIAL ROLE OF CLIMATE CHANGE AND GLOBAL WARMING

The similarity between the various epidemics has placed special emphasis on the role of heat stress and dehydration in CKD. The sites where these endemic nephropathies are reported are usually extremely hot and located between the equator and the Tropic of Cancer. Although mean temperatures have increased only 0.8°C in the last 50 years, the frequency of extreme heat events (exceeding the 99th percentile) has increased by nearly 75%.[10] Remarkably, the sites where reports are emerging of epidemic CKD in India correlate with areas of increased extreme heat events such as heat waves (Fig. 66.5). This has led to the hypothesis that these epidemics may represent a type of heat stress nephropathy or that global warming may have a role in accelerating the epidemics. If true, the increase in frequency being observed is likely related to increasing world temperatures. It also remains possible that toxins may contribute to the various epidemics or may be acting in synergy with heat stress to cause CKD, as suggested by the presence of some Fanconi-like features in Mesoamerica and other locales.

To date, none of the proposed hypotheses has been able to explain the origin of these endemic nephropathies alone. Thus, two or more factors could be required.[7] Many facts support a possible genetic or epigenetic role in the development of the disease: its localized endemic nature, frequent familiar recurrence, Hispanic ethnicity selection in Mesoamerica, and its absence from other places where similarly severe environmental and occupational conditions are present.[7] [9] A successful research approach to these disorders will require a multidisciplinary approach, the establishment of systematic registries and reinforcing the local capacity for kidney biopsies, genetic and environmental studies, and controlled trials of current diagnosis and management protocols. Given the linkage with heat stress and climate, there is also a need to determine whether similar epidemics are occurring in other hot regions where similar conditions are present.

Sites of Endemic Nephropathy in
India Correlate With Sites of Prolonged Heat Waves

35N

Avg HW days: March-July
1961-2010

30N

25N

Odisha

20N
Akola

8

6
15N

Goa

Andhra Pradesh
4

2

10N

Fig. 66.5 Reported Sites in India With Increased Frequency of Chronic Kidney Disease (CKD) Correlate With Sites of Prolonged Heat Waves. Shown is the average number of heat wave days between March and July (hottest time of the year) in India, based on the number of heat wave days over the 50-year period. A heat wave is usually defined as sustained temperatures of greater than 40°C or an increase of 5 to 6°C over the normal maximal temperature of that region. Andhra Pradesh (including the Uddanam region) has had some of the longest heat waves, with one recorded at 35 days. Other suspected sites of CKD of unknown etiology include the Akola district of Maharashtra and the central Odisha region. HW, Heat wave. (Data from Pai DS, Nair S, Ramanathan AN. Long term climatology and trends of heat waves over India during the recent 50 years [1961–2010]. MAUSAM. 2013;64[4]:585–604; and Glaser J, Lemery J, Rajagopalan B, et al. Climate change and the emergent epidemic of chronic kidney disease from heat stress in rural communities: the case for heat stress nephropathy. Clin J Am Soc Nephrol. 2016;11[8]:1472–1483.)

SELF-ASSESSMENT QUESTIONS

1. Endemic nephropathies refer to:
A. regions where CKD of any cause is highly prevalent.
B. regions with a high prevalence of CKD that is unrelated to common causes such as hypertension and diabetes.
C. ethnic groups with high susceptibility to CKD.
D. ethnic groups with high prevalence of CKD.
E. regions with high prevalence of patients undergoing renal replacement therapy.

2. Which statement best describes Mesoamerican nephropathy?
A. A type of CKD of undetermined cause highly prevalent in the Pacific coast of Central America
B. A type of CKD caused by exposure to aristolochic acid
C. A type of CKD related to exposure to cadmium
D. A type of CKD often seen in Mesoamerican Maya ethnicity patients
E. A type of CKD that locals call itai-itai

3. Which of the following are similarities between Sri Lankan endemic nephropathy and Mesoamerican endemic nephropathy?
A. Highly symptomatic, predominantly glomerular damage with proteinuria, young patients from hot regions

B. Mostly asymptomatic, predominantly tubulointerstitial damage with low proteinuria, young workers from hot regions
C. Fanconi-like syndrome with high mortality rates and exposure to lead
D. Fanconi-like syndrome with high mortality rates and exposure to heat stress
E. Highly symptomatic, predominantly tubulointerstitial damage with proteinuria, elderly patients

4. The idea of a potential role of climate change and global warming is suspected in emerging endemic nephropathies because of which of the following?
A. Most emerging endemic regions correlate with areas of increased extreme heat.
B. Chronic kidney disease is much more common in workers in warmer areas despite similar working conditions.
C. Patients are exposed to extreme heat stress and dehydration; dehydration may be fueled by the fear of water contamination.
D. Most emerging endemic regions are located between the equator and the Tropic of Cancer.
E. All the above.

REFERENCES

1. Garcia-Trabanino R, Aguilar R, Silva CR, et al. End-stage renal disease among patients in a referral hospital in El Salvador. Pan Am J Public Health. 2002;12(3):202–206.
2. Wesseling C, van Wendel de Joode B, Crowe J, et al. Mesoamerican nephropathy: geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. Occup Environ Med. 2015;72(10):714–721.
3. Raines N, Gonzalez M, Wyatt C, et al. Risk factors for reduced glomerular filtration rate in a Nicaraguan community affected by Mesoamerican nephropathy. MEDICC Rev. 2014;16(2):16–22.
4. Valcke M, Levasseur ME, Soares da Silva A, et al. Pesticide exposures and chronic kidney disease of unknown etiology: an epidemiologic review. Environ Health. 2017;16(1):49.
5. Diyabalanage S, Fonseka S, Dasanayake DMSNB, et al. Environmental exposures of trace elements assessed using keratinized matrices from patients with chronic kidney diseases of uncertain etiology (CKDu) in Sri Lanka. J Trace Elem Med Biol. 2017;39:62–70.
6. Schaeffer JW, Adgate JL, Reynolds SJ, et al. A pilot study to assess inhalation exposures among sugarcane workers in Guatemala: implications for chronic kidney disease of unknown origin. Int J Environ Res Public Health. 2020;17(16):5708.
7. Sanchez Polo V, Garcia-Trabanino R, Rodriguez G, et al. Mesoamerican nephropathy (MeN): what we know so far. Int J Nephrol Renovasc Dis. 2020;13:261–272.
8. Fischer RSB, Unrine JM, Vangala C, Sanderson WT, Mandayam S, Murray KO. Evidence of nickel and other trace elements and their relationship to clinical findings in acute mesoamerican nephropathy: a case-control analysis. PLoS One. 2020;15(11):e0240988.
9. González-Quiroz M, Pearce N, Caplin B, Nitsch D. What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and metaanalysis. Clin Kidney J. 2018;11(4):496–506.
10. Glaser J, Lemery J, Rajagopalan B, et al. Climate change and the emergent epidemic of chronic kidney disease from heat stress in rural communities: the case for heat stress nephropathy. Clin J Am Soc Nephrol. 2016;11(8):1472–1483.
11. Wijkström J, Jayasumana C, Dassanayake R, et al. Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause (CKDu): similarities and differences with Mesoamerican Nephropathy. PLoS One. 2018;13(3):e0193056.
12. Fischer RSB, Vangala C, Truong L, et al. Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy. Kidney Int. 2018;93(3):681–690.
13. Herrera R, Orantes CM, Almaguer M, et al. Clinical characteristics of chronic kidney disease of nontraditional causes in Salvadoran farming communities. MEDICC Rev. 2014;16(2):39–48.
14. Kupferman J, Amador JJ, Lynch KE, et al. Characterization of Mesoamerican nephropathy in a kidney failure hotspot in Nicaragua. Am J Kidney Dis. 2016;68(5):716–725.

15. Garcia-Trabanino R, Hernandez C, Rosa A, et al. Incidence, mortality, and prevalence of end-stage chronic renal disease in the Bajo Lempa region of El Salvador: a ten-year community registry. Nefrologia. 2016;36(5):517–522.
16. Wimalawansa SJ. Escalating chronic kidney diseases of multifactorial origin (CKD-MFO) in Sri Lanka: causes, solutions, and recommendations-update and responses. Environ Health Prev Med. 2015;20(2):152–157.
17. Anand S, Montez-Rath ME, Adasooriya D, et al. Prospective biopsy-based study of CKD of unknown etiology in Sri Lanka. Clin J Am Soc Nephrol. 2019;14(2):224–232.
18. Wijetunge S, Ratnatunga NV, Abeysekera TD, et al. Endemic chronic kidney disease of unknown etiology in Sri Lanka: correlation of pathology

with clinical stages. Indian J Nephrol. 2015;25(5):274–280.
19. Nanayakkara N, Wazil AWM, Gunerathne L, et al. Tackling the fallout from chronic kidney disease of unknown etiology: why we need to focus on providing peritoneal dialysis in rural, low-resource settings. Kidney Int Rep. 2016;2(1):1–4.
20. Rango T, Jeuland M, Manthrithilake H, McCornick P. Nephrotoxic contaminants in drinking water and urine, and chronic kidney disease in rural Sri Lanka. Sci Total Environ. 2015:574–585. 518-519.
21. Nanayakkara S, Senevirathna STMLD, Parahitiyawa NB, et al. Wholeexome sequencing reveals genetic variants associated with chronic kidney disease characterized by tubulointerstitial damages in North Central Region, Sri Lanka. Environ Health Prev Med. 2015;20(5):354–359.
22. Siriwardhana EA, Perera PA, Sivakanesan R, et al. Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka. Indian J Nephrol. 2015;25(3):146–151.
23. Ranasinghe AV, Kumara GWGP, Karunarathna RH, et al. The incidence, prevalence and trends of chronic kidney disease and chronic kidney disease of uncertain aetiology (CKDu) in the north central province of Sri Lanka: an analysis of 30,566 patients. BMC Nephrol. 2019;20(1):338.
24. Reddy DV, Gunasekar A. Chronic kidney disease in two coastal districts of Andhra Pradesh, India: role of drinking water. Environ Geochem Health. 2013;35(4):439–454.
25. Ganguli A. Uddanam nephropathy/regional nephropathy in India: preliminary findings and a plea for further research. Am J Kidney Dis. 2016;68(3):344–348.
26. Aguilar-Ramirez D, Raña-Custodio A, Villa A, et al. Decreased kidney function and agricultural work: a cross-sectional study in middle-aged adults from Tierra Blanca, Mexico. Nephrol Dial Transplant. 2020: gfaa041.
27. Aguilar DJ, Madero M. Other potential CKD hotspots in the world: the cases of Mexico and the United States. Semin Nephrol. 2019;39(3):300–307.
28. Bragg-Gresham J, Morgenstern H, Shahinian V, et al. An analysis of hot spots of ESRD in the United States: potential presence of CKD of unknown origin in the USA? Clin Nephrol. 2020;93(1):113–119.
29. Anand S, Staniec A, Montez-Rath M, et al. Using GIS mapping to track hot spots of kidney disease in California. N Engl J Med. 2020;382(23):2265–2267.

SECTION XIII

Renal Disease and Cancer

67

Oncology: Kidney Disease in Cancer Patients

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CANCER AND KIDNEY DISEASE

Malignancy is commonly associated with acute and chronic kidney disease (Box 67.1), which in turn increases morbidity and mortality in cancers patients.1-3 Rapid advancements in oncology over the past 2 decades have turned many previously fatal cancers into chronic diseases. This relates mainly to recognition of gene mutations in various malignancies that are prime targets of anticancer therapies and using drugs to leverage the immune system for killing tumor cells. Cancer therapy with conventional chemotherapeutic agents, as well as targeted agents, immunotherapies, cytotoxic T-cell therapies, and stem cell transplantation, underpins this transition. However, these positives come with a price, including acute and chronic kidney disease. Nephrologists have been inundated with information on the nephrotoxicity of new drugs and appropriate dosing of anticancer drugs in chronic kidney disease (CKD) and end-stage kidney disease (ESKD) patients, as well as the need to manage CKD in cancer survivors. An increased knowledge gap for many clinicians providing kidney care for these patients and the need for targeted education in this area has fueled the birth of onconephrology, an area of subspecialization within nephrology.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is common in cancer patients, particularly in those who are hospitalized or admitted to the intensive care unit (ICU). In these settings, AKI is associated with increased lengths of stay and higher costs. The 1-year risk for AKI as defined by the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) in a large Danish study of incident cancer patients was 17.5%.1 The 1-year risk for more severe AKI, defined as the injury and failure categories, was 8.8% and 4.5%, respectively. Moreover, the 5-year risks for the risk, injury, and failure AKI categories were even higher, at 27%, 14.6%, and 7.6%, respectively. The incidence of AKI was highest in patients with renal cell cancer, liver cancer, multiple myeloma, and leukemia. Among 9613 cancer patients with any AKI stage, 5.1% required renal replacement therapy (RRT) within 1 year of AKI onset. Unsurprisingly, older patients were most heavily represented in this analysis. In patients admitted to a comprehensive cancer center, AKI was 12%, nearly threefold higher than most noncancer settings, and was associated with worse clinical outcomes.4 Among those with acute kidney injury, 45% of AKI developed in the first 48 hours and the remainder developed thereafter.4

Critically ill cancer patients are at even higher risk of AKI than critically ill patients without cancer. Of 288 patients admitted to a cancer-focused ICU from 2006 to 2008, 54.1% developed AKI.5 The risk category occurred in 33.3% of patients, and the injury and failure categories each developed in 10.4% of patients. In addition to an increased risk for AKI, critically ill cancer patients have a higher incidence of AKI requiring RRT compared with patients without cancer. Depending on the AKI definition employed and the underlying case mix, 13% to 42% of critically ill patients with cancer may develop AKI, and 8% to 60% require RRT.6 Those with hematologic malignancies, myeloma, and septic shock are at highest risk to develop AKI. A study of 429 cancer patients admitted to the ICU demonstrated that AKI was an independent risk factor for both ICU and 28-day mortality. In addition, developing AKI after 24 hours in ICU was associated with higher mortality than admission AKI.7

Hospital-acquired AKI in cancer patients can be due to prerenal, intrarenal, and postrenal causes (see Chapter 70). Risk factors for AKI in cancer patients include typical comorbidities such as underlying diabetes mellitus and CKD, as well as exposure to radiocontrast, chemotherapy, nonsteroidal antiinflammatory drugs (NSAIDs), and antibiotics.4 It is therefore critical to identify at-risk cancer patients to allow prophylactic measures. This will allow clinicians to avert AKI and improve clinical outcomes for this fragile group.4

Prerenal Acute Kidney Injury

Nearly one-third of AKI in cancer patients is prerenal and results from volume depletion from chemotherapy-induced nausea, vomiting, and diarrhea; chemotherapy-associated hypoalbuminemia contributes to the reduction in effective plasma volume and to compromised renal perfusion. Extracellular volume depletion as a result of third spacing, as in malignant ascites or pleural effusion or insensible losses from neutropenic fever, also can lead to prerenal AKI. Abdominal compartment syndrome from tense ascites can lead to AKI from renal underperfusion.

Intrarenal Acute Kidney Injury

Intrarenal AKI is one of the most common forms of renal injury in cancer patients. The cause is often multifactorial (see Chapter 70). Several chemotherapeutic agents and other nephrotoxic medications commonly used in cancer patients may cause toxic acute tubular necrosis (ATN). Cancer patients with sepsis are also at risk to develop severe ischemic ATN.7 High and repetitive doses of chemotherapy,

BOX 67.1

Kidney Disease Associated With Common Cancers and Cancer Treatments

impairment, and bulky retroperitoneal adenopathy associated with lymphoma may cause obstruction.

Leukemia
Common: AKI from sepsis, volume depletion, drug toxicity
Rare: infiltrative disease, GN, AKI from TLS, and leukostasis

CHRONIC KIDNEY DISEASE

Multiple Myeloma
Common: cast nephropathy, AKI from volume depletion and drug toxicity
Rare: amyloidosis, LCDD, Fanconi syndrome, AKI from hypercalcemia, C3 glomerulopathy, PGNMIgD
Lymphoma
Common: AKI from TLS and volume depletion
Rare: obstructive uropathy, infiltrative disease, MCD (Hodgkin lymphoma), MPGN (non-Hodgkin lymphoma)
Renal Cell Carcinoma
Common: anti–vascular endothelial growth factor toxicity, postnephrectomy CKD
Rare: obstructive uropathy, membranous GN
Lung and Head and Neck Cancer
Common: platinum toxicity
Rare: SIADH, membranous GN
Genitourinary and Gynecologic Cancers
Common: obstructive uropathy
Rare: platinum toxicity
Kidney Disease in Commonly Used Cancer Treatments
Common: AKI, tubulopathy and CKD from chemotherapeutic agents (e.g., cisplatin, ifosfamide, methotrexate), complications of conditioning regimen and HSCT, and from toxicities of targeted anticancer therapies (includes proteinuria, TMA, and hypertension), acute interstitial nephritis from immune checkpoint inhibitors
Rare: radiation nephritis, TMA, GN
Obstructive Uropathy
Common: genitourinary and gynecologic cancers
Rare: lymphoma

AKI, Acute kidney injury; CKD, chronic kidney disease; GN, glomerulonephritis; HSCT, hemopoietic stem cell transplantation; LCDD, light chain deposition disease; MCD, minimal change disease; MPGN, membranoproliferative GN; PGNMIgD, proliferative GN with monoclonal immunoglobulin deposits; SIADH, syndrome of inappropriate antidiuretic hormone; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy.

concurrent with other nephrotoxic agents, may increase AKI risk. Drug-induced acute interstitial nephritis (AIN) is a common cause of AKI in cancer patients, and exposure to the new immunotherapies and targeted therapies is increasing the prevalence of AIN.8

Postrenal Acute Kidney Injury

Genitourinary cancers may cause urinary tract obstruction and postrenal AKI. Cancers commonly associated with urinary tract obstruction involve the bladder, prostate, cervix, and ovary. Among these, pelvic irradiation and urogenital surgery for cancer are more likely to cause urinary obstruction. Cervical and ovarian cancers with metastatic spread involving the ureters or bladder are associated with postrenal AKI. In hematopoietic stem cell transplantation (HSCT) recipients with BK infection, ureteral obstruction is a common cause of renal

Chronic kidney disease is also a complication of many cancers and their therapy, and, like AKI, it is associated with increased morbidity and mortality. Preexisting CKD from underlying comorbidities is highly prevalent in patients with various types of malignancy.

Additionally, CKD may develop after multiple episodes of AKI, after nephrectomy for kidney cancer, and from nephrotoxic medications that cause glomerulosclerosis and tubulointerstitial fibrosis. The Renal Insufficiency and Anticancer Medications (IRMA) studies observed that 53% (IRMA-1) and 50% (IRMA-2) of patients with active malignancy had an estimated glomerular filtration rate (eGFR) less than 90 mL/min/1.73 m2, respectively.9 In this group, the prevalence of stage 3 CKD was 12% in both studies, whereas stage 4 CKD was rare (0.9% and 0.7%, respectively). In an Australian cohort with various cancers (n = 4077), eGFR less than 60 mL/min/1.73 m2 was observed in 30% of patients, and 8% had eGFR less than 45 mL/min/1.73 m2 10 In a cohort of Chinese patients with cancer, eGFR 30 to 59.9 mL/min/1.73 m2 was noted in 13% of 8223 patients.11 The relatively common occurrence of CKD in many cancer patients has been confirmed in other studies.

The relationship between kidney disease and cancer appears to be bidirectional. Although there is an increase in CKD prevalence in cancer patients, both CKD and ESKD are risk factors for development of a number of malignancies1 (see Chapter 92). In a retrospective cohort study of more than 1 million adults, lower eGFR was associated with an increased risk for kidney cancer after adjustment for time-updated confounders. In addition, the adjusted hazard ratio was 2.28 (95% confidence interval, 1.78–2.92) for eGFR less than 30 mL/min/1.73 m2 12 In patients with ESKD on dialysis, there is an increased risk for renal parenchymal cancer in patients with acquired renal cystic disease.

MORTALITY IN CANCER PATIENTS WITH KIDNEY DISEASE

The increased mortality associated with cancer-related AKI and CKD is related to a number of factors. The occurrence of AKI may require cessation of effective chemotherapeutic regimens, allowing unhindered tumor growth. Preexisting CKD may limit use of chemotherapeutic agents or promote underdosing of curative anticancer regimens. CKD and AKI may alter the bioavailability and/or safety profile of some anticancer drugs leading to use of suboptimal therapies. In addition, CKD and ESKD may impair immune surveillance, allowing cancers to grow and metastasize, especially when combined with insufficient drug dosing. It is also possible that anticancer agent nephrotoxicity is associated with worsening of preexisting CKD, which leads to increased all-cause mortality unrelated to cancer. A recent retrospective study of 128,489 patients from Ontario, Canada, with newly diagnosed solid cancer concluded that survival among patients with advanced kidney disease (stages 3a–5), ESKD, and transplants was inversely correlated with kidney function. In addition, receipt of all treatment modalities (systemic therapy, radiation, and palliative care) was significantly reduced in this group of patients.13

IMPORTANT MALIGNANCIES ASSOCIATED WITH KIDNEY DISEASE

Multiple Myeloma and Amyloidosis

Kidney involvement occurs in about 50% of patients with myeloma but varies depending on the myeloma type14 (see Chapters 28 and 68

). Monoclonal light chain (LC) overproduction is commonly associated with kidney injury, with as many as 50% of patients requiring dialysis.15 The LC type is also important; cast nephropathy and renal amyloidosis are common with λ LCs, whereas severe proximal tubular injury causing Fanconi syndrome and LC deposition disease are common with κ LCs. Cast nephropathy has been diagnosed in 41% of patients with myeloma and kidney disease, and the use of therapeutic plasma exchange or high cut-off hemodialysis has not been demonstrated to improve kidney or overall survival outcomes.16 Prior to the use of proteasome inhibitors, kidney failure in patients with myeloma was associated with reduced overall survival. Myeloma and amyloid patients’ outcomes have further improved with autologous stem cell transplantation (ASCT), which is now standard care in patients who have adequate organ function. Multiple studies have demonstrated improved kidney function following ASCT.17 Importantly, myelomarelated kidney failure did not affect progression-free survival or overall survival.18 Primary systemic amyloidosis in patients with LC disease is another infrequent manifestation of myeloma (see Chapter 28). When amyloidosis complicates myeloma, it carries a grave prognosis. Kidney enlargement, gross proteinuria, and amyloid deposition are hallmarks of renal amyloidosis, which occurs in about 5% to 10% of patients with myeloma based on autopsy studies.19

A

Leukemia and Lymphoma

Various forms of kidney disease occur in patients with lymphoma and leukemia. Those admitted to an ICU had an AKI hazard ratio of 2.23 for AKI, compared with otherwise comparable patients without ICU admission.20 In 200 patients with newly diagnosed high-grade lymphoma and leukemia, the incidence of RIFLE AKI was 68.5%, with 50% requiring RRT.21 Possible causes of AKI in patients with leukemia and lymphoma include prerenal processes,22 intrarenal causes such as ATN (especially from sepsis and nephrotoxic medications),23 or postrenal causes such as mechanical obstruction from lymphadenopathy or retroperitoneal fibrosis.24 Patients with leukemia or lymphoma commonly develop infiltrative disease of the kidney.25 Most often, renal infiltration is asymptomatic or subclinical, as noted in autopsy studies in which 34% of patients were found to have lymphomatous infiltration of the kidneys.25 Leukemic or lymphoma cell infiltration is suggested by large kidneys on imaging (Fig. 67.1A), and urinalysis shows bland urine sediment and tubular proteinuria.26 When AKI does occur, it is thought to be due to tubular compression and increased interstitial pressure from the massive malignant cell infiltration (see Fig. 67.1B).27 Overproduction of lysozyme, which is a freely filtered cationic protein reabsorbed in the proximal tubule, may cause ATN and/or proximal tubular injury with full-blown Fanconi syndrome.28 Intrarenal leukostasis may cause AKI in patients with acute myeloid leukemia (>100,000 white blood cells). Renal leukostasis is associated with reduced kidney perfusion, blast aggregation within the renal microvasculature, and endothelial damage triggered by soluble cytokines. Emergent treatment with cytoreductive chemotherapy and leukapheresis is generally required.29

ANTICANCER DRUGS AND KIDNEY DISEASE

Chemotherapeutic Agents

Oncologists generally assess kidney function before initiation of chemotherapeutic agents. Nevertheless, chemotherapy-related nephrotoxicity has become an important area for the nephrologist. Understanding renal metabolism and excretion of these drugs is critical in ensuring efficacy while also avoiding toxicity. Nephrotoxicity associated with the more common chemotherapeutic drugs includes AKI primarily from ATN and AIN, as well as other metabolic

B

Fig. 67.1 (A) Computed tomographic scan demonstrating large kidneys from lymphomatous infiltration of the kidneys. (B) Kidney biopsy demonstrating low-grade B-cell lymphoma cells within the renal parenchyma (H&E stain; ×400).

perturbations (Box 67.2). However, emergence of immunotherapies and targeted therapies has been associated with an increased incidence of various nephrotoxicities (Table 67.1).30

Immunotherapies

Immune Checkpoint Inhibitors

Leveraging the immune system to destroy cancer cells has become an attractive strategy for several different malignancies. Immune checkpoint inhibitors (ICIs) impair the checkpoints that function to suppress adaptive immune response and prevent autoimmunity. T cells possess surface receptors, such as programmed death-1 protein (PD1) and cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), which bind to their ligands on antigen-presenting cells, leading to T-cell exhaustion. This normally prevents the development of autoimmunity. Tumor survival may be enhanced in malignancies that overexpress ligands that bind these inhibitory T-cell receptors, thereby decreasing activated T-cell infiltration into the tumor microenvironment and inhibiting antitumor T-cell responses. To combat this, monoclonal antibody drugs that block ligand binding to PD-1 and CTLA-4 receptors and antibodies directed at PD-L1 were designed to facilitate T-cell rescue and restore antitumor immunity (Fig. 67.2). Ipilimumab, a fully human immunoglobulin G1 (IgG1) monoclonal antibody blocking CTLA-4; nivolumab, a fully human IgG4 antibody blocking the PD-1 receptor; and pembrolizumab, a humanized monoclonal IgG4-κ isotype antibody against PD-1, are the more common ICIs available in clinical practice. Many more have entered the clinical arena, including PD-L1 antibodies (atezolizumab, avelumab, and durvalumab).

However, blocking immune checkpoints risks development of pathologic autoimmunity and end organ injury, such as AIN. Several single and multicenter studies evaluating AKI after ICIs note the incidence to

BOX 67.2

Commonly Used Cancer Therapies Associated With Kidney Toxicity

Tubular Injury
Acute Tubular Injury
- Platinum-based agents, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed, zoledronate

Tubular Syndromes

Renal Tubular Acidosis
- Ifosfamide, amphotericin, calcineurin inhibitors

Fanconi Syndrome
- Cisplatin, ifosfamide, azacitidine, diaziquone, imatinib, pemetrexed

Salt Wasting
- Cisplatin, azacitidine

Magnesium Wasting
- Cetuximab, cisplatin, panitumumab

Nephrogenic Diabetes Insipidus
- Cisplatin, ifosfamide, pemetrexed

Acute Interstitial Nephritis
- Sorafenib, sunitinib, checkpoint inhibitors

Syndrome of Inappropriate Antidiuretic Hormone
- Cyclophosphamide, vincristine

Glomerular Injury
Focal Segmental Glomerulosclerosis
- IFN, pamidronate, tyrosine kinase inhibitors

Minimal Change Disease
- IFN, pamidronate

Proteinuria
- Sorafenib, sunitinib, vatalanib, axitinib

Renal Vascular Injury
Thrombotic Microangiopathy
- Bevacizumab (anti-VEGF monoclonal antibody)

Tyrosine Kinase Inhibitors
- Sorafenib, sunitinib, imatinib

Other Agents
- Gemcitabine, mitomycin C, IFN- α, calcineurin inhibitors

Crystalline Nephropathy
- Methotrexate, acyclovir, sulfa-based drugs

IFN, Interferon; VEGF, vascular endothelial growth factor.

range from 1.4% to 4.9%.31-33 Among a number of lesions that have been described, AIN is the most common cause of AKI.34-36 Although some patients develop rash and eosinophilia, AKI is the only consistent clinical manifestation. A small number of cases have required RRT, but most respond to drug discontinuation and steroid therapy. The mechanisms associated with ICI-induced nephrotoxicity are poorly understood, but drugs such as NSAIDs and proton pump inhibitors (PPIs) are associated with increased risk of AIN in several studies.31-33 Immune checkpoint inhibitor (ICI)-induced loss of tolerance to these drug antigens may lead to development of AIN. Induction of autoimmune disease or reactivation of preexisting autoimmune disease in the kidney has also been demonstrated with ICI exposure and poses a further challenge in cancer therapy, as treatment of ICI-associated inflammation often requires aggressive immunosuppression, which may promote cancer progression and offset the antitumor effects.37-39 In addition, ICI therapy for cancer may increase the risk of graft loss in kidney transplant recipients, a group with high risk for certain cancers due to immunosuppression. Single center retrospective studies and multicenter cohorts note rejection rates as high as 40% with ICI therapy in organ transplant patients and more specifically in those with kidney transplants.40 The median time from therapy to rejection ranged from 14 days to 24 days. There are no accepted guidelines for immunosuppression management during ICI use in kidney transplants. However, prioritizing cancer treatment over salvaging a kidney transplant has been the general approach.

Chimeric Antigen Receptor T Cells

Infusion of autologous ex vivo modified T lymphocytes that express chimeric antigen receptors (CARs) targeting specific tumor antigens is a more focused approach to immune destruction of tumor cells (Fig. 67.3).41 A more expansive approach is the use of CAR-expressing natural killer (NK) cells or macrophages. These therapies are effective in treating patients with refractory/relapsing leukemias and lymphomas with potential future use for multiple myeloma and solid tumors. CAR T-cell therapy is often associated with cytokine release syndrome (CRS), that can be severe and lethal. In addition to capillary leak syndrome and other end-organ injury such as AKI, patients may progress to hemophagocytic lymphohistiocytosis, characterized by high ferritin, low fibrinogen, and cytopenias. Prerenal physiology and ATN are toxicities associated with CRS in clinical trials. A recent single-center study of 78 patients receiving CAR T-cell therapy noted CRS in 85% of the patients, of which 19% developed AKI, split between prerenal and ATN.42 In addition to AKI and a high mortality, electrolyte abnormalities were also reported, including hypophosphatemia (75%), hypokalemia (56%), and hyponatremia (51%). Because CRS is primarily driven by interleukin 6 (IL-6), the anti–IL-6 antibody tocilizumab has proven effective in reversing this life-threatening complication.

Interferon Therapy

Treatment with interferon (IFN) is associated with proteinuria secondary to glomerular injury that is primarily a podocytopathy.43 Minimal change disease (MCD) was first described, but more recent reports describe collapsing and noncollapsing focal segmental glomerulosclerosis (FSGS). Nephrotic-range proteinuria and AKI are observed within weeks of commencing IFN therapy. Although proteinuria declines with IFN discontinuation, complete resolution is more common with MCD than with FSGS. Corticosteroids are associated with complete remission in fewer than one-third of patients with IFN-associated FSGS; however, an attempt at corticosteroid therapy is still warranted with rapid taper if no response.

Targeted Therapies

Antiangiogenesis Therapy

The discovery that vascular endothelial growth factor (VEGF) is an important mediator of tumor growth and angiogenesis led to the development of drugs targeting this pathway for cancer therapy.

TABLE 67.1
Drug Class

Kidney Toxicities Associated With Targeted Therapies
Renal Excretion

VEGF/VEGFR–Targeting Agents
Bevacizumab
No
Aflibercept
No
Sunitinib
16%
Pazopanib
<4%
Axitinib
23%
Other Multikinase Inhibitors
Sorafenib
19%

EVIDENCE FOR DOSE REDUCTION in CKD
Most Frequent Adverse Kidney
Events
Mild/Moderatea
Severeb
Dialysis
Hypertension, proteinuria
Hypertension, proteinuria
Hypertension, proteinuria
Hypertension, proteinuria
Hypertension, proteinuria

No
No
No
No
No

No
No
No
No
No

No
No
No
No
No

Hypertension, proteinuria,
hypophosphatemia
Hypertension, proteinuria, electrolyte
disorders
Hypertension, proteinuria, AKI
More renoprotective effects, AKI
described

No

No

No

No

No

No

No
No

Yes
No

No
No

Regorafenib

19%

Vandetanib
Imatinib

25%
13%

mTOR Inhibitors
Everolimus
Temsirolimus

2%
4.6%

Proteinuria, AKI, electrolyte disorders
Proteinuria, AKI, electrolyte disorders

No
No

No; suspend if AKI
No; suspend if AKI

No
No

EGFR Inhibitors
Gefitinib
Erlotinib
Afatinib
Cetuximab

<4%
<9%
<5%
No

No
No
No
No

No
No
No
No

No
No
No
No

Panitumumab

No

Electrolyte disorders
Electrolyte disorders
Electrolyte disorders
Hypomagnesemia, other electrolyte disorders
Hypomagnesemia, other electrolyte disorders

No

No

No

AKI (tubular necrosis?)

No

No

Hypophosphatemia (granulomatous nephritis?)
Hypertension, hyponatremia (with dabrafenib)

No

No

Possible (risk for arrhythmia)
No

No

No

No

Hypertension, AKI (with cisplatin)
No issues
No issues
Hypokalemia

No
No
No
No

No
No
No
No

No
No
No
No

Autoimmune nephritis, (potential drug
No
reaction with eosinophilia and systemic
symptom syndrome)

No

No

Reduction of eGFR (tubular necrosis?),
renal cysts
No issues

Possible, with
caution
No

No

B-RAF Inhibitors ± MEK Inhibitors
Vemurafenib
1%
Dabrafenib

23%

Trametinib

<20%

ERBB2-Targeting Agents
Trastuzumab
No
Pertuzumab
No
Lapatinib
2%
Trastuzumab emtansine <5%
Antibodies Against CTLA-4
Ipilimumab
No

Other Agents
Crizotinib

No

Catumaxomab

No

Possible, with caution
No

No

[a]30–90 mL/min/1.73 m2.
[b]<30 mL/min/1.73 m2.
AKI, Acute kidney injury; CKD, chronic kidney disease; CTLA-4, cytotoxic T-lymphocyte–associated antigen-4; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin complex; VGEF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Effect of Monoclonal Immune Checkpoint Inhibitors
on T-Cell Function
Lymph node

Antigenpresenting cell

Quiescent
T-cell
CD28

CD80/86
MHC-Ag

TCR

CD80/86

CTLA-4
Anti
CTLA-4

Tumor
Microenvironment

Peripheral
Tissues

Activated
T-cell

Tubular
cells

CD28

CD80/86
Ag
PD-L1

TCR
CD28PD-1

TCR
PD-1

Cancer
cell

Tumor
Ag

PD-L1

Anti
Anti
Anti
Anti
PD-1
PD-L1
PD-L1

PD-1

Fig. 67.2 Effect of Monoclonal Immune Checkpoint Inhibitors on T-Cell Function. In the lymph tissue, T cells are quiescent but can be activated by antigen presentation by an antigen-presenting cell. Antigen binding to the T-cell receptor (TCR) is modulated by costimulatory signals such as CD80/86 binding CD28 and coinhibitory signals such as CD80/86 binding cytotoxic T-lymphocyte–associated protein-4 (CTLA-4), which is shuttled to the cell surface upon antigen binding the TCR. Blocking the CTLA-1 receptor with monoclonal antibody allows T-cell activation, which can participate in cancer destruction. In peripheral tissues, activated T cells can be deactivated by the binding of programmed cell death ligand-1 (PD-L1; or PD-L2) to the PDL1 receptor. Host tissues prevent autoimmune injury by deactivating T cells, whereas cancer cells prevent tumor killing through the same process. Blocking the PD-1 receptor (or blocking PD-L1) with immune checkpoint inhibitors allows T cells to remain activated and allows eradication of cancer cells. However, this can also be associated with host organ injury such as acute kidney injury. Ag, Antigen; MHC-Ag, major histocompatibility complex antigen.

However, VEGF is also an essential growth factor to maintain glomerular endothelial health. It is secreted by podocytes and traverses the basement membrane, where it binds to VEGF receptors on endothelial cells and maintains glomerular endothelial cell integrity and filtration barrier function. In addition, VEGF enhances production of local regulatory complement factors, thereby preventing pathologic endothelial injury and thrombosis.44 Anti-VEGF drugs (e.g., the monoclonal antibody bevacizumab) and drugs that inhibit tyrosine kinase (e.g., sunitinib) both block VEGF function. This leads to glomerular endothelial cell dysfunction and filtration barrier disruption, resulting in proteinuria, thrombotic microangiopathy (TMA), hypertension, and AKI.45 TMA may also develop from loss of VEGF-associated regulatory complement factor production. Mild and asymptomatic albuminuria is common, and heavy proteinuria occurs in less than 10% of subjects.46 Hypertension or aggravation of preexisting hypertension is common. The reported incidence varies between 17% and 80%.47 Development of hypertension reflects efficacy of VEGF blockade therapy, perhaps explaining why bevacizumab-induced hypertension correlates with clinical outcomes.48 Hypertension is managed with standard antihypertensive medications, although the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is preferable in patients

with proteinuria. Kidney side effects that develop with anti-VEGF therapy (especially TMA) may require dose reduction or drug discontinuation.46

B-RAF Inhibitors

Malignant melanoma frequently has a B-RAF V600 mutation that can be effectively targeted by the selective B-RAF inhibitors vemurafenib and dabrafenib. Although they are effective anticancer agents, these drugs are nephrotoxic. A GFR decline at 1 and 3 months of therapy occurred in 15 of 16 patients, which was complicated by persistent kidney injury after 8 months of follow-up. Eight patients developed AKI after vemurafenib, with ATN seen in 1 patient. AKI that was clinically suggestive of AIN was observed in 4 patients treated with vemurafenib, with 3 of 4 patients recovering kidney function after drug discontinuation, although no biopsy data were available.49 Nearly 60% of 74 patients treated with vemurafenib developed AKI, primarily Kidney Disease: Improving Global Outcomes (KDIGO) stage 1, within 3 months of drug exposure.50 Kidney biopsy revealed tubulointerstitial injury in 2 patients. Kidney function recovered within 3 months of

B-RAF discontinuation. The combination of dabrafenib and trametinib was shown to cause AKI in 21% of 199 patients in a retrospective cohort study.51 Although the mechanism of kidney injury is unknown,

Creation of CAR T Cells
Hinge region
CD3-ζ chain
signaling domain

Antigen-binding
domain
domain

T cell

CAR T cell

Cancer cell

T-cell receptor

CXCL10

IL-Ra

INF-γ

Lentiviral
vector
TNF-α

T-cell receptor
Cancer cell
surface antigen

IL-6

Fig. 67.3 The creation of chimeric antigen receptor (CAR) T cells involves harvesting T cells from patients and subsequently genetically modifying them using a lentiviral vector to place an antigen-binding domain, which recognizes tumor antigen. The antigen-binding receptor is linked to an intracellular costimulatory domain (CD28 or 4–1BB) and CD3-ζ signaling domain to amplify the immune response against tumor cells. Chimeric antigen receptor T cells engage tumor antigen by using extracellular antigen receptors, which are linked to intracellular costimulatory and signaling domains to amplify the immune response against tumor cells. Proinflammatory cytokines and chemokines are produced, which participate in eradication of cancer cells. CXCL10, C-X-C motif chemokine ligand 10; IL-Ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; INF-γ, interferon-γ; TNF-α; tumor necrosis factor-α.

these drugs may interfere with the downstream mitogen-activated protein kinase pathway, increasing susceptibility to ischemic tubular injury. Therapy is supportive along with drug discontinuation.

Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase 1 (ALK-1) is a member of the insulin receptor tyrosine kinase family, for which small molecule inhibitors include crizotinib and ceritinib. Crizotinib is an effective agent for treatment of advanced ALK-positive non–small cell lung cancer and appears to be associated with two major issues: AKI and an increased risk for the development and progression of renal cysts.52 In addition, this agent is also associated with development of peripheral edema and, rarely, electrolyte disorders. Crizotinib is associated with true and pseudo-AKI, the latter due to drug-induced reduced tubular creatinine secretion. If true AKI, temporary discontinuation of drug is recommended. Rechallenge with drug is possible if full recovery of kidney function has occurred.

METABOLIC COMPLICATIONS

Tumor Lysis Syndrome

High-grade lymphomas, acute leukemias, and other rapidly proliferating tumors are prone to tumor lysis syndrome (TLS). Among these, patients with Burkitt lymphoma are particularly at risk. Volume depletion, hypotension, large primary or metastatic tumor load, preexisting CKD, and concurrent exposure to potential nephrotoxic agents are common risk factors for TLS-induced AKI. Cell lysis leads to hyperuricemia,

hyperkalemia, hyperphosphatemia, and acidosis causing AKI, primarily from urate crystal deposition in the tubules. Hyperuricemia may also play a role in TLS-associated AKI independent of crystals, possibly as a result of inflammation and endothelial dysfunction.53 Myocardial deposition of calcium-phosphate crystals may contribute to the development of life-threatening arrhythmias. TLS prevention in high-risk patients involves hydration to maintain a high urine output (>100 mL/h) and allopurinol or rasburicase to reduce hyperuricemia. Rasburicase, which degrades uric acid to water-soluble allantoin, effectively lowers uric acid levels but has not been shown to be superior to allopurinol for prevention of TLS-associated AKI.54 Early dialysis should be considered when progressive AKI develops in patients with TLS who will be unable to handle the excessive cellular contents (e.g., potassium, phosphate) to prevent life-threatening electrolyte abnormalities. Furthermore, accumulation of tumor lysis products can aggravate renal injury. In patients with severe TLS and oliguric AKI, continuous RRT may be required to control hyperkalemia and persistent hyperphosphatemia.

Common Electrolyte Disorders

Although electrolyte abnormalities are common in cancer patients, factitious laboratory findings may occur. Paraproteins, especially IgM, may cause assay interferences with several tests that are mostly due to their physical interferences with reagents, reactions, or both.55 Pseudohyperkalemia secondary to in vitro release of potassium from cells may occur in patients with acute leukemia, chronic lymphocytic leukemia, and chronic myeloproliferative disorders. When factitious values are suspected, careful collection and prompt analysis of repeat samples are required.

Hyponatremia is the most common electrolyte abnormality and affects nearly 50% of hospitalized cancer patients.56 57 Hyponatremia is frequently due to the syndrome of inappropriate antidiuretic hormone (SIADH), which occurs with many malignancies, including lung cancers, head and neck cancers, and some hematologic cancers.58 Nausea, pain, and analgesics such as morphine and its derivatives, antidepressants, and several chemotherapeutic agents may cause hyponatremia either by increasing arginine vasopressin secretion or enhancing its effect. Although SIADH is common, one-third of cancer cases develop hyponatremia from volume depletion, which is responsive to normal saline repletion. Treatment with fluid restriction is difficult in cancer patients with SIADH, especially in subjects receiving chemotherapy or HSCT, because these procedures require high intravenous fluid intake. Oral sodium chloride (titrated to target sodium correction) and loop diuretics are sometimes effective in those not receiving large intravenous fluid volumes, whereas vasopressin V2 receptor antagonists may be an option to correct hyponatremia in such patients.58

Hypernatremia is much less frequent compared with hyponatremia (3% vs. 47%) but is associated with higher mortality and longer hospital stays.59 Most hypernatremia occurs in the hospital and is observed primarily in critically ill leukemia and HSCT patients who are receiving loop diuretics.

Other common electrolyte abnormalities in cancer patients (especially those who are receiving chemotherapy) include hypokalemia, hypomagnesemia, and hypophosphatemia. Nausea/vomiting, diarrhea, and poor nutrition from chemotherapy account for many of these abnormalities. However, severe abnormalities are usually due to drug-induced Fanconi syndrome. Ifosfamide and cisplatin are the most common agents, but κ LC myeloma also can cause this syndrome. Cetuximab causes hypomagnesemia, which occasionally can be severe. In health, epidermal growth factor (EGF) binds its receptor (EGFR) and stimulates distal tubular magnesium reabsorption. Cetuximab (EGFR antibody) competes with EGF for its receptor, thereby inhibiting normal reabsorption of luminal magnesium and causing hypermagnesiuria.

Hypercalcemia is common in patients with advanced cancer with bone metastasis and heralds a poor prognosis (see Chapter 11). Hypercalcemia is frequently associated with multiple myeloma and can be the presenting feature. Several mechanisms may underlie tumoral hypercalcemia such as elevated parathyroid hormone–related peptide levels associated with lung cancer, ectopic vitamin D in certain lymphomas, or tumor resorption of bones as in advanced cancer (see Chapter 11). Treatment of hypercalcemia mandates vigorous intravenous fluid administration in those who are volume depleted (Box 67.3). Although corticosteroids (for myeloma and vitamin D–related hypercalcemia) and calcitonin are useful, persistent hypercalcemia often requires bisphosphonate therapy for long-term control. Rarely, hemodialysis with low calcium dialysate alone is sufficient to control severe hypercalcemia in symptomatic patients. Use of bisphosphonates, especially zoledronate and pamidronate, can be complicated by AKI and collapsing FSGS, respectively. Ibandronate and denosumab are less nephrotoxic options.60

CANCER-RELATED GLOMERULONEPHRITIS

Cancer-related glomerulonephritis is a relatively rare but important entity in patients with certain malignancies. Proteinuria or (rarely) nephrotic syndrome can be the manifesting feature of cancer. Membranous nephropathy (MN) (see Chapter 21) is the most common glomerular pathology associated with solid tumors. In the largest series of 240 patients with biopsy-proven MN, a cancer diagnosis was noted in 10%.61 Common cancers associated with MN are lung, gastric, colon, and renal carcinomas, but several other solid tumors, such as prostate and breast cancer, are also linked (Table 67.2). In Hodgkin disease, the most common lesion is MCD (see Chapter 18), possibly related to tumor-related T-cell dysfunction. Chronic lymphocytic leukemia is commonly associated with a histologic pattern of membranoproliferative glomerulonephritis (see Chapter 22), especially in the presence of cryoglobulinemia. HSCT is associated with membranous nephropathy, and, rarely, MCD can be a manifestation of chronic graft-versus-host disease.62 The use of IFN-α, anti-VEGF therapies, and bisphosphonates in cancer therapy is associated with various glomerular diseases and thrombotic microangiopathy.63

Management of Cancer-Related Hypercalcemia

BOX 67.3

1. General measures: IV fluids followed by loop diuretics if hypervolemia.
2. Administer calcitonin (4 U/kg SQ every 6–12 h based on calcium response), corticosteroids (prednisone 20–40 mg/d PO depending on cause), or both for acute and short-term calcium control.
3. If patient severely symptomatic and with reduced urine output and impaired kidney function, consider dialysis with low bath calcium.
4. Start bisphosphonates (pamidronate 30–90 mg IV over 2–4 h depending on GFR; zoledronate 4 mg IV over 15 min, dose adjusted for GFR, contraindicated for GFR <30 mL/min) for longer-term hypercalcemia control (adjust for kidney dysfunction or switch to denosumab; see step 6).
5. Treat the underlying malignancy.
6. For bone resorption–associated hypercalcemia: humanized anti-RANKL antibody (denosumab 60–120 mg SQ) appears to be safer and more effective than bisphosphonates (particularly in patients with AKI or CKD).
7. For PTHrP-related hypercalcemia: humanized monoclonal antibody against human PTHrP may be more effective than bisphosphonates (under evaluation)

GFR, Glomerular filtration rate; IV, intravenous; PO, orally; PTHrP, parathyroid hormone–related peptide; RANKL, receptor activator of nuclear factor κ-B ligand; SQ, subcutaneously.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Among the types of HSCT, the myeloablative allogeneic form requires higher doses of irradiation, chemotherapy, or a combination and carries the highest risk for developing AKI (up to 70%). Acute kidney injury can have multiple causes in HSCT recipients and is associated with poor clinical outcomes in patients receiving any form of HSCT.64 In addition to the usual causes of AKI (volume depletion, intravenous contrast, sepsis, and drug toxicity), there are several specific renal syndromes that should be suspected based on the length of time between HSCT and the development of AKI (Table 67.3).

CANCER THERAPY IN CHRONIC KIDNEY DISEASE AND END-STAGE KIDNEY DISEASE

Reduced GFR complicates the selection and administration of chemotherapy and may lead to unduly high doses and drug accumulation.65 Careful dosing and dialysis timing are critical because overdosing can aggravate systemic toxicities, whereas underdosing can lead to ineffective cancer treatment. Common risk factors for chemotherapy-induced nephrotoxicity include volume depletion,

TABLE 67.2

Diseases

Cancer-Associated Glomerular

Malignancy

Glomerular Diseases

Lung cancer
Colon cancer
Stomach cancer
Pancreas cancer
Bladder cancer
Renal cell cancer
Prostate cancer
Breast cancer
Esophageal cancer
Gastrointestinal stromal tumor
Gastric cancer
Spleen sarcoma
Head and neck cancer
Wilms tumor
Teratoma
Ovarian cancer
Cervical cancer
Endometrial cancer
Tongue cancer
Mesothelioma
Melanoma
Skin cancers (basal cell, squamous cell)
Pheochromocytoma
Thymoma
Hodgkin disease

MN,a MCD, MPGN, IgAN, FSGS, CGN, TMA
MN,a MCD, CGN
MN
MN,a MCD, IgAN
MCD
AAA,a CGN, IgAN, MCD, FSGS, MPGN
MN,a CGN
MN,a FSGS, MPGN, TMA
MPGN,a FSGS
AAA
MPGN,a CGN, TMA
AAA
MN,a IgAN
MN,a MPGN
MN
MN,a MCD
MN
MN
IgAN
MCD
MN,a MPGN
MN

Non-Hodgkin disease
CLL

AML
CML
MGUS
T-cell leukemia
[a]Most

MN
MCD,[a] FSGS, CGN, MPGN
MCD,[a] MN, MPGN, IgAN, FSGS, CGN,
AAA, anti-GBM
MPGN,[a] MCD, MN, IgAN, FSGS
MPGN,[a] MCD, MN, FSGS, CGN
MN,[a] FSGS
MN,[a] MCD, MPGN
MPGN
FSGS

common glomerular lesion.
AAA, Secondary amyloidosis; AML, acute myelogenous leukemia;
CGN, crescentic glomerulonephritis; CLL, chronic lymphocytic leukemia; CML,
chronic myelogenous leukemia; FSGS, focal segmental
global sclerosis; GBM, glomerular basement membrane; IgAN, IgA
nephropathy; MCD, minimal change disease; MGUS, monoclonal
gammopathy of unclear significance; MN, membranous nephropathy;
MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic
microangiopathy.
From Luciano RL, Brewster UC. Kidney involvement in leukemia and
lymphoma. Adv Chronic Kidney Dis. 2014;21(1):27–35.

Causes of Acute Kidney Injury and Other Kidney Disease in Relation to the Timing of Hemopoietic Stem Cell Transplantation

TABLE 67.3

Before and hours after
HSCT

Days to weeks after
HSCT
Weeks to months after
HSCT

Months to years after
HSCT

Tumor lysis syndrome from conditioning regimen
(rare)
Systemic toxicity from conditioning regimen (e.g.,
volume depletion [common])
DMSO toxicity from hemolysis, acidosis, and
pigment nephropathy (rare)
Prerenal AKI from volume depletion, AKI from
neutropenic sepsis and drug toxicity (common)
AKI related to engraftment syndrome (rare)
AKI from sepsis, volume depletion, drug and
radiocontrast toxicity (common)
AKI from sinusoidal obstruction syndrome of the
liver, GVHD, thrombotic microangiopathy, and BK
virus nephropathy (rare)
CKD from previous AKIs, continuous use of

calcineurin inhibitors especially with GVHD, and from preexisting cancer, such as myeloma (common)

AKI, Acute kidney injury; CKD, chronic kidney disease; DMSO, dimethyl sulfoxide; GVHD, graft-versus-host disease; HSCT, hemopoietic stem cell transplantation.

hypoalbuminemia, metabolic derangements, older age, presence of diabetes and other comorbid conditions, underlying AKI or CKD, presence of sepsis, and concomitant use of other potential nephrotoxins. Therefore, optimizing kidney function in those with CKD before chemotherapy can reduce risk for AKI and chemotoxicity. Moreover, administration of platinum compounds requires dose adjustments and timing with dialysis. Other commonly used agents for cancer treatment that need dose adjustment for GFR and dialysis or that should be avoided completely are melphalan, methotrexate, pemetrexed, capecitabine, hydroxyurea, fludarabine, etoposide, irinotecan, and lenalidomide.66 In contrast, the ICIs do not need dose adjustments for liver or kidney disease. Tumor lysis developing in CKD/ESKD patients can be particularly challenging because the reduced ability to eliminate the tumor products can be lifethreatening. In this situation, institution of daily dialysis or continuous RRT may become necessary. Moreover, in CKD/ESKD patients on active cancer treatment, erythropoietin should be used judiciously because higher doses may be associated with poorer cancer outcomes.67 A suggested approach is noted in Fig. 67.4 68

ESA Treatment in CKD/ESKD: Issues to Consider Regarding Cancer
No history
of cancer

Active diagnosis
of cancer

Are
major
risk factors
present?

If acute severe anemia, treat
with blood transfusion

No
Treat per
usual
CKD/ESKD
protocols

Yes

Consider
conservative
Hgb target

Before ESA, evaluate for
other correctible causes
of anemia

If ESA is initiated or
continued, limit treatment
to upper Hgb target 10 g/dL

Past history
of cancer

Is
cancer
considered
cured?

Yes

Consider
continuing
conservative
treatment
Hgb target

No
Follow
goals for
active cancer

Treat under the APPRISE
REMS program

Place special emphasis

on carefully monitoring for and preventing thromboembolic events

Fig. 67.4 `Recommended approach to erythropoietin-stimulating agent (ESA) use in cancer patients with anemia and chronic kidney disease (CKD)/end-stage kidney disease (ESKD). APPRISE, Assisting Providers and Cancer Patients With Risk Information for the Safe Use of ESAs; Hgb, hemoglobin; REMS, risk evaluation and mitigation strategy.

SELF-ASSESSMENT QUESTIONS

1. Which one of the following kidney lesions is most likely to be observed on kidney biopsy in a patient with multiple myeloma that develops acute kidney injury with urinalysis showing trace protein and a spot urine protein/creatinine ratio of 4.8 mg/mg?

A. Light chain–associated proximal tubulopathy
B. Light chain deposition disease
C. Primary systemic amyloidosis
D. Light chain cast nephropathy
E. Plasma cell interstitial infiltration

2. A 67-year-old woman with a history of metastatic melanoma is undergoing therapy with nivolumab. After 6 weeks, the patient develops AKI (serum creatinine 3.8 mg/dL). Urinalysis reveals 1+ protein, blood, and leukocyte esterase; 3 to 5 white blood cells per high-power field (HPF), 5 to 10 red blood cells/HPF, and 3 to 5 granular casts per low-power field are noted on urine microscopy. Which one of the following lesions is most likely to be observed on kidney biopsy?

A. Acute tubular injury/necrosis
B. Isolated proximal tubular injury
C. Acute interstitial nephritis

D. Acute glomerulonephritis
E. Acute fibrinoid necrosis of glomerulus

3. A 69-year-old woman presented with weight loss and nausea/vomiting. A computed tomography scan of the chest and abdomen demonstrated 18-cm bilateral kidneys without hydronephrosis. There was also associated retroperitoneal lymphadenopathy. Labs revealed the following: sodium 135 mEq/L; potassium 5.1 mEq/L; chloride 101 mEq/L; bicarbonate 18 mEq/L; blood urea nitrogen 59 mg/dL; creatinine 4.5 mg/dL (baseline 1.0 mg/dL); serum albumin 3.7 g/dL; calcium 11.1 mg/dL; phosphorus 7.6 mg/dL; and uric acid 11.7 mg/dL. Urinalysis showed specific gravity of 1.018, pH 5.0, and a negative dipstick examination. Urine output was 800 mL/24 h. What is the most likely cause of acute kidney injury in this patient?

A. Retroperitoneal lymphadenopathy with nonhydronephrotic urinary obstruction
B. Tumor lysis syndrome with acute crystalline nephropathy
C. Hypercalcemic AKI
D. Lymphomatous infiltration of the kidneys
E. Prerenal AKI from nausea and vomiting

REFERENCES

1. Christiansen CF, Johansen MB, Langeberg WJ, et al. Incidence of acute kidney injury in cancer patients: a danish population-based cohort study. Eur J Intern Med. 2011;22(4):399–406.
2. Salahudeen AK, Bonventre JV. Onconephrology: the latest frontier in the war against kidney disease. J Am Soc Nephrol. 2013;24(1):26–30.
3. Janus N, Launay-Vacher V, Byloos E, et al. Cancer and renal insufficiency results of the BIRMA study. Br J Cancer. 2010;103(12):1815–1821.
4. Salahudeen AK, Doshi SM, Pawar T, et al. Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. Clin J Am Soc Nephrol. 2013;8(3):347–354.
5. Liborio AB, Abreu KL, Silva Jr GB, et al. Predicting hospital mortality in critically ill cancer patients according to acute kidney injury severity. Oncology. 2011;80(3–4):160–166.
6. Darmon M, Ciroldi M, Thiery G, et al. Clinical review: specific aspects of acute renal failure in cancer patients. Crit Care. 2006;10(2):211.
7. Seylanova N, Crichton S, Zhang J, Fisher R, Ostermann M. Acute kidney injury in critically ill cancer patients is associated with mortality: a retrospective analysis. PLoS One. 2020;15(5). e0232370.
8. Salahudeen AK, Kumar V, Madan N, et al. Sustained low efficiency dialysis in the continuous mode (C-SLED): dialysis efficacy, clinical outcomes, and survival predictors in critically ill cancer patients. Clin J Am Soc Nephrol. 2009;4(8):1338–1346.
9. Launay-Vacher V. Epidemiology of chronic kidney disease in cancer patients: lessons from the IRMA study group. Semin Nephrol. 2010;30(6):548–556.
10. Iff S, Craig JC, Turner R, et al. Reduced estimated GFR and cancer mortality. Am J Kidney Dis. 2014;63(1):23–30.
11. Na SY, Sung JY, Chang JH, et al. Chronic kidney disease in cancer patients: an independent predictor of cancer-specific mortality. Am J Nephrol. 2011;33(2):121–130.
12. Lowrance WT, Ordonez J, Udaltsova N, et al. CKD and the risk of incident cancer. J Am Soc Nephrol. 2014;25(10):2327–2334.
13. Kitchlu A, Luo B, Jeyakumar N, et al. CKD Prevalence, Patterns of Treatment, and Outcomes in Patients with Cancer: A Population-Based Cohort Study. ASN Abstract TH-OR39
14. Blade J, Fernandez-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. Arch Intern Med. 1998;158(17):1889–1893.
15. Hutchison CA, Blade J, Cockwell P, et al. Novel approaches for reducing free light chains in patients with myeloma kidney. Nat Rev Nephrol. 2012;8(4):234–243.
16. Małyszko J, Bamias A, Danesh FR, et al. Conference Participants. KDIGO controversies conference on onco-nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation. Kidney Int. 2020;98(6):1407–1418.
17. Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica. 2007;92(4):546–549.
18. Abudayyeh A, Lin H, Mamlouk O, et al. Impact of autologous stem cell transplantation on long term renal function and associated progressionfree and overall survival in multiple myeloma. Leuk Lymphoma. 2020;61(13):3101–3111.
19. Iványi B. Renal complications in multiple myeloma. Acta Morphol Hung. 1989;37(3–4):235–243.
20. de Mendonca A, Vincent JL, Suter PM, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26(7):915–921.
21. Canet E, Zafrani L, Lambert J, et al. Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival. PLoS One. 2013;8(2).
22. Soares M, Salluh JIF, Carvalho MS, et al. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol. 2006;24(24):4003–

4010.
23. Harris KP, Hattersley JM, Feehally J, Walls J. Acute renal failure associated with haematological malignancies: a review of 10 years experience. Eur J Haematol. 1991;47(2):119–122.

24. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. Lancet. 2006;367(9506):241–251.
25. Strati P, Nasr SH, Leung N, et al. Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the mayo clinic experience. Haematologica. 2015;100(9):1180–1188.
26. Tornroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. Am J Kidney Dis. 2003;42(5):960–971.
27. Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. Adv Chronic Kidney Dis. 2014;21(1):27–35.
28. Patel TV, Rennke HG, Sloan JM, et al. A forgotten cause of kidney injury in chronic myelomonocytic leukemia. Am J Kidney Dis. 2009;54(1):159–164.
29. Porcu P, Danielson CF, Orazi A, et al. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol. 1997;98(2):433–436.
30. Porta C, Cosmai L, Gallieni M, et al. Renal effects of targeted anticancer therapies. Nat Rev Nephrol. 2015;11(6):354–370.
31. Cortazar FB, Kibbelaar ZA, Glezerman IG, et al. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. J Am Soc Nephrol. 2020;31(2):435–446.
32. Seethapathy H, Zhao S, Chute DF, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol. 2019;14:1692–1700.
33. Meraz-Munoz A, Amir E, Ng P, et al. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. J Immunother Cancer. 2020;8.
34. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am J Kidney Dis. 2016;68(2):287–291.
35. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90:638–647.
36. Mamlouk O, Selamet U, Machado S, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. J Immunother Cancer. 2019;7:2–14.
37. Lin JS, Wang DY, Mamlouk O, et al. Immune checkpoint inhibitor associated reactivation of primary membranous nephropathy responsive to rituximab. J Immunother Cancer. 2020;8(2). e001287.
38. Gallan AJ, Alexander E, Reid P, et al. Renal vasculitis and Pauci-immune glomerulonephritis associated with immune checkpoint inhibitors. Am J Kidney Dis. 2019;74:853–856.
39. Mamlouk O, Lin JS, Abdelrahim M, et al. Checkpoint inhibitor-related renal vasculitis and use of rituximab. J Immunother cancer. 2020;8(2): e000750.
40. Murakami N, Mulvaney P, Danesh M, et al. Immune checkpoint inhibitors in solid organ transplant consortium. A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant. Kidney Int. 2020;(20):S0085-2538(20)31534-9.
41. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. J Am Soc Nephrol. 2018;29(8):2039–2052.
42. Gupta S, Seethapathy H, Strohbehn IA, et al. Acute kidney injury and electrolyte abnormalities after chimeric antigen receptor T-cell (CAR-T) therapy for diffuse large B-cell lymphoma. Am J Kidney Dis. 2020;76(1):63–71.
43. Markowitz GS, Nasr SH, Stokes MB, D’Agati VD. Treatment with IFN-α, -β, or -γ is associated with collapsing focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2010;5(4):607–615.

44. Keir LS, Firth R, Aponik L, et al. VEGF regulates local inhibitory complement proteins in the eye and kidney. J Clin Invest. 2017;127:199–214.
45. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med. 2008;358(11):1129–1136.
46. Izzedine H, Massard C, Spano JP, et al. VEGF signalling inhibitioninduced proteinuria: mechanisms, significance and management. Eur J Cancer. 2010;46(2):439–448.
47. Mouhayar E, Salahudeen A. Hypertension in cancer patients. Tex Heart Inst J. 2011;38(3):263–267.

References

48. Scartozzi M, Galizia E, Chiorrini S, et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol. 2009;20(2):227–230.
49. Wanchoo R, Jhaveri KD, Deray G, Launay-Vacher V. Renal effects of BRAF inhibitors: a systematic review by the cancer and the kidney International network. Clin Kidney J. 2016;9(2):245–251.
50. Teuma C, Perier-Muzet M, Pelletier S, et al. New insights into renal toxicity of the B-RAF inhibitor, vemurafenib, in patients with metastatic melanoma. Cancer Chemother Pharmacol. 2016;78(2):419–426.
51. Seethapathy H, Lee MD, Strohbehn IA, et al. Clinical features of acute kidney injury in patients receiving dabrafenib and trametinib. Nephrol Dial Transplant. 2020.
52. Izzedine H, El-Fekih RK, Perazella MA. The renal effects of ALK inhibitors. Invest New Drugs. 2016;34(5):643–649.
53. Shimada M, Johnson RJ, May Jr WS, et al. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. Nephrol Dial Transplant. 2009;24(10):2960–2964.
54. Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. Am J Kidney Dis. 2013;62(3):481–492.
55. Dalal BI, Brigden ML. Factitious biochemical measurements resulting from hematologic conditions. Am J Clin Pathol. 2009;131(2):195–204.
56. Doshi SM, Shah P, Lei X, et al. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis. 2012;59(2):222–228.
57. Sorensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med. 1995;238(2):97–110.
58. Salahudeen AK, Ali N, George M, et al. Tolvaptan in hospitalized cancer patients with hyponatremia: a double-blind, randomized, placebo-

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60.
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62.

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64.

65.

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67.
68.

controlled clinical trial on efficacy and safety. Cancer. 2014;120(5):744–751.
Salahudeen AK, Doshi SM, Shah P. The frequency, cost, and clinical outcomes of hypernatremia in patients hospitalized to a comprehensive cancer center. Support Care Cancer. 2013;21(7):1871–1878.
Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74(11):1385–1393.
Lefaucheur C, Stengel B, Nochy D, et al. Membranous nephropathy and cancer: epidemiologic evidence and determinants of high-risk cancer association. Kidney Int. 2006;70(8):1510–1517.
Lin J, Markowitz GS, Nicolaides M, et al. Membranous glomerulopathy

associated with graft-versus-host disease following allogeneic stem cell transplantation. Report of 2 cases and review of the literature. Am J Nephrol. 2001;21(5):351–356.

Jhaveri KD, Shah HH, Calderon K, et al. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int. 2013;84(1):34–44.

Abudayyeh A, Hamdi A, Lin H, et al. Symptomatic BK virus infection is associated with kidney function decline and poor overall survival in allogeneic hematopoietic stem cell recipients. Am J Transplant. 2016;16(5):1492–1502.

Boesler B, Czock D, Keller F, et al. Clinical course of haemodialysis patients with malignancies and dose-adjusted chemotherapy. Nephrol Dial Transplant. 2005;20(6):1187–1191.

Janus N, Thariat J, Boulanger H, et al. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol. 2010;21(7):1395–1403.

Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. N Engl J Med. 2007;356(24):2445–2448.

Hazzan AD, Shah HH, Hong S, et al. Treatment with erythropoiesisstimulating agents in chronic kidney disease patients with cancer. Kidney Int. 2014;86(1):34–39.

68

Myeloma and the Kidney

Ashley B. Irish

Myeloma is an uncommon malignancy; it accounts for 1% of total malignancies and 10% of hematologic malignancies in the United States, with a stable age-adjusted incidence of 40 per 1 million. The incidence of myeloma is twice as high in African Americans as in Whites, and is higher for males than females. Myeloma is a disease of older people, with the median age at diagnosis exceeding 65 years.1 Myeloma is characterized by a neoplastic proliferation of plasma cell clones producing monoclonal immunoglobulin, which in 95% of cases includes an excess of the light chain (LC) component, which can be nephrotoxic. Various causes and manifestations of acute kidney injury (AKI) are possible in myeloma (Table 68.1), but the major risk is myeloma cast nephropathy (MCN), which is a medical emergency that requires prompt diagnosis and intervention to avoid irreversible kidney failure. Other monoclonal B-cell–derived kidney disorders have been collectively described as monoclonal gammopathy of renal significance (MGRS); they differ from myeloma because they do not depend on expansion of the clonal mass for their nephrotoxicity and usually lack the additional features characteristic of myeloma, such as bone disease.2

ETIOLOGY AND PATHOGENESIS OF MYELOMA

Plasma cells derive from mature uncommitted B cells and after antigen stimulus undergo heavy-chain class switching from μ (immunoglobulin M [IgM]) expression to α, δ, ε, and γ. Whole immunoglobulin production requires the intracellular assembly of two heavy chains and two LCs, either kappa (κ) or lambda (λ), to derive whole IgG, IgA, IgD, and IgE. Normally, LCs are excreted in slight excess, with a κ/λ ratio of approximately 2:1. In myeloma a clone of cells secretes excessive quantities of a specific immunoglobulin and/or LCs (the paraprotein or M-protein). All myelomas (whole immunoglobulin or LC only) arise from a preclinical phase of monoclonal gammopathy (monoclonal gammopathy of undetermined significance [MGUS]) into a clinical or symptomatic phase as a consequence of somatic mutations. Mutations have important implications for prognosis and treatment and are incorporated into diagnostic and prognostic stratification tools.3 Myeloma remains an incurable disease because of multiple subclones, which engender resistance to chemotherapy and account for the natural history of remission and relapse over time. Both deregulation of cell cycling and impaired apoptosis account for their progressive and dysfunctional accumulation within the bone marrow and occasionally other organs. Plasma cells express little surface immunoglobulin and are recognized by surface expression of CD38 and CD138; they normally reside only in the bone marrow. In myeloma, unrestrained plasma cell growth is supported by a complex milieu of autocrine and paracrine cytokines, especially interleukin-6 (IL-6). These cytokines are secreted from stromal cells, endothelial cells,

and/or osteoclasts and maintain myeloma cell growth, survival, and migration; they also contribute to local organ dysfunction, such as bone resorption, fracture, and anemia.4

ETIOLOGY AND PATHOGENESIS OF KIDNEY DISEASE IN MYELOMA

Free light chains (FLCs) circulate as monomers (predominantly κ ≅ 25 kDa) and dimers (predominantly λ ≅ 50 kDa) with a very short half-life (2–6 hours) because of free glomerular filtration, whereas the much larger whole immunoglobulin circulates intact for several weeks. The filtered FLC is reabsorbed in the proximal tubule cell (PTC) by receptor-mediated endocytosis after binding with the glycoprotein receptor cubilin[5] (Fig. 68.1). LCs in excess can induce an inhibitory effect on endocytosis in vitro and are associated with lysosomal overload and rupture, releasing enzymatic contents into the cytosol, manifested histologically by crystallization, vacuolation, and desquamation of the PTC. Endocytosis of LCs induces the release of the proinflammatory cytokines IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) by activation of nuclear factor-κB (NF-κB) in the PTC.[6]

Inhibition of proximal tubule uptake of LCs by silencing the megalin/cubilin genes with small interfering RNAs prevents proximal tubular toxicity.[7] This suggests that LC overload induces factors promoting interstitial injury and fibrosis, as described in other proteinuric states.

Less common manifestations of PTC injury include the Fanconi syndrome, which is invariably associated with specific variant κ LCs and often with pathologic evidence of crystalline inclusions.[8]

Injury to the PTC allows escape or overflow of LCs to the distal nephron, where they can interact with uromodulin (Tamm-Horsfall protein) secreted by the cells of the thick ascending loop of Henle.

Variations in the specificity of the binding region of different LCs modify the affinity of the LC for binding with uromodulin, which could in part explain the variable nephrotoxicity of LCs.[9] This specificity of the individual LC for uromodulin was illustrated by the finding that the intraperitoneal instillation of LCs isolated from humans with specific kidney LC-associated disease induces the same kidney injury in animals.[10] Inhibiting the binding of LCs to uromodulin prevents cast formation.[11] Not all LCs are associated with tubular injury, and neither the amount nor type of urinary LCs correlates with the severity of cast formation. Nevertheless, in general, the higher the urinary excretion of LCs, the greater is the risk for kidney failure and reduced response to chemotherapy.[12-14] In addition to LC-specific factors, tubular solute composition and tubular flow rates modulate the risk for cast formation. In animals, urinary acidification, furosemide, and urinary sodium and calcium concentrations may affect the tendency to increased binding or aggregation of LCs with uromodulin, whereas colchicine may reduce this tendency in animals but not in humans.[15] [16]

The formation and passage of casts distally can occlude the tubule and

Etiology of Kidney Injury and
Clinical Manifestations in Myeloma
TABLE 68.1

Prerenal
Volume
depletion

Hemodynamic
Other
Intrarenal

Postrenal

risk for kidney disease and are present in nearly 50% of patients with kidney failure requiring dialysis.17

Cause

Manifestation

CLINICAL PRESENTATION

Hypercalcemia
Gastrointestinal losses (nausea
and vomiting)
Sepsis
Hemodynamic effects of NSAIDs
Hyperviscosity (IgA, IgG3)
Hyperuricemia
Proximal tubular injury from light
chains, uric acid, distal tubular
injury from casts
Glomerular disease (LCDD,
amyloid)

Polyuria and polydipsia
Hypotension
Fever

Most patients present with constitutional symptoms (fatigue, weight loss) and skeletal pain, especially back pain. Kidney impairment is common and has a variety of causes (see Fig. 68.1). In a smaller proportion of patients, kidney failure is the presenting manifestation of myeloma and these patients often have more advanced disease with high morbidity/mortality.17 Kidney findings are nonspecific, typically normal-size kidneys and bland urine. Urinary protein excretion may be increased because of the presence of LCs (Bence Jones protein). Urinary dipstick (or measurement of albuminuria) may indicate only small amounts of protein because they measure albumin only. Significantly increased levels of urinary albumin are suggestive of amyloidosis or other monoclonal kidney disorders, which affect the glomerulus (see Chapter 28). Normal or elevated ionized calcium, a decreased serum anion gap, lytic bone lesions on radiographs, hypogammaglobulinemia, reduced levels of other immunoglobulin classes (immunoparesis), significant cytopenias, or blood film changes (plasma cells and/or leukoerythroblastic film) are suggestive of myeloma. Clinical and laboratory findings that may distinguish MCN from other monoclonal B-cell disorders affecting the kidney are listed in Table 68.2

Calculi

Oliguria, hyperkalemia
Mental state alterations
Tumor lysis
Fanconi syndrome
Tubular proteinuria
Crystalluria
Nephrotic proteinuria
Hematuria, active
sediment
Colic

Ig, Immunoglobulin; LCDD, light chain deposition disease; NSAIDs, nonsteroidal antiinflammatory drugs.

PATHOLOGY

Fig. 68.1 Uptake of Light Chains by Proximal Tubular Cells. Kidney biopsy from a patient excreting κ light chains. Immunoperoxidase staining (brown color) showing κ light chains along the brush border and in the cytoplasm of proximal tubular cells.

allow intratubular obstruction, with rupture and even backflow of contents (Fig. 68.2).

EPIDEMIOLOGY

Most myeloma manifests de novo, although around 1% evolves from patients with a known MGUS each year. In patients with newly diagnosed myeloma, the prevalence of IgG, IgA, IgD, and FLC-only myeloma was 52%, 21%, 2%, and 16%, respectively.13 IgM and IgE myeloma are extremely uncommon. Approximately 70% of patients with myeloma also have a urinary M-protein. At the time of diagnosis, up to 50% of patients have evidence of impaired kidney function judged by increased serum creatinine, around 25% presenting with serum creatinine greater than 2 mg/dL (177 μmol/L).13 14 In unselected series, 2% to 10% of patients present with severe kidney failure requiring dialysis; this figure is higher in series reported from nephrology units. In contrast to the general distribution of M-protein types in myeloma, LC and IgD myeloma are particularly associated with higher

Histologic examination of the kidney in myeloma and AKI has diagnostic and prognostic utility, although it is not always required.18-21 The introduction of the serum (FLC) ratio as a rapid diagnostic tool has reduced the requirement for biopsy for diagnosis. Cast nephropathy is the most common histologic finding, occurring in 30% to 50% of patients; however, a diverse range of diseases have been reported depending on the indication for biopsy (Table 68.3). Cast nephropathy is characterized by many distal tubular casts, which are strongly eosinophilic and consist of the monoclonal LC and laminated uromodulin, which often appear fractured after fixation. Casts promote local inflammation with giant cell formation.22 23 In 30% of cases, cast formation may not be prominent despite extensive tubulointerstitial injury24 (Box 68.1 and Fig. 68.3). Glomeruli are usually spared unless there is associated LC deposition disease or amyloidosis (see Chapter 28).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The International Myeloma Working Group (2014) diagnostic criteria for symptomatic myeloma require one or more myeloma-defining events in addition to bone marrow clonally restricted plasma cells of 10% or greater or biopsy-proven plasmacytoma. A myeloma-defining event is a CRAB event (hypercalcemia, renal failure, anemia or lytic bone lesions) or one of three biomarkers: clonal bone marrow plasma cells greater than 60%, serum FLC ratio of 100 or greater (involved to uninvolved LC and the involved LC absolute value >100 mg/L), or more than one focal bone lesion on magnetic resonance imaging. To meet the criteria for kidney failure as a myeloma-defining event, a reduction in estimated glomerular filtration rate (eGFR) to less than 40 mL/min/1.73 m2 and a histologic diagnosis of cast nephropathy (or presumptive diagnosis based on a serum involved FLC of typically >1500 mg/L) is necessary to distinguish this from other paraproteindefined kidney diseases.25 About 97% of patients with a diagnosis of myeloma have a detectable intact whole immunoglobulin and/or a free LC by serum protein electrophoresis (SEP) and immunofixation

Kidney Injury Caused by Light Chains

Glomerulus

Distal tubule

Light chains
filtered
Cortex

Proximal
convoluted
tubule
Toxic
injury

Cast
injury

Outer
medulla

Thick
ascending
limb

Light chains +
uromodulin
(Tamm-Horsfall
protein) produce
casts

Inner
medulla

Fig. 68.2 Kidney Injury Caused by Light Chains. Sites (white boxes) where light chains injure the tubule. In the proximal tubule, there is direct tubular cytotoxicity. In the distal tubule, there is cast injury.

Differentiating Features of Myeloma Kidney and Other Monoclonal Immune Deposition Diseases

TABLE 68.2

Myeloma Kidney

Other MIDDs

Proteinuria
Hematuria

<3 g/L
Rare

Hypercalcemia
Hypertension

Common

Uncommon

Cytopenias

Anemia very common
Leukopenia and
thrombocytopenia,
occasional
Very common
Very common
Common
IgA, IgD, IgG

>3 g/L
LCDD, occasional
Amyloidosis, rare
Absent
LCDD, common
Amyloidosis, uncommon
Uncommon

Immunoparesisa
Lytic bone lesions
Reduced GFR
Associated whole
immunoglobulin
Type of light chain
Serum light chain
elevation
aImmunoparesis,

Either
>500 mg/L

Uncommon
Absent
Common
None
Amyloid λ > κ
LCDD κ > λ
<500 mg/L

reduction in noninvolved immunoglobulin classes.
Ig, Immunoglobulin; LCDD, light chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; GFR, glomerular filtration rate.

(IFE). The quantity of the M-protein is estimated from the SEP and may be used both for diagnosis and to monitor response to therapy. Urinary LC (Bence Jones protein) is determined from a concentrated sample, but despite this LC may be below the level of detection by IFE. The specific quantitative FLC assay (which measure only LC not bound to whole immunoglobulin in serum) is significantly more sensitive than SEP and IFE alone and is an automated assay that allows rapid diagnosis.26 27 An abnormal monoclonal FLC increases the specific LC fraction and may suppress the other LC, which alters the normal ratio of FLC (0.26–1.65 κ/λ) to reflect the oversecretion of the abnormal LC clone (<0.26 for λ FLC clone, >1.65 for κ clone). The normal serum levels of FLC are very low (7–13 mg/L), but in patients with reduced GFR, accumulation of both (κ and λ) FLCs occurs as a result of reduced excretion, and because λ free light chains tend to circulate as dimers, their clearance is reduced more than the monomeric κ FLC. The use of an extended reference range of 0.37 to 3.1 improves diagnostic sensitivity for myeloma to 99% with 100% specificity in the presence of acute kidney failure requiring dialysis.28 In patients with kidney failure and biopsy-proven cast nephropathy, the ratios are highly abnormal, and the absolute increase in the affected LC is of the order of 100 to 200 times normal with values greater than 500 mg/L at presentation and a median of 7000 mg/L[28,29] (Fig. 68.4).

Measurement of serum FLC has significant advantages over SEP and IFE and is now incorporated into international clinical guidelines for the diagnosis and management of myeloma.[30]

Diagnostic difficulties can arise when elderly patients who are evaluated for newly diagnosed kidney impairment have an M-protein on routine SEP. Approximately 3% of the population older than 70 years

TABLE 68.3 Kidney Pathology in Patients With Myeloma

Histologic Finding	Prevalence (%)
Myeloma kidney (myeloma cast nephropathy)	30–50
Interstitial nephritis/fibrosis without cast nephropathy	20–30
Amyloidosis	10
Light chain deposition disease	5
Acute tubular necrosis	10
Other (urate nephropathy, tubular crystals, hypercalcemia, focal segmental glomerulosclerosis)	5

Data from Nasr SH, Valeri AM, Sethi S, et al. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. Am J Kidney Dis. 2012;59(6):786–794; Herrera GA, Joseph L, Gu X, Hough A, Barlogie B. Renal pathologic spectrum in an autopsy series of patients with plasma cell dyscrasia. Arch Pathol Lab Med. 2004;128(8):875–879; and Sanders PW, Herrera GA, Kirk KA, Old CW, Galla JH. Spectrum of glomerular and tubulointerstitial renal lesions associated with monotypical immunoglobulin light chain deposition. Lab Invest. 1991;64(4):527–537.

BOX 68.1 Histologic Features of Myeloma Cast Nephropathy

- Many eosinophilic, often fractured casts (medullary portion of the distal nephron predominantly)
- Intratubular and interstitial macrophages and giant cells in response to casts
- Interstitial inflammation, fibrosis, tubular atrophy, crystalline inclusions
- Minimal glomerular abnormality
- Minimal or no vascular changes

will have a serum M-protein, most consistent with MGUS. A diagnosis of MGUS is more likely if the serum level of the M-protein is low (<3 g/dL), there is absent or very low urinary LC (<1 g/24 h), and the absence of end-organ injury (no lytic lesions, <10% plasma cells on bone marrow aspirate).31 The FLC ratio should be normal using an extended reference range (0.82–3.6) for patients with eGFR less than 55 mL/min.32 This distinction is important because most patients with MGUS will die of an unrelated disease, and only 1% a year progress to myeloma.33 Previously it was considered that most kidney disease in patients with MGUS was unrelated to the M-protein.34 However, it is now recognized that the spectrum of paraprotein and LC disorders associated with specific kidney diseases histologically noted on biopsy is extensive and heterogeneous, but most are not associated with the malignant clonal expansion characteristic of myeloma. These disorders are now described as MGRS (see Chapter 22).2 Evidence suggesting an alternative cause of the kidney disease (most commonly diabetes or vascular disease), along with a period of observation, may clarify the significance of the M-protein, although kidney and/or bone marrow biopsy is often required when diagnostic uncertainty persists.35

NATURAL HISTORY

Most patients with reduced eGFR at presentation will show resolution of these predominantly functional changes with therapeutic measures that include withdrawal of nephrotoxins, rehydration, treatment of hypercalcemia, treatment of sepsis, and reduction in LC load with chemotherapy. Response to treatment with improvement in kidney function is associated with better clinical outcomes.36 Reversibility occurs more frequently with higher GFR at presentation, lower LC

excretion, and presentation with hypercalcemia. The number of casts and degree of interstitial fibrosis/tubular atrophy present at biopsy are independently associated with kidney recovery, itself associated with improved patient survival.18 Although GFR improves in the majority of patients, approximately 10% of patients presenting with reduced GFR at diagnosis may require dialysis. Before the introduction of modern chemotherapy strategies, patients requiring dialysis had reported rates of recovery of kidney function as low as 5% to 15%. However, the introduction of specific LC reduction strategies has increased kidney recovery in up to 80% of patients if a significant reduction in the FLC level is achieved by day 21, with improvement in GFR and independence from dialysis being associated with improved patient outcomes.37 38

TREATMENT

There are three key issues in the management of MCN. The first is to suspect and diagnose myeloma in the differential diagnosis of AKI. The inclusion of serum FLC measurement for routine evaluation of otherwise unexplained AKI in the appropriate clinical circumstances is essential. This is because kidney injury in myeloma is directly related to FLC excess and the increased sensitivity and specificity of FLC measurement, along with its rapid availability, may implicate or refute myeloma as a likely diagnostic possibility well in advance of results from SPE/IFE or kidney biopsy. Early diagnosis is crucial to allow implementation of the second strategy, which is to prevent or reverse oliguria by rapid identification and management of possible contributing factors to kidney impairment, which are present in around 50% of patients. Hypercalcemia, sepsis, and nonsteroidal antiinflammatory agents (NSAIDs) are the most common precipitants. Intravenous volume expansion is helpful to increase glomerular filtration, reduce single-nephron LC concentration, and increase tubular flow. The use of furosemide to promote diuresis should be avoided because it may favor cast formation. There is no clinical evidence of the superiority of volume expansion with sodium bicarbonate over sodium chloride, although prevention of urinary acidification is in theory desirable and in severe kidney failure may be necessary for management of metabolic acidosis. The maintenance of a high fluid intake (3 L/d) with water after initial volume correction and restoration of urine output with intravenous crystalloid is recommended to maintain high urine flow rates.

The third key requirement is the rapid reduction of FLC in the serum by chemotherapy. The immediate initiation of high-dose dexamethasone 40 mg/d is recommended, because plasma cells are highly responsive to corticosteroids, which induce rapid apoptosis and lowering of LC concentration. The addition of newer chemotherapy strategies (see later discussion) with high immediate LC-lowering effects in combination with corticosteroids is critical to achieving a rapid response.30 Reducing the LC load with plasma exchange did not improve either recovery from kidney failure or patient survival.39 The large volume of distribution of LC (which freely cross cell membranes) is not well suited to plasma exchange. The use of high cutoff dialysis membranes (molecular cutoff up to 50 kDa), in conjunction with chemotherapy, was initially shown to be associated with a reversal of kidney failure and the rapid reduction in circulating FLC in patients with cast nephropathy.38 40 However, two randomized controlled trials did not confirm an independent benefit of high cutoff membranes when combined with bortezomib chemotherapy, confirming that early response to chemotherapy is the more important factor.41 42 A suggested algorithm for management of myeloma with AKI is shown in Fig. 68.5

B

A

C

Fig. 68.3 Myeloma Cast Nephropathy. (A) Myeloma kidney. Many dilated tubules are obstructed by densely eosinophilic hard casts, with giant cell reaction and inflammatory cell infiltrates. There is also vacuolation and degeneration of tubules (hemoxylin and eosin stain; ×160). (B) Light chain deposition along tubular basement membrane (TBM) in myeloma kidney without casts. There is marked thickening of the TBM by periodic acid–Schiff (PAS)-positive deposits and interstitial fibrosis and mild chronic inflammation (PAS stain; ×160). (C) Light chain deposition along TBM. Strong linear deposition of κ light chain in the thickened TBM (direct immunofluorescence anti-κ light chain; ×160). (Courtesy R. Sinniah, Perth, Australia.)

Chemotherapy

Although myeloma is incurable, chemotherapy will induce clinical improvement by control of the underlying disease in most patients. Chemotherapy involves an immediate induction treatment followed by consolidation strategy after disease control. Bortezomib, a reversible proteasome inhibitor whose clearance is independent of kidney function, has been successfully and safely used in patients with kidney failure and myeloma without significant toxicity and is the agent of choice for rapid reduction of LCs in combination with dexamethasone.30 Bortezomib lowers the LC load by direct effects on plasma cells and also may protect kidney proximal tubular cells by inhibiting activation of IL-6 and NF-κB induced by LC endocytosis.43 Immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide are also frequently used for induction (triple therapy), as consolidation therapy, or for relapsed disease in conjunction with dexamethasone.3 Agents used for management of myeloma in patients with AKI are summarized in Table 68.4 44 Autologous stem cell transplantation (ASCT) significantly extends survival and is now the treatment of choice for eligible patients.30 Patients on dialysis are suitable for ASCT, which is associated with kidney recovery and freedom from dialysis, although with greater toxicity and increased morbidity and mortality.45-47 For patients unsuited for ASCT, chemotherapy selection depends on comorbidity, and dexamethasone/lenalidomide may be useful. Close multidisciplinary management and discussion with hematology and oncology staff is required to individualize decisionmaking because of the continuous advances in this area.

Serum Free Light Chain Ratio and Values
100,000

10,000

SEP sensitivity

λ FLC (mg/L)

1000

Normal sera
κ LCMM

100

λ LCMM
Reduced GFR

10

1
IFE sensitivity
0.1
0.1

1

10

100

1000

10,000

100,000

κ FLC (mg/L)
Fig. 68.4 Serum free light chain ratio and values in normal individuals, patients with reduced glomerular filtration rate (GFR) and light chain myeloma. FLC, free light chain; IFE, Immunofixation; LCMM, light chain multiple myeloma; SEP, serum protein electrophoresis.

Infection and progression of disease remain the major impediments to long-term survival in myeloma, especially within the higherrisk end-stage kidney disease (ESKD) group. Median survival in recent ESKD series with conventional chemotherapy before ASCT was only 4 to 8 months; however, survival of up to 7 years is reported in selected cases of ESKD managed with ASCT, and overall patient survival has improved with the advent of newer treatment strategies.48 49
The improved overall management of myeloma with prolonged survival of patients will increase the referral of patients with relapsed and treatment-refractory disease presenting with MCN. The management of this patient group is challenging and must be individualized based on overall prognosis and potential for salvage chemotherapy and likelihood of benefit from dialysis.

Adjunctive Therapies

Patients with myeloma and chronic kidney disease or kidney failure respond to erythropoiesis-stimulating agents (although may require higher doses), and these should be used along with other hematopoietic agents, including granulocyte colony-stimulating factor (G-CSF) as required, although early in the disease frequent transfusion may be necessary. Intravenous bisphosphonates rapidly correct hypercalcemia and are preferred to furosemide (which may aggravate tubular LC injury) and in the longer term reduce bone fracture.50 However, there are several reports of toxicity (acute tubular necrosis, proteinuria) with full dose and/or rapid infusion of pamidronate and zoledronic acid; the use of reduced doses (pamidronate 30–60 mg, zoledronic acid 4 mg) and slower infusion rates is recommended.51 52 Alternatively,

bisphosphonates could be avoided in patients with eGFR less than 30 mL/min/1.73 m2 by using denosumab to manage hypercalcemia.53

DIALYSIS AND TRANSPLANTATION

Where kidney replacement therapy is required in the long term, both hemodialysis and peritoneal dialysis have been successfully used and there are no data to indicate that outcome is influenced by dialysis modality. Choice of long-term therapy requires individual assessment of patient circumstances. Aggressive measures to reduce the risk for systemic infection (antibiotic catheter locking solutions; mupirocin at exit sites) should be routinely considered because initially central venous catheters are often required for dialysis and chemotherapy. The timing of arteriovenous fistula placement requires an individualized risk assessment because it may be several months before irreversibility of kidney failure or a response to chemotherapy is proven. Kidney transplantation has a high risk for disease recurrence in the allograft and patient mortality, and given the incurability of the disease, has rarely been appropriate.54 Current advances in chemotherapy and prolonged patient survival have prompted reconsideration of the role, timing, and management of kidney transplant.55 The use of kidney transplant after successful induction therapy and ASCT may be considered for younger patients when disease remission by standard criteria and normalization of the serum FLC ratio is achieved. Allogeneic bone marrow and kidney allograft transplant have been reported, demonstrating the ability to induce allograft tolerance in haploidentical pairs.56 This treatment is limited in availability and is not suitable for the majority of patients.

Management Pathways for Acute Kidney Injury
and Myeloma Cast Nephropathy
No

Serum FLC ratio >100 for
involved/uninvolved LC and absolute
value involved LC >500 mg/L ± BJ
proteinuria

Consider kidney biopsy
for diagnosis of MGRS

Consider kidney biopsy for
confirmation of MCN

Yes

Identify and treat reversible factors:
- Stop/avoid NSAIDs and aminoglycosides
- Volume expansion saline/bicarbonate to establish or maintain urine output
- Reverse hypercalcemia with IV hydration and dose-adjusted bisphosphonates or denosumab
- Treat sepsis
- Exclude obstruction (ultrasound/noncontrast CT)
- Immediately lower light chain load with high-dose dexamethasone 40 mg/day

Nonoliguric
No indication for dialysis

Indication for dialysis

Improved or can discontinue
dialysis

Dialysis-dependent
HD or CAPD

Nonalkylating chemotherapy and
autologous stem cell transplant

No

ESKD

Consider for kidney
transplant if complete
and enduring remission

Age and/or comorbidity
high?

Yes

Allogeneic bone marrow
transplant and kidney transplant
in very selected cases

- Steroids/lenalidomide
- Palliation

Fig. 68.5 Management Pathways for Acute Kidney Injury and Multiple Myeloma. BJ, Bence Jones;

CAPD, continuous ambulatory peritoneal dialysis; CT, computed tomography; ESKD, end-stage kidney disease; FLC, free light chain; HD, hemodialysis; IV, intravenous; LC, light chain; MCN, myeloma cast nephropathy; MGRS, monoclonal gammopathy of renal significance; NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 68.4

Chemotherapeutic Drugs Used in Myeloma and Kidney Failure

Class

Agent

Route of Administration

Dose Reduction for CrCl
<30 mL/min/1.73 m2

Corticosteroids
Alkylating agents

Dexamethasone, Prednisone
Melphalan
Cyclophosphamide
Thalidomide
Lenalidomide
Pomalidomide
Bortezomib
Carfilzomib
Ixazomib
Daratumumab
Isatuximab

PO/IV
PO/IV
PO/IV
PO
PO
PO
IV/SC
IV
PO
IV

None
Yes
No
No
Yes
No
None
No
Yes
No

Immunomodulatory drugs

Proteasome inhibitors

Anti-CD38 monoclonal
antibodies

Side Effects
Standard
Bone marrow suppression,

infection
Neuropathy, venous thrombosis,
hyperkalemia, cytopenias
Neuropathy, cytopenias, TMA

Cytopenias

CrCl, Creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; TMA, thrombotic microangiopathy.

SELF-ASSESSMENT QUESTIONS

1. Kidney injury in patients with myeloma is most usually due to an excess of which of the following?
A. Calcium
B. Uric acid
C. Light chains
D. Immunoglobulins
E. β2-Microglobulin
2. What is the most common histologic lesion noted in patients with acute kidney injury and myeloma?
A. Amyloidosis
B. Light chain deposition disease
C. Cast nephropathy
D. Urate nephropathy
E. Tubular crystals
3. In addition to corticosteroids, which therapy should be commenced urgently for the management of myeloma cast nephropathy?
A. Vincristine
B. Adriamycin

C. Melphalan
D. Cyclophosphamide
E. Bortezomib
4. A 72-year-old man has a 3-month history of back pain and is managed with nonsteroidal antiinflammatory agents. He presents with anemia, hypercalcemia, and acute kidney injury. You suspect myeloma. What is the most appropriate investigation to rapidly confirm the diagnosis?
A. Urine Bence Jones protein
B. Serum protein electrophoresis
C. Serum immunoglobulins
D. Serum free light chains
E. Kidney biopsy

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, riskstratification and management. Am J Hematol. 2020;95(5):548–567.
2. Bridoux F, Leung N, Hutchison CA, et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int. 2015;87(4):698–711.
3. Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. Blood Cancer J. 2020;10(9):94.
4. Ninkovic S, Quach H. Shaping the treatment paradigm based on the current understanding of the pathobiology of multiple myeloma: an overview. Cancers (Basel). 2020;12(11).
5. Batuman V, Verroust PJ, Navar GL, et al. Myeloma light chains are ligands for cubilin (gp280). Am J Physiol. 1998;275(2 Pt 2):F246–F254.
6. Sengul S, Zwizinski C, Simon EE, Kapasi A, Singhal PC, Batuman V. Endocytosis of light chains induces cytokines through activation of NFkappaB in human proximal tubule cells. Kidney Int. 2002;62(6):1977–1988.
7. Li M, Balamuthusamy S, Simon EE, Batuman V. Silencing megalin and cubilin genes inhibits myeloma light chain endocytosis and ameliorates toxicity in human renal proximal tubule epithelial cells. Am J Physiol Renal Physiol. 2008;295(1):F82–F90.
8. Aucouturier P, Bauwens M, Khamlichi AA, et al. Monoclonal Ig L chain and L chain V domain fragment crystallization in myeloma-associated fanconi’s syndrome. J Immunol. 1993;150(8 Pt 1):3561–3568.
9. Ying WZ, Sanders PW. Mapping the binding domain of immunoglobulin light chains for tamm-horsfall protein. Am J Pathol. 2001;158(5):1859–1866.
10. Solomon A, Weiss DT, Kattine AA. Nephrotoxic potential of bence jones proteins. N Engl J Med. 1991;324(26):1845–1851.
11. Ying WZ, Allen CE, Curtis LM, Aaron KJ, Sanders PW. Mechanism and prevention of acute kidney injury from cast nephropathy in a rodent model. J Clin Invest. 2012;122(5):1777–1785.
12. Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica. 2007;92(4):546–549.
13. Kyle RA, Gertz MA, Witzig TA, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(21–33).
14. Alexanian R, Barlogie B, Dixon D. Renal failure in multiple myeloma. Pathogenesis and prognostic implications. Arch Intern Med. 1990;150(8):1693–1695.
15. Huang ZQ, Sanders PW. Biochemical interaction between Tamm-Horsfall glycoprotein and Ig light chains in the pathogenesis of cast nephropathy. Lab Invest. 1995;73(6):810–817.
16. Sanders PW, Booker BB. Pathobiology of cast nephropathy from human bence jones proteins. J Clin Invest. 1992;89(2):630–639.
17. Irish AB, Winearls CG, Littlewood T. Presentation and survival of patients with severe renal failure and myeloma. Qjm. 1997;90(12):773–780.
18. Royal V, Leung N, Troyanov S, et al. Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study. Blood. 2020;135(21):1833–1846.
19. Nasr SH, Valeri AM, Sethi S, et al. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. Am J Kidney Dis. 2012;59(6):786–794.
20. Herrera GA, Joseph L, Gu X, Hough A, Barlogie B. Renal pathologic spectrum in an autopsy series of patients with plasma cell dyscrasia. Arch Pathol Lab Med. 2004;128(8):875–879.
21. Sanders PW, Herrera GA, Kirk KA, Old CW, Galla JH. Spectrum of glomerular and tubulointerstitial renal lesions associated with monotypical immunoglobulin light chain deposition. Lab Invest. 1991;64(4):527–537.
22. Schwartz MM. The dysproteinemias and amyloidosis. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, eds. Hepinstall’s Pathology of the Kidney. 5th ed. Vol. 2. Philadelphia: Lippincott-Raven; 1998:1321–1369.
23. Start DA, Silva FG, Davis LD, D’Agati VD, Pirani CL. Myeloma cast nephropathy: immunohistochemical and lectin studies. Mod Pathol.

1988;1(5):336–347.
24. Ivanyi B. Development of chronic renal failure in patients with multiple myeloma. Arch Pathol Lab Med. 1993;117(8):837–840.

25. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–e548.
26. Nowrousian MR, Brandhorst D, Sammet C, et al. Serum free light chain analysis and urine immunofixation electrophoresis in patients with multiple myeloma. Clin Cancer Res. 2005;11(24):8706–8714.
27. Katzmann JA, Abraham RS, Dispenzieri A, Lust JA, Kyle RA. Diagnostic performance of quantitative kappa and lambda free light chain assays in clinical practice. Clin Chem. 2005;51(5):878–881.
28. Hutchison CA, Plant T, Drayson M, et al. Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. BMC Nephrol. 2008;9:11.
29. Yadav P, Sathick IJ, Leung N, et al. Serum free light chain level at diagnosis in myeloma cast nephropathy-a multicentre study. Blood Cancer J. 2020;10(3):28.
30. Dimopoulos MA, Sonneveld P, Leung N, et al. International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34(13):1544–1557.
31. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106(3):812–817.
32. Molina-Andujar A, Robles P, Cibeira MT, et al. The renal range of the kappa/lambda sFLC ratio: best strategy to evaluate multiple myeloma in patients with chronic kidney disease. BMC Nephrol. 2020;21(1):111.
33. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton 3rd LJ. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original mayo clinic series 25 years later. Mayo Clin Proc. 2004;79(7):859–866.
34. Paueksakon P, Revelo MP, Horn RG, Scappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. Am J Kidney Dis. 2003;42(1):87–95.
35. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019;15(1):45–59.
36. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol. 2000;65(3):175–181.
37. Yadav P, Hutchison CA, Basnayake K, et al. Patients with multiple myeloma have excellent long-term outcomes after recovery from dialysisdependent acute kidney injury. Eur J Haematol. 2016;96(6):610–617.
38. Hutchison CA, Cockwell P, Stringer S, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol. 2011;22(6):1129–1136.
39. Clark WF, Stewart AK, Rock GA, et al. Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. Ann Intern Med. 2005;143(11):777–784.
40. Hutchison CA, Cockwell P, Reid S, et al. Efficient removal of immunoglobulin free light chains by hemodialysis for multiple myeloma: in vitro and in vivo studies. J Am Soc Nephrol. 2007;18(3):886–895.
41. Hutchison CA, Cockwell P, Moroz V, et al. High cutoff versus highflux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial. Lancet Haematol. 2019;6(4):e217–e228.
42. Bridoux F, Carron PL, Pegourie B, et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence Among patients with myeloma cast nephropathy: a randomized clinical trial. JAMA. 2017;318(21):2099–2110.
43. Sarkozi R, Perco P, Hochegger K, et al. Bortezomib-induced survival signals and genes in human proximal tubular cells. J Pharmacol Exp Ther.

2008;327(3):645–656.
44. Wanchoo R, Abudayyeh A, Doshi M, et al. Renal Toxicities of novel agents used for treatment of multiple myeloma. Clin J Am Soc Nephrol. 2017;12(1):176–189.
45. Abudayyeh A, Lin H, Mamlouk O, et al. Impact of autologous stem cell transplantation on long term renal function and associated progressionfree and overall survival in multiple myeloma. Leuk Lymphoma. 2020:1–11.

46. Breitkreutz I, Heiss C, Perne A, et al. Bortezomib improves outcome after SCT in multiple myeloma patients with end-stage renal failure. Bone Marrow Transplant. 2014;49(11):1371–1375.
47. Parikh GC, Amjad AI, Saliba RM, et al. Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma. Biol Blood Marrow Transplant. 2009;15(7):812–816.
48. Webster AC, Irish AB, Kelly PJ. Changing survival of people with myeloma and end stage kidney disease: a cohort study using Australian and New Zealand dialysis and transplant registry 1963-2013. Nephrology (Carlton). 2018;23(3):217–225.
49. Decourt A, Gondouin B, Delaroziere JC, et al. Trends in survival and renal recovery in patients with multiple myeloma or light-chain amyloidosis on chronic dialysis. Clin J Am Soc Nephrol. 2016;11(3):431–441.
50. Ashcroft AJ, Davies FE, Morgan GJ. Aetiology of bone disease and the role of bisphosphonates in multiple myeloma. Lancet Oncol. 2003;4(5):284–292.
51. Munier A, Gras V, Andrejak M, et al. Zoledronic acid and renal toxicity: data from French adverse effect reporting database. Ann Pharmacother. 2005;39(7):1194–1197.

52. Desikan R, Veksler Y, Raza S, et al. Nephrotic proteinuria associated with high-dose pamidronate in multiple myeloma. Br J Haematol. 2002;119(2):496–499.
53. Hageman K, Patel KC, Mace K, Cooper MR. The role of denosumab for prevention of skeletal-related complications in multiple myeloma. Ann Pharmacother. 2013;47(7–8):1069–1074.
54. Heher EC, Spitzer TR, Goes NB. Light chains: heavy burden in kidney transplantation. Transplantation. 2009;87(7):947–952.
55. Van den Bosch I, Sprangers B, Gertz M. Multiple myeloma and kidney transplantation: the beginning of a new era. Clin Kidney J. 2019;12(2):213–215.
56. Spitzer TR, Sykes M, Tolkoff-Rubin N, et al. Long follow-up of recipients of combined human leukocyte antigen-matched bone marrow and kidney transplantation for multiple myeloma with end-stage renal disease. Transplantation. 2011;91(6):672–676.

69

Kidney Disease in Liver, Cardiac, Lung, and Hematopoietic Stem Cell Transplantation

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Kidney disease can complicate all forms of nonrenal solid organ transplantation (SOT) and is associated with longer hospitalization, higher morbidity and mortality, and greater expense. Although there are organ-specific factors that impact on the incidence and severity of kidney disease, some useful generalizations can be made.

GENERIC KIDNEY ISSUES IN NONRENAL SOLID ORGAN TRANSPLANTATION

Estimation of Glomerular Filtration Rate

Transplant candidates and recipients often have low muscle mass and low creatinine generation. Hence, a mildly elevated creatinine concentration may represent a markedly reduced glomerular filtration rate (GFR). Such patients should have their GFR estimated by 24-hour urinary creatinine clearance (which will tend to overestimate because of tubular secretion) or, preferably, measured directly by iothalamate or other radioisotopes. Of the various creatinine-based equations that estimate GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations appear to correlate best with true posttransplantation GFR.1

Calcineurin Inhibitor Nephrotoxicity

Calcineurin inhibitors (CNIs; e.g., cyclosporine, tacrolimus) are the cornerstone of immunosuppression in SOT recipients, but also directly contribute to acute kidney injury (AKI) and CKD. CNIs also exacerbate posttransplantation hypertension and diabetes, both of which can cause CKD in the long term. It is probable that CNI nephrotoxicity is more severe in nonrenal (than kidney) transplantation because higher blood concentrations of CNIs may be used; furthermore, the denervated transplanted kidney may be protected from early sympatheticmediated injury.2

Acute CNI nephrotoxicity is mainly a prerenal syndrome caused by reversible vasoconstriction of the afferent glomerular arteriole; tubular damage and microvascular disease may occur in severe cases. Acute CNI-induced thrombotic microangiopathy (TMA) is rare after SOT but is associated with a poor prognosis. In many cases TMA is precipitated by excessively elevated blood levels of CNI, or by infection, allograft rejection, or addition of a mammalian target of rapamycin (mTOR) inhibitor to CNI-based immunosuppression. Treatment usually involves discontinuation of the CNI (and/or mTOR inhibitor).

Electrolyte and other metabolic disturbances may be seen with acute and/or chronic CNI toxicity. Hyperkalemia, hyperuricemia, metabolic acidosis, and hypomagnesemia have been described, due to effects on renal tubular function.

Chronic CNI nephrotoxicity is probably the result of prolonged kidney ischemia and other effects, such as direct stimulation of kidney fibrogenesis. The patient is typically hypertensive with a steady fall in GFR, most marked in the first 6 to 12 months after transplantation (Fig. 69.1).2 3 Urinalysis usually shows minimal/no hematuria and minimal/mild proteinuria. In practice, biopsies are often reserved for those with clinical features suggestive of a kidney disorder other than CNI toxicity.

Histologic examination shows changes in all compartments with “striped” interstitial fibrosis and tubular atrophy, arteriolar hyalinosis, arteriosclerosis, and secondary focal glomerulosclerosis.2

There may also be features of chronic TMA.2 However, these “typical” histologic findings of CNI toxicity are nonspecific, making it difficult to estimate the actual contribution of CNI toxicity to posttransplant CKD.

The presumed high prevalence of chronic CNI nephrotoxicity has generated interest in low- or zero-dose CNI protocols (discussed later).2 There remains reluctance to pursue these protocols because CNIs are such effective immunosuppressants, and organ replacement therapy analogous to dialysis is not available for other SOT recipients if severe rejection occurs. Another strategy is to preferentially use tacrolimus over cyclosporine, given that tacrolimus provides equivalent or superior immunosuppression with less nephrotoxicity.4 The roles of calcium channel blockers, renin-angiotensin system (RAS) blockers, and spironolactone in ameliorating CNI nephrotoxicity remain controversial. Control of hypertension is probably more important than the use of a particular antihypertensive agent.

Pretransplant Acute Kidney Injury

AKI is common in the days to weeks immediately before liver, heart, or (less commonly) lung transplantation and is typically prerenal (e.g., kidney hypoperfusion or hepatorenal syndrome), intrarenal (ischemic or toxic tubular injury), or a combination. Management focuses on treatment of the underlying cause and provision of dialytic support according to standard criteria. Because the patients are critically ill, continuous renal replacement therapy (CRRT) may be preferred to intermittent hemodialysis (HD), but there are no randomized controlled trials (RCTs) showing better outcomes with CRRT.

When severe or prolonged AKI occurs before anticipated transplantation, estimation of reversibility becomes very important, because presumed irreversible severe AKI shifts the management toward simultaneous dual-organ (e.g., liver plus kidney) transplantation. Kidney biopsy may help prognosticate but is not commonly performed because of technical difficulties in critically ill patients, who often also have coagulopathy.

The advantages and disadvantages of dual-organ transplantation are shown in Box 69.1. There is uncertainty about whether dual organ transplantation represents the best use of scarce donor organs, and some suggest prioritizing kidney transplantation after SOT instead. Liver, lung, and heart allocation is based on medical urgency, whereas kidney allocation is generally based on waiting time and immunologic factors. As a result, multiorgan transplants assume the priority of the

Changes in Measured Iothalamate GFR in
Individual Patients After Lung Transplantation

Causes of Acute Kidney Injury
After Solid Organ Transplantation

BOX 69.2

Prerenal
- Hypovolemic shock (e.g., aggressive diuresis)
- Cardiogenic shock (e.g., severe cardiac allograft dysfunction)
- Distributive shock (e.g., sepsis)
- Cyclosporine or tacrolimus

GFR, mL/min
200

Intrarenal (Acute Tubular Injury)
- Prolonged shock
- Cyclosporine or tacrolimus
- Aminoglycosides, amphotericin
- Intravenous contrast
- Massive hemolysis

150

100

Postrenal
- Rare

50

Posttransplant Acute Kidney Injury

0
Pre-Tx

1

6

12

18

24

30

Months post-Tx

Fig. 69.1 Changes in Measured Iothalamate Glomerular Filtration Rate (GFR) in Individual Patients After Lung Transplantation. Note the variation in GFR before transplant and the large fall in GFR in many patients within the first 6 months. Tx, Transplantation. (Modified from Navis G, Broekroelofs J, Mannes GP, et al. Renal hemodynamics after lung transplantation. A prospective study. Transplantation. 1996;61[11]:1600–1605.)

Advantages and Disadvantages
of Simultaneous Kidney and Nonrenal

BOX 69.1

Advantages
- Potentially provides much better kidney function over the short and long term
- Single donor: potential for lower cumulative dose of immunosuppression (as opposed to kidney transplantation later)

Disadvantages
- Surgery is more technically complex and prolonged
- Deprives patients with “definite” end-stage kidney disease of a kidney transplant
- Not needed when the acute kidney injury is reversible

nonkidney organ and may therefore divert kidneys from those with “definite” end-stage kidney disease (ESKD), who may wait a long time for a kidney-only transplant. The kidney in a multiorgan transplant typically has a low kidney donor profile index (KDPI), again diverting these kidneys from the kidney-only wait list, where they would have likely been offered to pediatric recipients or other priority groups.5 Recent guidelines and policy updates have tried to address some of these controversies and are discussed later.5 6

AKI is common in the days to weeks after transplant and is often multifactorial (Box 69.2). It is associated with higher mortality and increased risk for CKD in survivors.7 Delayed introduction or reduced doses of CNIs may be used, usually under the cover of induction antibody immunosuppression.7

Passenger lymphocyte syndrome is uncommon but can occur in the early weeks after transplant (usually liver, but also other SOT) in the setting of a minor ABO or other blood group system mismatch. Donor lymphocytes (“passengers” with the transplant) produce anti–blood group antibodies, which cause hemolysis. Severe cases may be complicated by AKI.

Severe rhabdomyolysis has been reported, typically when a statin is prescribed with cyclosporine and an inhibitor of the cytochrome P-450 system, such as diltiazem or an azole-based antifungal agent.

BK polyomavirus nephropathy should be considered in the differential diagnosis of unexplained kidney dysfunction after SOT, especially in the context of intensive immunosuppression. However, the absolute risks of BK viremia and nephropathy remain low, and routine screening is not recommended.8

Chronic Kidney Disease

With the growing number and longer survival of transplant recipients worldwide, the absolute number of recipients with CKD has increased. The CKD-EPI equation (despite its limitations) is useful in identifying CKD in this setting.

In the most comprehensive study to date, the cumulative incidence of posttransplant CKD (defined as estimated GFR < 30 mL/min/1.73 m2) at 5 years varied according to organ transplanted, from 6.9% (heart-lung) to 21.3% (intestinal) (Fig. 69.2).7 Pretransplant variables that increase the risk for CKD include older age, female sex, lower GFR, diabetes, hypertension, hepatitis C virus, and need for dialysis. Posttransplant variables were also implicated: postoperative AKI and initial use of cyclosporine (as opposed to tacrolimus). Minimizing posttransplantation AKI and controlling hypertension and diabetes are therefore likely to prevent or slow CKD. Many studies have confirmed that CKD (particularly ESKD) after SOT portends a poor prognosis (Fig. 69.3), as well as increased hospitalization and infection rates. Referral to a nephrologist should be considered in those with progressive decline in eGFR. The initial evaluation should include a thorough review of kidney function pre- and peritransplant, as well as exposure to nephrotoxins. If urinalysis shows moderate/severe

Cumulative Incidence of Stage 4 or 5 Chronic Kidney Disease in Nonrenal Organ Transplant Recipients
0.35
Cumulative Incidence
of Chronic Renal Failure

0.30

Liver
Intestine

0.25

Lung

0.20

Heart

0.15
0.10

Heart-lung

0.05
0.00
0

12

24

36

48

60

72

84

96

108

120

Months since Transplantation
No. at Risk
Heart-lung
Heart
Intestine
Liver
Lung

576
375
295

219
194
156
133
107
72
46
24,024
19,885
17,238
14,687
12,341
10,022
7997
6104
4526
3096
228
152
110
84
57
33
23
13
8
5
36,849
28,495
24,041
19,508
15,724
12,564
9844
7345
5292
3614
7643
5633
4316
3184
2327
1629
1136
745
468
258

Fig. 69.2 Cumulative incidence of chronic kidney disease (CKD) (estimated GFR <30 mL/min/1.73 m 2) after transplantation of various solid organs. (Modiﬁed from Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349[10]:931–940.)

30
1991
5
2261
133

Mortality Associated With Chronic Kidney Disease in Organ Transplant Recipients
45

No CKD

Deaths per 100 person-years

40

CKD

35
30
25
20
15
10
5
0
Heart/lung

Heart

Intestine

Liver

Lung

Overall

Transplanted organ

Fig. 69.3 Mortality associated with stage 4 and 5 chronic kidney disease (CKD) in organ transplant recipients.
(From Scientific Registry of Transplant Recipients.)

proteinuria or hematuria or both, biopsy should be considered, as it may identify pathologies other than CNI nephrotoxicity.

Close consultation with the primary transplant team is important. When CNI toxicity is deemed the main cause of CKD, several approaches can be taken to reduce ongoing CNI toxicity and CKD progression.

A reduction in CNI dosage with a compensatory increase in antimetabolite dosing for patients at low immunologic risk should be considered. If the patient is on a cyclosporine-based regimen, a switch from cyclosporine to tacrolimus may be beneficial. An alternative strategy (one that we favor less) is to substitute an mTOR inhibitor for the CNI. This approach is not recommended in the early posttransplant period because of the impact of mTOR inhibitors on wound/anastomosis healing. The mTOR inhibitors themselves have some important kidney adverse effects: experimental models demonstrate delayed recovery from AKI due to effects on tubular cell proliferation.

The mTOR inhibitors also potentiate the nephrotoxicity of cyclosporine when coadministered and can induce or exacerbate proteinuria.

CKD complications may be exacerbated by other posttransplant factors. For example, antiproliferative immunosuppressants may exacerbate anemia, and corticosteroids may exacerbate CKDrelated mineral and bone disorder (CKD-MBD). In the absence of specific studies, it seems reasonable to apply standard guidelines to manage these and other CKD complications. Although there is experimental evidence that RAS blockers may have antifibrotic effects in nonrenal transplant CKD, there are no trials showing improved kidney outcomes with these compared with other antihypertensive agents.

End-Stage Kidney Disease

There is little doubt that kidney transplantation is the best form of RRT in SOT recipients with advanced CKD who are fit enough for the procedure. Where feasible, a preemptive living donor transplant is the best option. Maintenance immunosuppression is typically increased in the perioperative period; induction immunosuppression is not without risk and is not used in all cases.9 In the immediate posttransplant period, mortality is higher than remaining on the waiting list (reflecting the complications of surgery and more immunosuppression), but mortality in the medium to long term is much lower.7 The number of patients with a nonrenal transplant subsequently wait-listed for a kidney transplant in the United States has increased dramatically over the last 15 years.10 Mortality is much higher in SOT recipients wait-listed for kidney transplant than in wait-listed controls.10

Patients who do not receive a preemptive kidney transplant start dialysis for the usual indications. Home dialysis (home hemodialysis and peritoneal dialysis) should be explored and modality choice individualized for each patient.11

KIDNEY DISEASE IN LIVER TRANSPLANTATION

AKI in cirrhosis has been defined as an absolute rise in serum creatinine of 0.3 mg/dL or greater (≥26.5 µmol/L) within 48 hours or a 50% or greater increase from baseline over 7 days.12 AKI is common before liver transplantation and is usually due to hepatorenal syndrome (HRS), acute tubular necrosis (ATN), or both. Prolonged HRS may cause ATN.

If RRT is required in patients with severe HRS, CRRT is often preferred, in part because it may have less effect on intracranial pressure than intermittent dialysis. The need for dialysis in liver transplant candidates portends a very poor prognosis if liver transplantation does not occur.13 Some centers use intraoperative CRRT during liver transplantation in patients with severe preoperative AKI who are predicted to tolerate the surgery poorly from a volume or electrolyte perspective. This practice remains somewhat controversial.14

The Model for End-Stage Liver Disease (MELD) scoring system measures severity of liver dysfunction based on international normalized ratio, serum creatinine and bilirubin, and predicts 90-day mortality risk. The MELD-Na score includes sodium to further refine the short-term prognosis and has become the tool of choice to guide allocation of deceased donor liver allografts in many jurisdictions. As both tools include serum creatinine, patients with severe AKI are prioritized.

Posttransplantation AKI occurs in over 60% of recipients of donation after circulatory death (DCD) grafts and approximately 40% of recipients of donation after brain death (DBD) grafts or living donor grafts.15 Requirement for RRT is associated with higher mortality rates.

Although relatively low doses of CNIs are traditionally used in liver transplantation (because rejection is less of a concern than in other SOT), CKD remains common, suggesting other factors (such as diabetes and hepatitis virus-associated glomerulonephritis) play an important role.

Various protocols involving reduction or cessation of CNIs have been studied with mixed results. Induction with interleukin-2 (IL2) receptor blockers, and maintenance with mycophenolate mofetil (MMF), corticosteroid, and delayed (day 5) introduction of low-dose tacrolimus was less nephrotoxic than other regimens while maintaining excellent allograft and patient outcomes.16 Conversion to sirolimus does not have clearly proven benefits and is associated with certain risks, and so is not routinely performed. CNI withdrawal to MMF monotherapy was shown to be a reasonable option for selected patients who were several years out from transplant.17

The number and percentage of simultaneous liver-kidney (SLK) transplants in the United States have increased since the MELD score was adopted into allocation policy, such that over 700 SLK transplants are performed annually (>8% of all liver transplants).6 This is much higher than in many other jurisdictions (e.g., Canada, United Kingdom), where SLK accounts for fewer than 2% of all liver transplants.

Although selected patients with severe pretransplant kidney disease benefit from SLK transplant, it can be difficult to predict which patients are likely to have meaningful kidney recovery without kidney transplant. Prognostication is further complicated by the risk of kidney biopsy in this patient cohort.

In the United States the Organ Procurement and Transplantation Network (OPTN) has provided updated clinical recommendations (which do not mandate a kidney biopsy) as to who should receive SLK transplants (Box 69.3).6 This policy also includes a safety net of priority for kidney transplant in those patients who have advanced CKD following liver transplantation (eGFR ≤ 20 mL/min/1.73 m2 or dialysis dependent and registered on the kidney transplant wait list in the first year post–liver transplant). The Canadian Forum guidelines suggest that patients are eligible for SLK if they are dialysis dependent for more than 3 months. They are “possibly eligible” (determined on a case-bycase basis) if they are on dialysis for a shorter time or if they have an eGFR less than 30 mL/min/1.73 m2 for more than 1 month.5

UNOS and OPTN Policy
Regarding Candidacy for Simultaneous LiverKidney Transplant in Patients Listed for Liver
Transplant

BOX 69.3

- CKD defined as GFR ≤60 mL/min/1.73 m2 for >90 consecutive days and one of the following:
- Dialysis dependence (ESKD)
- GFR ≤30 mL/min/1.73 m2 at transplant wait-listing
- AKI defined as ≥6 weeks of one or a combination of the following:
- GFR ≤25 mL/min/1.73 m2 at least once every 7 days
- Dialysis at least once every 7 days
- Specific metabolic diseases
- Hyperoxaluria
- Atypical hemolytic uremic syndrome (from factor H or I deficiency)
- Methylmalonic aciduria
- Familial nonneuropathic systemic amyloidosis

AKI, Acute kidney injury; CKD, chronic kidney disease; ESKD, endstage kidney disease; GFR, glomerular filtration rate; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

Modified from Boyle G. Simultaneous Liver Kidney (SLK) Allocation Policy. https://optn.transplant.hrsa.gov/media/1192/0815-12_SLK_Allocation.pdf.

KIDNEY DISEASE IN CARDIAC TRANSPLANTATION

Preoperative AKI is common, and approximately 1% of heart transplant recipients require RRT before transplantation.7 The main cause of AKI is kidney hypoperfusion from severe congestive heart failure (type 1 cardiorenal syndrome). In some patients there may also be a component of CKD for a variety of reasons, including chronic hypoxia, renovascular disease, hypertension, and atheroembolism. Ventricular assist devices are increasingly used as a bridge to cardiac transplantation and may improve kidney perfusion and function in this setting.

Postoperative AKI is also common, with 5% to 30% of cardiac transplant recipients requiring dialysis, depending on patient- and center-specific characteristics.18 There is a strong association between the severity of postoperative AKI and both mortality and kidney dysfunction at 1 year.18 In addition to the causes shown in Box 69.2, risk factors for AKI after cardiac transplant surgery are prolonged aortic cross-clamping, large fluid volume shifts, prolonged cardiac allograft ventricular dysfunction, postoperative bleeding, and reexploration.

CKD is an important complication in the medium to long term and portends a worse prognosis19 (see Fig. 69.2). The cumulative incidence of stage 4 or stage 5 CKD in cardiac transplant recipients has been reported as 11% at 5 years, which is lower than in bowel, liver, or lung transplant recipients.7

The principal cause of CKD after cardiac transplantation is CNI toxicity. A number of studies have assessed the impact of CNI modification, reduction, or withdrawal after cardiac transplantation. A small RCT compared tacrolimus to cyclosporine and reported a favorable side effect profile (including kidney function) with tacrolimus, with similar survival and rejection rates.20 Since this study, tacrolimus use has continued to increase (and the use of cyclosporine greatly decreased), such that more than 95% of cardiac transplant recipients now receive tacrolimus-based immunosuppression.21 Despite some encouraging short- and medium-term results with everolimus and reduced CNI dosing in patients at low immunologic risk, fewer than 10% of cardiac transplant recipients receive an immunosuppression regimen that includes everolimus or sirolimus.22

The absolute number of simultaneous heart-kidney transplants remains low but is steadily increasing in the United States (in 2018 approximately 7% of total heart transplants).23 The criteria for simultaneous heart-kidney transplant eligibility are generally less welldefined than in the case of SLK, and the SLK criteria (Box 69.3) are often used as a reference point.8

KIDNEY DISEASE IN LUNG TRANSPLANTATION

Preoperative AKI is less common, with 0.1% of lung transplant recipients requiring dialysis before transplantation.7 Postoperative AKI is common and associated with significantly reduced survival. A systematic review and meta-analysis showed that approximately 53% of patients had postoperative AKI (KDIGO criteria), and 9.3% required RRT after lung transplantation.24

AKI can occur for the usual reasons (see Box 69.2), but factors specific to lung transplantation include aggressive diuresis and nephrotoxic antimicrobial agents for resistant infections (e.g., aminoglycosides, amphotericin). Acute oxalate nephropathy leading to irreversible kidney failure has been described. It is thought that enteric hyperoxaluria is caused by either prolonged antibiotic administration (which interferes with colonic flora) and/or cystic fibrosis–related pancreatic exocrine insufficiency.25 Although probably rare, this “new disease” emphasizes the importance of maintaining a broad differential diagnosis for kidney disease occurring after SOT and the importance of biopsy when the clinical manifestation is unusual.

CKD, although often underappreciated, is common in the first year after lung transplantation, and the incidence increases thereafter. As with other forms of posttransplantation CKD, the most common cause is probably CNI toxicity. CNI dosages tend to be higher because of the increased risk for rejection in lung transplantation. Although CNI withdrawal is poorly tolerated in this setting, a few studies have reported improvements in GFR when doses of CNIs were reduced. CNI reduction should be accompanied by addition/optimization of MMF. De novo use of mTOR inhibitors is not recommended because they may be associated with breakdown of the bronchial anastomosis; later use is associated with pneumonitis. Simultaneous lung-kidney transplantation is very rarely performed.

KIDNEY DISEASE IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) involves the administration of chemotherapy with or without radiotherapy, followed by bone marrow engraftment of stem or progenitor cells.26,27 Most commonly, HSCT is used to treat hematologic malignancies; however, other indications include certain solid tumors, nonmalignant hematologic conditions (e.g., aplastic anemia, sickle cell disease), genetic immunodeficiencies, and inborn errors of metabolism.28 Stem and progenitor cells may be harvested from peripheral blood, bone marrow, or umbilical cord blood, and may come from the affected patient (autologous) or a related or unrelated donor (allogeneic). In both myeloablative autologous and allogeneic HSCT, intensive pretransplant conditioning regimens using high-dose chemotherapy and radiation are given to eradicate the bone marrow and underlying cancer; the hematopoietic system is then reconstituted by infusion and engraftment of transplanted cells. Patients not eligible for aggressive myeloablative therapy because of older age or comorbidities may be candidates for nonmyeloablative (low-intensity) or reduced-intensity conditioning (RIC; intermediate intensity) regimens. These less toxic conditioning regimens provide sufficient immunosuppression to permit the engraftment of transplanted cells, which then target tumor cells (the graft-versus-tumor effect).29 Both myeloablative and nonmyeloablative allogeneic transplantation (but not autologous transplantation) require posttransplant immunosuppression to prevent acute and chronic graft-versus-host disease (GVHD); CNIs are often prescribed for this purpose.

Acute Kidney Injury After Hematopoietic Stem Cell Transplantation

Epidemiology

AKI is a common complication of HSCT, with reported incidence and severity varying by the conditioning regimen (myeloablative > nonmyeloablative), type of transplant (allogeneic > autologous), and definition of AKI used (Table 69.1). It is most common (>70% of patients in some series) after myeloablative allogeneic HSCT, likely reflecting the longer period of profound immunosuppression (with associated risk of sepsis) and much greater risk of hepatic sinusoidal obstruction syndrome (SOS), previously called venoocclusive disease (VOD) of the liver, compared with nonmyeloablative allogeneic regimens.27,30 Autologous transplantation carries the lowest risk of AKI (approximately 20%); this has been attributed to more rapid engraftment, the absence of GVHD, and lack of CNI exposure.31 AKI after HSCT confers poor short- and long-term prognoses.

The incidence of dialysis-requiring AKI ranges from 0% (autologous) to 33% (myeloablative allogeneic), with approximately 5% of patients requiring RRT overall. The prognosis is very poor for those

TABLE 69.1 Three Types of Hematopoietic Stem Cell Transplantation and Their Associated Kidney Complications

	Myeloablative Allogeneic	Myeloablative Autologous	Nonmyeloablative Allogeneic
Diseases treated	Many leukemias, lymphomas, myelodysplastic syndromes, myeloproliferative neoplasms, multiple myeloma, marrow failure states (e.g., aplastic anemia), select inherited immunodeficiencies, metabolic disorders, and hemoglobinopathies	Multiple myeloma, lymphomas, germ cell tumors, neuroblastoma	As for myeloablative allogeneic type
Used in patients >60 years	Rarely	Sometimes	Often
Comorbidities permissible before HSCT	Minimal	Minimal	Some
Intensity of conditioning regimen	High	High	Low (intermediate for RIC regimens)
GVHD after HSCT	Common	None	Common
CNIs used routinely	Yes		

No

Yes
Moderate-high

Mortality

Moderate-high

Low

Risk of relapse

Lower

Higher

Lower

Incidence of AKI36

Very common (19%–66%)

Common (12%–50%)

Common (29%–54%)

Causes of AKI

Hepatic SOS, shock syndromes, nephrotoxic drugs, CNIs, acute TMA

Shock syndromes, nephrotoxic drugs, occasionally hepatic SOS

Shock syndromes, nephrotoxic drugs, CNIs, acute TMA

Incidence of CKD

Common

Common

Mild forms probably common

Causes of CKD

Irreversible AKI, kidney TMA, CNIs, GVHD

Irreversible AKI, pretransplant CKD (e.g., kidney involvement by amyloidosis or multiple myeloma)

Pretransplant mild CKD, irreversible AKI, CNIs, GVHD

AKI, Acute kidney injury; CKD, chronic kidney disease; CNIs, calcineurin inhibitors; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy.

requiring dialysis (early mortality >80%).27 31 Fortunately, rates of post-HSCT AKI are decreasing, likely due to multiple improvements in peritransplant care.

Etiology

It is helpful to consider the causes of AKI according to the period after HSCT (Box 69.4).26 Tumor lysis syndrome is an immediate but rare complication after HSCT, as the cancer is often eliminated by the time of transplant. Marrow infusion syndrome occurs within 24 to 48 hours of stem/progenitor cell infusion when patients are exposed to products of red blood cell lysis (released during cryopreservation), as well as the cryoprotectant dimethyl sulfoxide (DMSO), leading to intratubular pigment cast formation and/or toxic ATN.32 This complication is now infrequent, likely related to advances in cell preservation.
Within the first few weeks of HSCT, when intense conditioning regimens have caused pancytopenia, mucositis, vomiting, and liver damage, recipients are at high risk of many forms of AKI. These include prerenal syndromes (e.g., hypovolemia, capillary leak syndrome, engraftment syndrome, hepatic SOS) and acute tubular injury from sepsis.
Medication-induced nephrotoxicity may take the form of acute tubular injury (aminoglycosides, amphotericin B, intravenous iodinated contrast), crystal-induced tubular toxicity (acyclovir, sulfonamides), or acute interstitial nephritis (many antibiotics, allopurinol, proton pump inhibitors).31 33 CNIs have toxicities as outlined previously.
Obstructive uropathy is much less common but can be caused by severe hemorrhagic cystitis or fungal infection of the collecting system. Causes of hemorrhagic cystitis include high-dose cyclophosphamide and viral infections (e.g., adenovirus, BK virus). Adenovirus and BK nephropathies have also been described.31

In addition to the prerenal AKI that occurs in the context of gastrointestinal GVHD, moderate and severe acute and chronic GVHD are correlated with intrarenal AKI and CKD, attributed in part to excessive release of proinflammatory cytokines.33 Animal models of GVHD have demonstrated infiltration of donor-type leukocytes into the kidneys, with associated cell-mediated injury to the kidney microvasculature and kidney tubules.34

Capillary Leak Syndrome and Engraftment Syndrome

Capillary leak syndrome and engraftment syndrome are caused by endothelial cell injury and the release of proinflammatory cytokines and are characterized by fluid retention and fever. Both lead to AKI due to intravascular volume depletion, and possibly by a direct inflammatory effect.33 Capillary leak syndrome presents within 2 weeks of HSCT and is seen most often in haploidentical transplants as a component of cytokine release syndrome (CRS). Engraftment syndrome presents similarly to capillary leak syndrome but occurs at the time of neutrophil regeneration, and is seen most commonly after autologous HSCT.33

Hepatic Sinusoidal Obstructive Syndrome (Previously Venoocclusive Disease of the Liver)

Hepatic SOS is an important cause of severe AKI after myeloablative HSCT, particularly myeloablative allogeneic HSCT (see Table 69.1 and Box 69.4). The incidence ranges from 2% (by updated European Society for Blood and Marrow Transplantation criteria) to 30%.30 Pathophysiology is thought to involve radio- and chemotherapy-induced damage to the endothelium of hepatic venules with subsequent venular thrombosis and sinusoidal and

Causes of Kidney Disease According to Time After Hematopoietic Stem Cell Transplantation

BOX 69.4

Immediate (Very Rare)
- Tumor lysis syndrome
- Marrow infusion syndrome

Early (AKI in First 3 Months)
- Prerenal
- Hypovolemia (gastrointestinal GVHD, drug-induced nausea and vomiting, salt and water losses due to diuretics or other tubular injury)
- Capillary leak syndrome, engraftment syndrome
- Hepatic SOS (early)
- Heart failure
- CNI toxicity (early)
- Intrarenal
- Ischemic acute tubular injury (prolonged prerenal ischemia, sepsis/septic shock, hepatic SOS [late], calcineurin inhibitor toxicity [late], intravenous iodinated contrast)
- Toxic acute tubular injury (aminoglycosides, amphotericin B, foscarnet, cidofovir)
- Crystal-induced tubular toxicity (acyclovir)
- Allergic interstitial nephritis (penicillins, cephalosporins, fluoroquinolones, macrolides, trimethoprim-sulfamethoxazole, allopurinol, proton pump inhibitors)
- Postrenal
- Hemorrhagic cystitis (cyclophosphamide, BK virus, adenovirus)

Late
- Thrombotic microangiopathy
- Calcineurin inhibitor toxicity
- Irreversible AKI
- Membranous nephropathy or other glomerular diseases
- Recurrence of original disease, which then affects the kidneys (e.g., amyloidosis, multiple myeloma)
- Retroperitoneal fibrosis (malignancy, radiotherapy)
- GVHD (?)

AKI, Acute kidney injury; CNIs, calcineurin inhibitors; GVHD, graftversus-host disease; SOS, sinusoidal obstruction syndrome.

portal hypertension that in turn decreases kidney perfusion. Independent risk factors include the use of antithymocyte globulin, myeloablative conditioning regimens (total body irradiation based and busulfan based), busulfan exposure (pediatric population), 2 or more HSCTs, and increased tacrolimus trough blood concentrations (>5–10 ng/mL).[30] The use of gemtuzumab ozogamicin and inotuzumab ozogamicin, novel antibody-drug conjugates sometimes administered prior to HSCT, have also been implicated.[30,31]

Clinically, SOS presents as a form of hepatorenal syndrome during the first 30 days after HSCT. There is frequently a precipitating factor such as sepsis. Initial symptoms and signs include weight gain, edema, and ascites, followed by right upper quadrant abdominal pain, jaundice, and abnormal liver function tests. Oliguria and rising creatinine follow.[33] In mild to moderate cases, patients may recover with supportive care alone. Severe SOS complicated by liver and kidney failure (and frequently respiratory failure) carries a mortality approaching 80%.[35] The differential diagnosis includes acute GVHD of the liver, sepsis, drug-induced cholestasis, gallstone disease, and hepatotoxic effects of parenteral nutrition.

The diagnosis of hepatic SOS is usually based on characteristic clinical and laboratory features, though liver biopsy is occasionally performed. Urine sodium concentration is low (<10 mEq/L). Urinalysis and urine sediment are typically bland; granular casts may be seen with progression to ATN. Kidney biopsy specimens have not revealed intrinsic kidney lesions, consistent with the understanding that SOS is most likely hemodynamic in pathophysiology.36

Transplant-Associated Thrombotic Microangiopathy

Transplant-associated thrombotic microangiopathy (TMA) is associated with subclinical kidney disease, AKI, and (most commonly) CKD. Recent studies reveal an incidence of 2.3% to 30%, with widely varying definitions of transplant-associated TMA and study populations.37 Transplant-associated TMA is characterized by endothelial cell injury leading to microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage; the kidneys are thought to be vulnerable to microvascular injury due to their extensive glomerular circulation.36 Patients typically present 4 to 12 months after HSCT with slowly rising creatinine, although some patients demonstrate a more fulminant presentation with severe nephritic syndrome. Clues to the diagnosis include disproportionate hypertension and progressive anemia. Urinalysis shows variable proteinuria and hematuria. Careful review of prior test results may show evidence of an intermittent or persistent low-grade TMA, although the classic laboratory findings (e.g., elevated serum lactate dehydrogenase, decreased haptoglobin, schistocytes) may not all be present. Diagnostic criteria (and their limitations) are summarized elsewhere.38 Histopathology reveals endothelial cell swelling, fibrin thrombi within capillary loops and arterioles, fragmented red blood cells, mesangiolysis, and thickened arteriolar vasculature. Chronic injury leads to glomerular capillary wall remodeling, double contour formation of the basement membrane, and tubular injury with interstitial fibrosis (Fig. 69.4).37

It is unclear if transplant-associated TMA is a direct complication of HSCT or a consequence of endothelial injury precipitated by GVHD or other exposures.31 37 Acute GVHD (especially grades 2–4) is a major risk factor for transplant-associated TMA, with emerging data suggesting that transplant-associated TMA might be an “endothelial complication” of GVHD.36 39 Other significant risk factors include unrelated donor type and CNI use. Transplant-associated TMA has also been associated with advanced primary malignancy, nonmyeloablative transplant, high-dose busulfan administration, total body irradiation (TBI), mTOR inhibitor use, and infections (e.g., systemic infections, Aspergillus species, BK virus, cytomegalovirus, parvovirus B19, and adenovirus).37 Recent studies demonstrate that complement activation and genetic susceptibility to complement dysregulation play major roles in the endothelial injury that drives transplant-associated TMA, with potential implications for therapy37 40 (Fig. 69.5).

Prevention, Detection, and Management of Acute Kidney Injury After Hematopoietic Stem Cell Transplantation

General Considerations

Strict control of fluid balance is essential for the prevention of posttransplant AKI. Weight, blood pressure, intake, and output (urine and stool) should be monitored regularly in all HSCT patients.31 Nephrotoxic medications and iodinated contrast should be used judiciously. Infections and gastrointestinal GVHD should be treated promptly. If CNI trough concentrations are high, dose reduction should be considered. Promising developments that may lower the risk of AKI include the use of CNI-free (e.g., cyclophosphamide-based) regimens for GVHD prophylaxis and personalized drug dosing protocols.31

As previously discussed, serum creatinine has limitations as an AKI biomarker in this context. Novel AKI biomarkers (e.g., urine

A

Fig. 69.4 Thrombotic Microangiopathy After Allogeneic Hematopoietic Stem Cell Transplantation (HSCT).

(A) Kidney biopsy specimen from a patient who had undergone allogeneic HSCT and developed subacute kidney failure 12 months later. Periodic acid–Schiff staining shows near occlusion of two small arteries by subintimal connective tissue and swollen endothelium (black arrows). The glomerulus shows thickened capillary walls with "double contours" and segmental occlusion and collapse of capillaries (orange arrows). (B) Severe mesangiolysis in a patient with thrombotic microangiopathy after HSCT. Note the aneurysmal capillary loops and the lack of mesangial cells or matrix. (Courtesy Dr. H. Rennke, Harvard Medical School, Boston.)

Pathogenesis of Renal Thrombotic Microangiopathy After
Hematopoietic Cell Transplantation
Radiotherapy

Chemotherapy

Aggravating Factors
GVHD
Proinflammatory
cytokines

Protective Factor

Infection

Renal shielding
CNI, sirolimus

Genetic factors (e.g., abnormalities
of the complement system)

Renal endothelial injury

Thrombotic microangiopathy
Platelet and fibrin deposition
Microvascular obstruction

Microangiopathic hemolytic anemia

Nephron ischemia

AKI

CKD

Hypertension

Fig. 69.5 Putative pathogenesis of kidney thrombotic microangiopathy after hematopoietic stem cell transplantation. AKI, Acute kidney injury; CKD, chronic kidney disease; CNI, calcineurin inhibitor; GVHD, graftversus-host disease. (Modified from Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005;16[1]:151–161.)

neutrophil gelatinase-associated lipocalin [NGAL]) have been evaluated in the research setting but are not yet in routine clinical use.36

Posttransplant AKI should be evaluated as for any patient with hospital-acquired AKI but with particular focus on the patient's cancer diagnosis, type of transplant, and conditioning regimen. Complications specific to HSCT, such as capillary leak syndrome/ engraftment syndrome, hepatic SOS, and transplant-associated TMA, should be considered in the appropriate clinical context. Nephrotoxic medications should be stopped where possible, and medications dose adjusted for eGFR.31 Urinalysis, urine microscopy, urine protein/creatinine ratio, and kidney ultrasound should be performed. Clinicians should have a low threshold to evaluate for TMA, BK virus, and adenovirus. Kidney biopsy may be considered in the following situations: (1) AKI of unclear etiology, (2) failure of kidney function to recover as anticipated after initial modifications in therapy, or (3) presence of nephrotic-range proteinuria. As many HSCT patients are thrombocytopenic and/or coagulopathic, biopsies should be performed with caution and appropriate transfusion support.31

The choice of RRT modality is usually based on hemodynamic stability and volume status; daily obligate fluid intake in this context is frequently massive, and fluid balance may be controlled most easily with continuous RRT. There is evidence in the pediatric literature that continuous convective therapies may be preferred, perhaps related to differences in the removal of small- and middle-sized molecules compared with diffusive therapies.41

Data supporting earlier (versus later) initiation of RRT after HSCT comes primarily from the pediatric population, with a small recent study demonstrating good outcomes in patients with SOS, AKI, and fluid overload treated with a standardized fluid balance protocol and early initiation of RRT.42 In the absence of consensus guidelines, some experts advocate for initiation of RRT when there is radiologic and clinical evidence of pulmonary edema, worsening oxygenation, poor response to high-dose diuretics, evidence of systemic inflammation, and ongoing oliguria.36

Importantly, vascular access can be problematic in these patients because of thrombocytopenia and neutropenia, predisposing to bleeding and infection, respectively.

Disease-Specific Considerations

Hepatic sinusoidal obstruction syndrome. Current strategies for preventing hepatic SOS are based on inconclusive evidence and include avoiding precipitating factors where possible and using ursodeoxycholic acid (UDCA) or low-dose heparin.43 Ursodeoxycholic acid alters the bile acid milieu, rendering bile less hydrophobic and toxic to parenchymal cells if cholestasis is present; it also exerts local cytokine-mediated immunomodulatory effects. Defibrotide, an oligonucleotide with antithrombotic and fibrinolytic effects on the microvascular endothelium but with apparently few systemic adverse effects, has demonstrated efficacy in both preventing and treating SOS.44 As discussed earlier, continuous RRT may have less effect on intracranial pressure than intermittent HD.

Transplant-associated thrombotic microangiopathy. Patients with suspected or confirmed transplant-associated TMA should be supported with transfusions, blood pressure control, and dialysis as indicated.37 All patients should be promptly evaluated for precipitating viral infections and acute GVHD. In patients receiving CNIs or mTOR inhibitors for GVHD prophylaxis, replacement with alternative agents (corticosteroids, MMF, IL-2 inhibitors, and anti-CD20 agents) may be appropriate, although not extensively studied.38 Plasma exchange has not been proven to be beneficial.37,38 Limited reports in pediatric and adult patients have demonstrated response rates of 80% (12 of 15 patients) with the use of rituximab.37 Given the complement pathway abnormalities described previously, there is interest in the C5 inhibitor eculizumab. Data for its use

comes primarily from the pediatric literature, with a relatively large study of 64 children with high-risk transplant-associated TMA demonstrating 66% 1-year post-HSCT survival compared with 16.7% in a previously reported untreated cohort.45 Of course, the risks and benefits of any extra immunosuppression in patients after HSCT must be very carefully considered.

Chronic Kidney Disease After Hematopoietic Stem Cell Transplantation

Epidemiology

CKD is an important long-term complication of HSCT, particularly allogeneic HSCT.27 The reported cumulative incidence of CKD after HSCT ranges from 7% to 48%, with approximately 4% of these patients progressing to ESKD and experiencing worse survival on dialysis compared with non-HSCT controls.27,38,46 The incidence of CKD after HSCT is expected to rise as the age of patients undergoing transplantation increases.31 Some causes of CKD are shown in Table 69.1.

Risk factors for posttransplant CKD include age 45 years or older at time of transplantation, baseline GFR less than 90 mL/min/1.73 m2, acute and chronic GVHD, prior AKI, and survival more than 1 year after transplantation.27 Exposure to high-dose total body irradiation has also been implicated, possibly by contributing to subacute or chronic transplant-associated TMA.28,31 Hypertension is a wellrecognized late complication of HSCT, with incidence linked to the development of CKD. Albuminuria has been associated with CKD progression and decreased posttransplant survival.31

CNIs are routinely prescribed after allogeneic HSCT to prevent and treat GVHD. They are often stopped after 3 to 6 months (unless there is ongoing GVHD), and so their contribution to CKD is thought to be limited.27 The contribution of CNIs to chronic kidney TMA is unclear, as transplant-associated TMA can certainly occur in patients on nonCNI protocols.46

Glomerular Disease

Nephrotic syndrome has been described after both allogeneic (particularly nonmyeloablative) and autologous HSCT. Nephrotic syndrome after allogeneic HSCT tends to occur more than 6 months after transplantation and appears to be strongly associated with tapering of immunosuppression and the presence of GVHD; de novo membranous nephropathy is the most common biopsy finding, followed by minimal change disease.47,48 Importantly, the original hematologic disease (e.g., amyloidosis, multiple myeloma) may recur with kidney involvement.

Management of Hematopoietic Stem Cell Transplantation–Related Chronic Kidney Disease

Proteinuria and hypertension should be monitored and controlled. There is limited evidence regarding the superiority of RAS blockade, but its use seems reasonable.49 Management of chronic transplantassociated TMA is discussed earlier. Clinical response in patients with post-HSCT membranous nephropathy or minimal change disease is usually seen with increased immunosuppression (typically corticosteroids and/or CNI); there are also limited reports of success with rituximab (particularly in membranous nephropathy).47,48

Suitability for kidney transplantation should be judged on a caseby-case basis. On occasion, the allogeneic stem cell donor can donate a kidney; the benefit of this approach is that tolerance to the kidney allograft should exist; hence minimal or no additional immunosuppression is required.50 If this option is not available and the patient receives a conventional kidney transplant, low-dose immunosuppression should generally be prescribed because HSCT recipients may not have normal immunity and remain at higher risk for infection. Good outcomes after kidney transplantation have been reported in carefully selected patients.50,51

SELF-ASSESSMENT QUESTIONS

1. A 28-year-old woman is referred to the nephrology clinic with serum creatinine 2.3 mg/dL (200 µmol/L). Six years ago she underwent lung transplantation because of respiratory failure associated with cystic fibrosis. The lung transplant is working well. However, her serum creatinine has increased slowly over the last 5 years from 1.1 mg/dL (97 µmol/L). Her medications are cyclosporine, azathioprine, prednisolone, simvastatin, and pancreas enzyme supplements. The main findings on examination are finger clubbing and blood pressure (BP) 148/84 mm Hg. The urine dipstick shows trace protein only. Which of the following is true?

A. The underlying cause of her CKD is most likely cyclosporine toxicity.
B. An urgent kidney biopsy is indicated.
C. Switching azathioprine to sirolimus is indicated.
D. If her CKD progresses, kidney transplant is contraindicated because of underlying cystic fibrosis.
E. Diltiazem should be added to control the hypertension.

2. A 30-year-old man is referred to the nephrology clinic because of rising serum creatinine and worsening hypertension. Eight months ago he underwent an allogeneic stem cell transplant for acute myeloid leukemia (AML). His conditioning regimen included total body irradiation and cyclophosphamide. His early posttransplant course was relatively uncomplicated. However, he remained on cyclosporine because of GVHD of the skin. Recent cyclosporine trough concentrations have been 60 to 90 ng/mL. His medications are low doses of cyclosporine, prednisolone, valacyclovir, and sulfamethoxazoletrimethoprim. The main findings on examination are BP 166/98 mm Hg (148/86 mm Hg, 3 weeks ago), mild GVHD of the skin, and mild leg edema. The urine dipstick shows 3+ blood and 3+ protein. Other test results are as follows: white blood cells 4.2 × 109/L, hematocrit 26.0 (32.0, 3 weeks ago), platelets 82 × 109/L (130 × 109/L, 3 weeks ago), creatinine 2.3 mg/dL (200 µmol/L) (1.2 mg/dL [105 µmol/L], 3 weeks ago), albumin 3.2 g/dL, and 24-hour urine protein 3.2 g. The prothrombin time and activated partial thromboplastin time are normal. Which of the following is true?

A. The main cause of the kidney disease is probably cyclosporine toxicity.
B. The patient has nephritic syndrome, most likely caused by membranous nephropathy.
C. The plasma lactate dehydrogenase, serum haptoglobin, and blood film should be checked urgently.
D. The main cause of the kidney disease is recurrence of AML, with infiltration of the kidneys.
E. Computed tomography with intravenous contrast should be performed urgently to exclude obstruction of the urinary tract.

3. A 30-year-old man is referred urgently to the nephrology clinic because of an increase in creatinine from baseline 2.0 mg/dL (176 µmol/L) to 2.9 mg/dL (255 µmol/L). One week ago he was diagnosed with community-acquired pneumonia and treated with antibiotics. His breathlessness and cough have improved, but he reports mild headache and pain in the right big toe. Ten years ago he underwent a heart transplant for severe heart failure caused by idiopathic dilated cardiomyopathy. The heart transplant is apparently working well. His medications are cyclosporine, azathioprine, prednisolone, ramipril, atorvastatin, and (in the last week) cefuroxime plus clarithromycin. Examination shows fine hand tremor, pulse 90/min and regular, BP 142/84 mm Hg, oxygen saturation 98% on room air, normal breath sounds with no added sounds, and no leg edema. The right big toe is inflamed, consistent with acute gout. The urine dipstick shows trace protein only.

Tests show serum creatinine 2.9 mg/dL (255 µmol/L), potassium 5.9 mmol/L, white blood cells 4.9 × 109/L (with normal differential), hematocrit 30, and platelets 189 × 109/L. Which of the following is true?

A. The most likely cause of the acute kidney dysfunction is allergic interstitial nephritis resulting from cefuroxime.

B. The main underlying cause of the CKD is cardiac failure (of the transplanted organ).

C. If the patient’s CKD progresses to a glomerular filtration rate below 15 mL/min, the treatment of choice would be peritoneal dialysis.

D. Allopurinol should be added to treat the gout.

E. The most likely cause of the acute kidney dysfunction is acute cyclosporine nephrotoxicity caused by impairment of cyclosporine metabolism by clarithromycin.

4. A 44-year-old woman is admitted to the intensive care unit with severe, decompensated liver disease. The underlying cause is cirrhosis from hepatitis C (HCV) infection. Over 1 week she becomes oliguric; serum creatinine increases from 1.0 mg/dL (88 µmol/L) to 2.5 mg/dL (221 µmol/L). The urine dipstick shows trace blood and trace protein only. The fractional urine excretion of sodium is 0.2%. Low-dose noradrenaline is started, causing the mean arterial pressure to increase to 65 mm Hg and the urine output to increase to 800 mL/24 h. A decision is made to list her for an emergency liver transplant. Which of the following is true?

A. The baseline serum creatinine of 1.0 mg/dL likely reflects normal eGFR.

B. The clinical picture is consistent with hepatorenal syndrome.

C. The acute renal dysfunction is a result of HCV-related glomerulonephritis.

D. At this time, a simultaneous liver-kidney rather than a liveralone transplant should be performed.

E. After successful liver transplantation, her risk for developing stage 4 or 5 CKD over the long term is negligible.

5. A 39-year-old woman is referred for opinion regarding kidney transplantation. She has a background of complex congenital cyanotic heart disease and has undergone several procedures for this. However, her cardiac function is worsening; therefore, she is being considered for cardiac transplantation. Her serum creatinine has steadily increased over the last 3 years. Medications are furosemide, digoxin, bisoprolol, omeprazole. She reports poor appetite and breathlessness on minimal exertion. On examination she is thin, pulse is 114 beats/min and regular, BP 152/92 mm Hg, and respiratory rate 22/min at rest. The fingertips are cyanosed. The jugular venous pressure is increased. There are reduced breath sounds in the left lung base. The liver edge is palpable; the femoral pulses are strong with no bruits. There is trace leg edema. Tests show urine dipstick 3+ protein and trace blood, plasma creatinine 4.0 mg/dL, potassium 5.1 mmol/L, albumin 3.1 g/dL, and 24-hour urine protein 4.2 g. Which of the following is true?

A. The kidney dysfunction is mainly a result of the severe heart failure and thus should improve significantly after successful cardiac transplantation.

B. Because of the risk that cyclosporine or tacrolimus will worsen kidney function after cardiac transplantation, you should advise the cardiologists to avoid using these drugs after transplantation.

C. Simultaneous heart-kidney transplant is a relatively common procedure and should be considered here.

D. Simultaneous heart-kidney transplant is an uncommon procedure but should be considered here.

E. You should recommend that a kidney transplant be performed first and only later consider cardiac transplantation.

REFERENCES

1. Shafi K, Uhlig K, Perrone RD, et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. Am J Kidney Dis. 2014;63(6):1007–1018.
2. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4(2):481–508.
3. Navis G, Broekroelofs J, Mannes GP, et al. Renal hemodynamics after lung transplantation. A prospective study. Transplantation. 1996;61(11):1600–1605.
4. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. Am J Transplant. 2009;9(8):1876.
5. Cantarovich M, Blydt-Hansen TD, Gill J, et al. Canadian Forum on combined organ transplantation. Transplantation. 2016;100(6):1339–1348.
6. Boyle G. Simultaneous Liver Kidney (SLK) Allocation Policy. https://optn.transplant.hrsa.gov/media/1192/0815-12_SLK_Allocation.pdf.
7. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931–940.
8. Viswesh V, Yost SE, Kaplan B. The prevalence and implications of BK virus replication in non-renal solid organ transplant recipients: a systematic review. Transplant Rev (Orlando). 2015;29(3):175–180.
9. Cassuto JR, Levine MH, Reese PP, et al. The influence of induction therapy for kidney transplantation after a non-renal transplant. Clin J Am Soc Nephrol. 2012;7(1):158–166.
10. Srinivas TR, Stephany BR, Budev M, et al. An emerging population: kidney transplant candidates who are placed on the waiting list after liver, heart, and lung transplantation. Clin J Am Soc Nephrol. 2010;5(10):1881–1886.
11. Cornelis T, Rioux JP, Bargman JM, Chan CT. Home dialysis is a successful strategy in nonrenal solid organ transplant recipients with end-stage renal disease. Nephrol Dial Transplant. 2010;25(10):3425–3429.
12. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62(4):968–974.
13. Wong LP, Blackley MP, Andreoni KA, et al. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. Kidney Int. 2005;68(1):362–370.
14. Adelmann D, Olmos A, Liu LL, et al. Intraoperative management of liver transplant patients without the routine use of renal replacement therapy. Transplantation. 2018;102(5):e229–e235.
15. Kollmann D, Neong SF, Rosales R, et al. Renal dysfunction after liver transplantation: effect of donor type. Liver Transpl. 2020;26(6):799–810.
16. Neuberger JM, Mamelok RD, Neuhaus P, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the ‘ReSpECT’ study. Am J Transplant. 2009;9(2):327–336.
17. Schmeding M, Kiessling A, Neuhaus R, et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation. 2011;92(8):923–929.
18. Wang L, Wang T, Rushton SN, et al. The impact of severe acute kidney injury requiring renal replacement therapy on survival and renal function of heart transplant recipients - a UK cohort study. Transpl Int. 2020;33(12):1650–1666.
19. Alam A, Badovinac K, Ivis F, et al. The outcome of heart transplant recipients following the development of end-stage renal disease: analysis of the Canadian Organ Replacement Register (CORR). Am J Transplant. 2007;7(2):461–465.
20. Kobashigawa JA, Patel J, Furukawa H, et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant. 2006;25(4):434–439.
21. Chambers DC, Cherikh WS, Goldfarb SB, et al. International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant

report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant. 2018;37(10):1169–1183.

22. Gustafsson F, Andreassen AK, Andersson B, et al. SCHEDULE (Scandinavian heart transplant everolimus de novo study with early calcineurin inhibitors avoidance) Investigators. Everolimus initiation with early calcineurin inhibitor withdrawal in de novo heart transplant recipients: long-term follow-up from the randomized SCHEDULE study. Transplantation. 2020;104(1):154–164.
23. Shaw BI, Sudan DL, Boulware LE, McElroy LM. Striking a balance in simultaneous heart kidney transplant: optimizing outcomes for all waitlisted patients. J Am Soc Nephrol. 2020;31(8):1661–1664.
24. Lertjitbanjong P, Thongprayoon C, Cheungpasitporn W, et al. Acute kidney injury after lung transplantation: a systematic review and metaanalysis. J Clin Med. 2019;8(10):1713.
25. Lefaucheur C, Nochy D, Amrein C, et al. Renal histopathological lesions after lung transplantation in patients with cystic fibrosis. Am J Transplant. 2008;8(9):1901–1910.
26. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005;16(1):151–161.
27. Hingorani S. Renal complications of hematopoietic-cell transplantation. N Engl J Med. 2016;374(23):2256–2267.
28. Center for International Blood and Marrow Transplant Research: Summary Slides 2015—HCT Trends and Survival Data. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx.
29. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124(3):344–353.
30. Corbacioglu S, Jabbour EJ, Mohty M. Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Biol Blood Marrow Transplant. 2019;25(7):1271–1280.
31. Renaghan AD, Jaimes EA, Malyszko J, Perazella MA, Sprangers B, Rosner MH. Acute kidney injury and CKD associated with hematopoietic stem cell transplantation. Clin J Am Soc Nephrol. 2020;15(2):289–297.
32. Zager RA. Acute renal failure in the setting of bone marrow transplantation. Kidney Int. 1994;46(5):1443–1458.
33. Jaguś D, Lis K, Niemczyk L, Basak GW. Kidney dysfunction after hematopoietic cell transplantation-Etiology, management, and perspectives. Hematol Oncol Stem Cell Ther. 2018;11(4):195–205.
34. Higo S, Shimizu A, Masuda Y, et al. Acute graft-versus-host disease of the kidney in allogeneic rat bone marrow transplantation. PLoS One. 2014;9(12):e115399.
35. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157–168.
36. Wanchoo R, Stotter BR, Bayer RL, Jhaveri KD. Acute kidney injury in hematopoietic stem cell transplantation. Curr Opin Crit Care. 2019;25(6):531–538.
37. Wanchoo R, bayer RL, Bassil C, Jhaveri KD. Emerging concepts in hematopoietic stem cell transplantation-associated renal thrombotic microangiopathy and prospects for new treatments. Am J Kidney Dis. 2018;72(6):857-865. Erratum in Am J Kidney Dis. 2019;73(2):291.
38. Rosenthal J. Hematopoietic cell transplantation-associated thrombotic microangiopathy: a review of pathophysiology, diagnosis, and treatment. J Blood Med. 2016;7:181–186.
39. Zeisbrich M, Becker N, Benner A, et al. Transplant-associated thrombotic microangiopathy is an endothelial complication associated with refractoriness of acute GvHD. Bone Marrow Transplant. 2017;52(10):1399–1405.
40. Jodele S, Zhang K, Zou F, et al. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. Blood. 2016;127(8):989–996.
41. Flores FX, Brophy PD, Symons JM, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from

the prospective pediatric CRRT Registry Group. Pediatr Nephrol. 2008;23(4):625–630.
42. Raina R, Abusin GA, Vijayaraghavan P, et al. The role of continuous renal replacement therapy in the management of acute kidney injury associated with sinusoidal obstruction syndrome following hematopoietic cell transplantation. Pediatr Transplant. 2018;22(2):10.

References

43. Cheuk DK, Chiang AK, Ha SY, Chan GC. Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation. Cochrane Database Syst Rev. 2015;(5):CD009311.
44. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656–1665.
45. Jodele S, Dandoy CE, Lane A, et al. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood. 2020;135(13):1049–1057.
46. Glezerman IG, Jhaveri KD, Watson TH, et al. Chronic kidney disease, thrombotic microangiopathy, and hypertension following T cell-depleted hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2010;16(7):976–984.
47. Beyar-Katz O, Davila EK, Zuckerman T, et al. Adult nephrotic syndrome after hematopoietic stem cell transplantation: renal Pathology is the

48.

49.

50.

51.

best predictor of response to therapy. Biol Blood Marrow Transplant. 2016;22(6):975–981.
Niscola P, Tendas A, Luo XD, et al. The management of membranous glomerulopathy in allogeneic stem cells transplantation: updated literature. Cardiovasc Hematol Agents Med Chem. 2013;11(1):67–76.
Cohen EP, Bedi M, Irving AA, et al. Mitigation of late renal and pulmonary injury after hematopoietic stem cell transplantation. Int J Radiat Oncol Biol Phys. 2012;83(1):292–296.
Butcher JA, Hariharan S, Adams MB, et al. Renal transplantation for end-stage renal disease following bone marrow transplantation: a report of six cases, with and without immunosuppression. Clin Transplant. 1999;13(4):330–335.
Koenecke C, Hertenstein B, Schetelig J, et al. Solid organ transplantation after allogeneic hematopoietic stem cell transplantation: a retrospective, multicenter study of the EBMT. Am J Transplant. 2010;10(8):1897–1906.

SECTION XIV

Acute Kidney Injury

70

Pathophysiology and Etiology of Acute Kidney Injury

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DEFINITION

Acute kidney injury (AKI) is defined as an abrupt decline in glomerular filtration rate (GFR) sufficient to decrease the elimination of nitrogenous waste products and other uremic toxins. This has traditionally been referred to as acute renal failure (ARF) but has been replaced with the term acute kidney injury, and standardized definitions of AKI have been developed (see Table 72.1) with stages based upon the magnitude of the rise in serum creatinine and changes in the urine output over 1 week.1

ETIOLOGY

AKI is caused by a broad range of etiologies, and the differential diagnosis must be considered in a systematic fashion. The traditional paradigm divides AKI into prerenal, renal, and postrenal causes. Prerenal causes may be due to hypovolemia or a decreased effective arterial volume. Postrenal kidney failure is usually due to obstruction. Intrinsic renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply, glomerular, tubular, and interstitial disease; Fig. 70.1). Major extrarenal artery or venous occlusion must also be considered (see Chapter 43). Disorders of the small intrarenal vasculature can also result in AKI (e.g., vasculitis, thrombotic microangiopathy, malignant hypertension, eclampsia, postpartum states, disseminated intravascular coagulation [DIC], scleroderma; see Chapters 26, 30, 38, 42, and 65). All forms of acute glomerulonephritis can present as AKI, as can acute inflammation and space-occupying processes of the kidney interstitium (e.g., drug-induced, infectious, and autoimmune disorders, leukemia, lymphoma, sarcoidosis).

Among inpatients, prerenal azotemia and acute tubular injury (ATI) account for most AKI cases2 (Fig. 70.2), often in the setting of AKI superimposed on chronic kidney disease (CKD), so-called acuteon-chronic kidney disease. The term ATN (acute tubular necrosis), although commonly used, is a misnomer because the alterations are not limited to the tubular structures, and true cellular necrosis in human ATN is often minimal. ATN should be reserved for cases of AKI in which a kidney biopsy (if performed) shows the characteristic changes of tubular cell injury (Fig. 70.3), or for patients with findings of tubular injury (e.g., renal tubular epithelial cells in the urine sediment) in an appropriate clinical setting. There are also geographic differences in the causes of AKI, with the spectrum of causes in tropical countries described in Chapter 71

PATHOPHYSIOLOGY AND ETIOLOGY OF PRERENAL AKI

Impaired kidney perfusion with a resultant fall in glomerular capillary filtration pressure is a common cause of AKI. In this setting, tubular function is typically normal, whereas kidney reabsorption of sodium and water is increased, so the urine exhibits low sodium concentration (<20 mmol/L) and high osmolality (>500 mOsm/kg), presuming a diuretic has not been administered. A marked reduction in kidney perfusion may overwhelm autoregulation and precipitate an acute fall in GFR. With lesser degrees of kidney hypoperfusion, glomerular filtration pressures and GFR are maintained by afferent arteriolar vasodilation (mediated by vasodilatory eicosanoids) and efferent arteriolar vasoconstriction (mediated by angiotensin II) that increases the filtration fraction. In this setting, AKI may be precipitated by agents that impair afferent arteriolar dilation (nonsteroidal antiinflammatory drugs [NSAIDs]) or efferent vasoconstriction (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]).

The hemodynamic mechanisms that drive the reduction in GFR and an adaptive increase in proximal tubular reabsorption in hypovolemic states originate from an interplay between hydraulic and oncotic pressures (Fig. 70.4). Under normal physiologic conditions, the glomerular capillary hydraulic pressure (PGC) is greater than the glomerular capillary oncotic pressure (πGC), and hydraulic pressure in Bowman’s space that opposes filtration and the oncotic pressure in Bowman’s space are negligible. Thus, the sum of these forces leads to the generation of ultrafiltrate (see Chapter 2). The directionality of fluid flow reverses in the proximal tubule, where the peritubular capillary oncotic pressure (πTC) is greater than the peritubular capillary hydraulic pressure (PTC), thus favoring reabsorption. As kidney perfusion falls beyond compensatory limits, PGC falls. When volume loss is pronounced, πGC may rise as a result of hemoconcentration and rise in serum total protein concentration. Those processes lead to a fall in GFR. Concomitantly, the dominance of πTC over PTC becomes more pronounced primarily as a result of further drop in PTC. This avid proximal tubular reabsorption in prerenal azotemia partly explains the increased reabsorption of molecules like sodium, urea, and calcium observed in this disease state.

Prerenal AKI is often secondary to gastrointestinal losses (diarrhea, vomiting, prolonged nasogastric drainage), renal losses (diuretics, osmotic diuresis in hyperglycemia), dermal losses (burns, extensive sweating), or sequestration of fluid, sometimes known as third spacing (e.g., acute pancreatitis, muscle trauma). Kidney perfusion may also be impaired in the setting of normal or increased extracellular fluid, when

Causes of AKI
2. Renal artery
Renal artery occlusion or dissection
Large- or medium-vessel vasculitis

3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
4. Glomerular disease (ANCA+ or –)
Small-vessel vasculitis
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/collapsing glomerulopathy

1. Renal hypoperfusion
Prerenal azotemia
- Hypovolemia, hemorrhage
- Acute decompensated heart failure

Vasomotor renal dysfunction
- Hepatorenal syndrome
- Drug-induced (eg, NSAIDs, RASi, CNI, amphetamines)
- Hypercalcemia

9. Renal vein
Abdominal compartment syndrome
Renal congestion

8. Postrenal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis
Neurogenic bladder (eg, drugs)

6. Acute interstitial nephritis
Non-granulomatous
- Allergic due to drugs
- Infection (eg, viral)

Granulomatous
- Drugs
- Infection
- Systemic disease

Pyelonephritis

5. Acute tubular injury
Ischemic
Toxic
- Endogenous toxins

Light chains (eg, myeloma)
Uric acid (eg, tumor lysis)
Myoglobin (eg, rhabdomyolysis)
Hemoglobin (eg, massive hemolysis)
Bile salts (eg, obstructive cholestasis)

- Exogenous toxins

Antimicrobials (eg, aminoglycosides)
Chemoagents (eg, cisplatin)
Radiocontrast media
Phosphate (eg, Na-Phos bowel prep)
Oxalate (eg, ethylene glycol)
Acetaminophen (intoxication level)
Synthetic cannabinoids

Fig. 70.1 Causes of Acute Kidney Injury (AKI). AKI is classified into prerenal, renal, and postrenal causes. Renal causes of AKI should be considered under the different anatomic components of the kidney (vascular supply, glomerular, tubular, and interstitial disease). ANCA, Antineutrophil cytoplasmic antibody; CNI, calcineurin inhibitor; GBM, glomerular basement membrane; IgA, immunoglobulin A; Na-Phos, sodiumphosphate; NSAID, nonsteroidal antiinflammatory drug; RASi, renal-angiotensin system inhibitor.

Causes of AKI in Hospital Setting
Acute tubular necrosis
RPGN
Vascular
Pre-renal

Acute interstitial nephritis

Obstruction
Acute-on-chronic kidney failure

Fig. 70.2 Causes of acute kidney injury (AKI) in the hospital setting. Madrid acute renal failure study (1996). RPGN, Rapidly progressive glomerulonephritis.

cardiac output is reduced (heart failure), or when there is systemic arterial vasodilation with redistribution of cardiac output to extrarenal vascular beds (e.g., sepsis, liver cirrhosis) (see Chapters 8 and 76). An unusual cause of prerenal AKI is the infusion of large quantities of osmotically active substances such as mannitol, dextran, or protein, which can increase the glomerular oncotic pressure enough to exceed the capillary hydrostatic pressure stopping filtration. Prerenal AKI can be corrected if the extrarenal factors causing the kidney hypoperfusion are rapidly reversed. Failure to restore renal

blood flow (RBF) during the functional prerenal stage will ultimately lead to tubular cell injury.

PATHOPHYSIOLOGY OF ATI

ATI commonly occurs in patients with trauma, vascular and cardiac surgery, severe burns, pancreatitis, sepsis, and chronic liver disease. ATI is responsible for most cases of hospital-acquired AKI and is usually due to ischemic or nephrotoxic injury, or a combination of both. In the intensive care unit, two-thirds of cases of AKI are due to the combination of impaired kidney perfusion, sepsis, and nephrotoxic agents. The importance of combined injury is highlighted by animal studies, in which severe and prolonged hypotension or a single nephrotoxic agent may not cause ATI. Fever may exacerbate ATI by increasing the renal tubular metabolic rate, thereby increasing adenosine triphosphate (ATP) consumption. The typical course of uncomplicated ATI is recovery over 2 to 3 weeks; however, superimposed kidney insults (e.g., episodes of hypotension induced by hemodialysis) or multiple comorbidities often alter this pattern.

Histology

The typical features of ATI include vacuolization and loss of brush border in proximal tubular cells. Sloughing of tubular cells into the lumen leads to cast obstruction, manifested by tubular dilation. Interstitial edema can produce widely spaced tubules, and a mild leukocyte infiltration may be present (see Fig. 70.3). Despite the term acute tubular

A

B

C

D

Fig. 70.3 Kidney Pathology in Acute Tubular Necrosis (ATN). (A) Normal cortical renal tubules. (B–C) ATN. Note the flattened epithelium, bare basement membranes, and intraluminal cellular debris. (D) Recovering ATN showing a tubular epithelial cell mitotic figure (arrow). (Courtesy Erika Bracamonte, MD, University of Arizona.)

“necrosis,” frankly necrotic cells are uncommon on kidney biopsy. Histologic evidence of injury frequently only involves 10% to 15% of the tubules despite marked functional impairment, implying that additional factors such as vasoconstriction and tubular obstruction are important in the loss of GFR.

Site of Tubular Damage in ATI

Tubular damage is usually due to a combination of ischemic injury resulting in depletion of cellular ATP and direct tubular epithelial cell injury by nephrotoxins. The S3 segment of the proximal tubule and the medullary thick ascending limb (mTAL) are particularly vulnerable to hypoxic injury (Fig. 70.5) for several reasons:

1. Blood supply: Most blood flow to the kidney is directed to the kidney cortex for glomerular filtration, where tissue Po2 is 50 to 100 mm Hg. By contrast, the outer medulla and medullary rays are watershed areas receiving their blood supply from vasa rectae. Countercurrent oxygen exchange occurs, leading to a progressive fall in Po2 from cortex to medulla. This results in medullary cells living on the “brink of hypoxia” (Po2 as low as 10–15 mm Hg). The S3 segments of proximal tubule cells and distal mTALs are thus exposed to chronic borderline oxygen deprivation.
2. High tubular energy requirements: The cells of the S3 region and mTAL have high metabolic activity due to sodium reabsorption driven by basolateral membrane Na^+,K^+-ATPase. Blocking sodium reabsorption in the mTAL with loop diuretics raises the medullary tissue Po2 from about 15 to 35 mm Hg. The low GFR in AKI may be renoprotective by diminishing sodium filtration and hence limiting the need for ATP-dependent sodium reabsorption. The drop in GFR in this setting has been called acute renal success. However, there is no clinical evidence that loop diuretics foster AKI recovery.
3. Glycolytic ability of tubular cells: Proximal tubular cells have minimal glycolytic machinery and rely almost solely on oxidative phosphorylation for the generation of ATP. In contrast, mTAL cells have a large glycolytic capacity and are more resistant to hypoxic or ischemic insults.

Hemodynamic Factors in the Development of ATI

Impaired Kidney Autoregulation

Autoregulation between systolic blood pressures of 80 and 150 mm Hg allows maintenance of RBF, glomerular pressures, and GFR in a stable range. Below 80 mm Hg, this autoregulation fails, and ischemic injury may result. In certain conditions, such as aging or CKD, autoregulation is impaired, and ischemic injury may occur more easily with reductions in perfusion pressure. In settings of low kidney perfusion (e.g., volume depletion, left ventricular failure, renal artery stenosis, chronic liver disease), GFR may be dependent on autoregulation mediated by vasodilatory prostaglandins acting on the afferent arteriole and angiotensin II–mediated efferent arteriolar vasoconstriction to maintain glomerular pressure. Any interference with these mechanisms (e.g., administration of ACE inhibitors or NSAIDs) may produce a precipitous fall in GFR.

abnormalities may be mediated by increased cytosolic calcium content in afferent arterioles as a result of ischemia.

Hemodynamic Mechanisms

Tubuloglomerular Feedback

The role of TGF (see Chapter 2) in the setting of AKI may be partly beneficial because the resultant decrease in GFR limits sodium chloride delivery to damaged tubules. This in turn leads to reduced ATPdependent tubular reabsorption of sodium, which protects against intracellular ATP depletion and thus kidney injury.

eff.
arteriol

흘TC

> PTC
πT < PT

Normal
aff.
arteriol

Favors reabsorption
PGC > πGC
πB < PB
Favors filtration

eff.
arteriol

흘TC > P

Prerenal
azotemia
aff.
arteriol

TC

πT < PT

PGC πGC
πB < PB
πGC

πTC
PTC
More reabsorption

GFR maintained
early on by FF
Later on: Less filtration

Fig. 70.4 Hemodynamic Mechanisms That Drive the Reduction in Glomerular Filtration Rate (GFR) and an Adaptive Increase in Proximal Tubular Reabsorption in Hypovolemic States Originate From an Interplay Between Hydraulic and Oncotic Pressures. Under normal physiologic conditions, the glomerular capillary hydraulic pressure (P GC) that drives fluid from the capillary tuft into Bowman’s space is greater

than the glomerular capillary oncotic pressure (πGC) that drives fluid into the glomerular capillary. The hydraulic pressure in Bowman's space (P B) that opposes filtration and the oncotic pressure in Bowman's space (πB) are of lesser magnitude or negligible. Thus, the sum of these forces leads to the generation of ultrafiltrate. The directionality of filtration fraction (FF) reverses in the proximal tubule where the peritubular capillary oncotic pressure (πTC) is greater than the peritubular capillary hydraulic pressure (PTC), thus favoring reabsorption. The hydraulic pressure inside the tubular lumen (PT) and the oncotic pressure inside the tubular lumen (πT) are of lesser magnitude. As kidney perfusion falls beyond compensatory limits, PGC falls. When volume loss is pronounced, πGC may rise as a result of hemoconcentration and rise in serum total protein concentration. Those processes lead to a fall in GFR. Concomitantly, the dominance of πTC over PTC becomes more pronounced primarily as a result of further drop in PTC. This avid proximal tubular reabsorption in prerenal azotemia partly explains the increased reabsorption of molecules like sodium, urea, and calcium observed in this disease state. RBF, Renal blood flow.

Intrarenal Vasoconstriction

In established ATI, RBF is decreased by 30% to 50%. Indeed, in AKI, rather than the normal autoregulatory renal vasodilation that occurs in response to decreased perfusion pressure, there is evidence of renal vasoconstriction. Vasoconstrictors implicated in this response include angiotensin II, endothelin-1, adenosine, thromboxane A2, prostaglandin H2, leukotrienes C4 and D4, sympathetic nerve stimulation (Fig. 70.6), and tubuloglomerular feedback (TGF). Some of these vascular

Tubular Epithelial Cell Injury and the Development of ATI

The tubular cell may be injured because of ischemia (depletion of cellular energy stores [ATP]) or from direct cytotoxic injury. Following acute kidney ischemia, tubular cell injury may also result from the restoration of RBF (reperfusion injury). Mediators of tubular cell injury include reactive oxygen species (ROS), intracellular calcium influx, nitric oxide, phospholipase A2, complement, and cell-mediated cytotoxicity.3 Mitochondrial injury can be caused by ROS, depletion of antioxidants, and increased intracellular calcium. Disruption of mitochondrial function exacerbates cellular injury due to disrupted energy metabolism and release of proapoptotic proteins. Autophagy is a mechanism by which cells degrade self-proteins, and it is a central part of the cellular response to stress and injury. Experimental work has shown that autophagy is important for removal of damaged mitochondria and the recovery of tubular epithelial cells from ischemic injury. ROS may be derived from local sources (including xanthine oxidase and cyclooxygenases secondary to mitochondrial injury) or from infiltrating leukocytes. In models of ischemic ATN, a variety of methods that inhibit ROS protect against kidney injury. Hypoxia inducible factor (HIF) and downstream mediators such as heme oxygenase 1 may serve to protect cells against ischemic injury.4

Factors that affect the integrity and function of the renal tubular epithelial cells and contribute to the reduction in GFR include (Fig. 70.7):

1. Cell death: Most tubular cells undergo cell death by apoptosis rather than necrosis. In animal models, kidney injury is ameliorated using caspase inhibitors and p53 inhibitors that decrease apoptosis.5
2. Disruption of actin cytoskeleton: A characteristic feature of sublethally injured cells is the disruption of the actin cytoskeleton. Activation of the cysteine protease calpain (partly due to increased intracellular calcium) can degrade actin-binding proteins such as spectrin and ankyrin. This leads to abnormal translocation of Na+K+-ATPase and other proteins from the basolateral membrane to the cytoplasm or apical membranes. In the proximal tubular cell, this loss of polarity results in impaired proximal reabsorption of filtrate with resultant increased distal NaCl delivery, which activates tubuloglomerular feedback.

3. Cast obstruction: Tubular cells are attached to the tubular basement membrane by α3β1 integrins, which recognize RGD (arginineglycine-aspartate) sequences in matrix proteins. Disruption of the actin cytoskeleton results in movement of integrins from basolateral positions to the apical membrane, leading to impaired cell matrix adhesion and cell detachment. Many of these detached cells are still viable and can be cultured from urine of patients with ATN. Sloughed proximal tubular cells can bind to RGD sequences in Tamm-Horsfall protein, resulting in cast formation and intratubular obstruction. In models of ischemic AKI, the elevation in tubular pressures may be inhibited by synthetic RGD peptides mitigating the obstructive process. Both increased sodium concentration in the tubular lumen resulting from lack of sodium reabsorption or back-leak (see below), as well as acidic pH observed in ATI, favor dimerization of uromodulin and cast formation. Casts seen in ATI include granular casts, waxy casts, and renal tubular epithelial cell casts.

Sites of Tubular Injury in ATN

Glomerulus

Distal tubule

Cortex
300 mOsm

Po2 50–100 mm Hg
Proximal
tubule –
segment

Outer
medulla

Medullary
thick
ascending
limb of the
loop of Henle

Po2 10–20 mm Hg
Inner
medulla
1200 mOsm

Fig. 70.5 Sites of Tubular Injury in Acute Tubular Necrosis (ATN). The S3 segment of the proximal tubule and the medullary thick ascending limb are particularly vulnerable to ischemic injury because of the combination of borderline oxygen supply and high metabolic demands.

4. Back-leak: The loss of adhesion molecules (E-cadherin) and tight junction proteins (ZO-1, occludin) weakens junctions between cells, allowing filtrate to leak back into the kidney interstitium. Although this does not alter the actual GFR at the level of the glomerulus, the net effect is a reduction in the measured GFR. Earlier dextran sieving experiments suggest only a modest effect of back-leak on the decrement of GFR in AKI (about 10%); however, in the kidney allograft with severe ATI, back-leak has been calculated to account for up to 50% of the GFR reduction.

Endothelial Cell Injury and the Development of ATN

Endothelial cell injury occurs partly as a result of acute kidney ischemia and oxidant injury.3 Endothelial injury is characterized by cell swelling, upregulation of adhesion molecules (with recruitment of inflammatory neutrophils and monocytes), and impaired vasodilation (decreased endothelial nitric oxide synthase and vasodilatory prostaglandins) and may mediate some of the impaired autoregulation and intrarenal vasoconstriction described earlier. Endothelial injury within the peritubular capillaries (vasa rectae) may produce congestion in the outer medulla, exacerbating interstitial edema and worsening hypoxic injury to the S3 segment of the proximal tubule and the thick ascending loop of Henle.

Inflammatory Factors in The Development of ATN

Although ischemia causes direct kidney cytotoxicity, tissue inflammation during reperfusion also contributes to kidney injury and may cause some of the systemic effects of AKI. Components of both the innate and the adaptive immune systems contribute to the pathogenesis of

ATN.6 The innate immune system is activated by cellular injury and certain pattern recognition molecules. Toll-like receptor 2 (TLR2) and TLR4 are upregulated within the ischemic kidney, activated by molecules released from injured cells, and induce renal epithelial cells to produce chemokines. The complement system is also activated within the tubulointerstitium after ischemia/reperfusion, predominantly by the alternative pathway. It can directly induce nearby epithelial cells to produce proinflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], IL-1β), and chemokines (e.g., MCP-1, IL-8, RANTES) that promote the infiltration of leukocytes and are also directly vasoactive.

A network of dendritic cells extends throughout the kidney interstitium, which help shape the inflammatory response within the kidney after ischemia/reperfusion, likely through their interactions with other inflammatory cell types. Neutrophils and mononuclear cells are seen in peritubular capillaries. Neutrophil activation and the release of proteases and ROS can exacerbate injury. By contrast, neutrophil depletion or the inhibition or genetic deletion of neutrophil adhesion molecules (ICAM-1) ameliorates injury in ischemic ATN. Monocytes infiltrate the kidney after reperfusion and differentiate into the M1 (proinflammatory) type exacerbating kidney injury after ischemia. These macrophages may later convert to an M2 (reparative) phenotype. Cells of the adaptive immune system, including T and B lymphocytes, also contribute to kidney injury in models of ATN, and their depletion ameliorates injury. It is not known whether these responses are antigen specific. Furthermore, some B and T cell subsets, such as T regulatory cells, help limit kidney injury.

AKI may have systemic effects on other organs.7 The injured kidney may prime and activate leukocytes, which produce proinflammatory cytokines that can mediate remote organ injury (Fig. 70.8). The lungs may be particularly vulnerable from the combined effects of volume

Vascular Factors Contributing to the
Development of Acute Tubular Necrosis
Renal ischemia

Vascular effects

Increased cytosolic
calcium in glomerular
afferent arterioles

↓ NO derived from eNOS;
↓ prostaglandins;
↑ endothelin

Endothelial injury

Endothelial cell swelling
Outer medullary
congestion

Upregulation of
adhesion molecules
(ICAM-1, P-selectin)

↑ Neutrophil adhesion

Intrarenal vasoconstriction
Impaired autoregulation

Hypoxia

↑ Reactive oxygen species

↓ GFR

Fig. 70.6 Vascular Factors Contributing to the Development of Acute Tubular Necrosis. Renal vasoconstriction and endothelial injury promote kidney ischemia and tubular injury. eNOS, Endothelial nitric oxide synthase; GFR, glomerular filtration rate; ICAM-1, intercellular adhesion molecule 1; NO, nitric oxide.

overload, increased vascular permeability and proinflammatory environment. These effects may partly account for the increased mortality in patients with AKI (see Chapter 73).

Recovery Phase

Recovery from ATI requires the restoration of tubular cell number and coverage of denuded tubular basement membrane. Marked cell proliferation occurs in recovering human ATI (see Fig. 70.3). The restoration of tubular cell number is due to the dedifferentiation and proliferation of surviving tubular cells rather than from a mesenchymal stem cell source.8 After tubular epithelial cell proliferation, the dedifferentiated cells must migrate to areas of denuded tubular basement membrane, attach to the basement membrane, and differentiate into mature polar tubular epithelial cells. The early inflammatory infiltrates of neutrophils and M1 monocytes are replaced by M2 monocytes, which support epithelial cell repair, after which their numbers decline by migration or apoptosis. When the injury process is persistent or severe, maladaptive repair may occur, leading to CKD.9

failure often is irreversible. About 20% of the cases have reversible bilateral acute cortical necrosis.

In cortical necrosis, there is microvascular and glomerular thrombosis with extensive death of kidney tissue. The process is distinct from that seen with infarction caused by arterial occlusion because some blood supply to the medulla is preserved. The type of shock, in particular placental abruption, rather than severity seems to predict the risk for cortical necrosis. Other causes include thrombotic microangiopathy, snakebite envenomation, and trauma-related hemorrhagic shock.

The diagnosis of cortical necrosis is most often considered when recovery from AKI attributed to ATN is delayed. Contrast-enhanced computed tomography (CT) may reveal characteristic anatomic distortion of the kidneys (Fig. 70.9), but the use of radiocontrast in this setting has to be considered judiciously. Calcification detected radiologically is a late and unreliable sign. Contrast angiography may show patchy loss of perfusion. Kidney biopsy may not be informative because cortical necrosis may be patchy.

ACUTE CORTICAL NECROSIS

PATHOPHYSIOLOGY AND ETIOLOGY OF POSTRENAL AKI

The same pathophysiological processes that lead to ATN can lead to bilateral acute cortical necrosis, but this only accounts for less than 2% of cases of ischemic ATN. If cortical necrosis is extensive, kidney

Obstruction must be excluded in any patient with AKI because prompt intervention can result in improvement or complete recovery of kidney function (see Chapter 61). Most causes of obstructive nephropathy

Tubular Factors in the Development of Acute Tubular Necrosis

Loss of polarity
Apical
surface
Basolateral
surface

Loss of
brush border

Ischemia and
reperfusion
Brush border

Viable
epithelial cell

Apoptotic
epithelial cell

Integrin

Tubular
lumen

Na+,K+-ATPase

Epithelial cell

Necrosis and
cell death

Luminal
obstruction

Fig. 70.7 Tubular Factors in the Development of Acute Tubular Necrosis. Loss of cell polarity results in weakening of cell-to-cell and cell matrix adhesion resulting in cast obstruction and back-leak of tubular fluid. (Modified from Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest. 2004;114[1]:5–14.)

are amenable to therapy, and the prognosis is often good if treatment or intervention is early (Chapter 61).

NEPHROTOXIC AGENTS AND MECHANISMS OF TOXICITY

The identification and avoidance of nephrotoxic agents in AKI is critical because AKI may be rapidly reversible upon removal of the offending agent. The mechanisms of nephrotoxicity include alterations in kidney hemodynamics, induction of direct tubular injury, allergic reactions resulting in interstitial nephritis, and intratubular obstruction. The list is extensive, but the more common agents are presented in Fig. 70.10

Nonsteroidal Antiinflammatory Drugs

NSAIDs commonly cause AKI in the community because of the large amounts of these drugs either prescribed or purchased over the counter. COX-2–specific NSAIDs have similar effects on kidney function as the nonselective NSAIDs and are not safer with respect to AKI.

NSAID-related AKI is most often due to a hemodynamically mediated reduction in GFR that occurs in patients who are particularly dependent on vasodilatory prostaglandins to maintain kidney perfusion.

These include elderly patients with atherosclerotic disease, volumedepleted patients, and those in sodium avid states such as cirrhosis, nephrotic syndrome, and congestive heart failure. This form of AKI is usually reversible in 2 to 7 days upon discontinuation of the drug and rarely occurs in otherwise healthy individuals. Concurrent use of

diuretics, ACE inhibitors, ARBs, and calcineurin inhibitors has been associated with an increased incidence of NSAID-related AKI. Less frequently, NSAIDs induce ATN or, even more rarely, papillary necrosis. NSAIDs may also cause an acute interstitial nephritis (AIN), often with significant proteinuria (see Chapter 64). Other renal side effects of NSAIDs include fluid and electrolyte disturbances such as sodium retention exacerbating hypertension and congestive heart failure, hyponatremia, and hyperkalemia.

Acetaminophen (Paracetamol)

Isolated ATN with acetaminophen may occur in rare cases, but kidney injury is more typically associated with acute hepatitis. Kidney and liver toxicity usually occurs when more than 15 g have been taken, but in alcoholics, normal doses may be toxic. Acetaminophen is conjugated in the liver and undergoes renal excretion. Less than 5% undergoes metabolism by P-450 (CYP2E1) enzymes to form a toxic metabolite, N-acetylimidoquinone, which is inactivated by the thiol group of glutathione. With high levels of acetaminophen, glutathione becomes depleted, and N-acetylimidoquinone can bind to thiol groups on intracellular proteins, resulting in cell injury. Because glutathione is a major intracellular antioxidant, its loss may predispose to oxidative injury of the tubular cells.

Clinically, acute liver failure and ATN only begin once glutathione levels are depleted, and clinical manifestations usually present 3 to 4 days after ingestion. N-acetylcysteine, which substitutes for glutathione by providing a free thiol group, can be protective if administered early.

Systemic Effects of Acute Kidney Injury
Lung

Brain

Volume overload
↑ Vascular permeability
↑ Neutrophil sequestration
↑ Proinflammatory cytokines

“Uremic” encephalopathy
↑ Blood-brain barrier permeability
↑ Proinflammatory cytokines

Heart
Volume overload and ↑ preload
Myocardial depression
↑ Myocyte apoptosis
↑ Proinflammatory cytokines
↑ Neutrophil trafficking

Bone marrow

Gut

Immune dysfunction
Anemia
Thrombocytopenia

Nausea and vomiting
Malnutrition

Liver
↑ Vascular congestion and permeability
Leukocyte influx
Elevated transaminases and cholestasis

Fig. 70.8 Systemic Effects of Acute Kidney Injury. Acute kidney injury may contribute to remote organ injury, partly due to abnormalities in inflammatory and immune function from renal tubular dysfunction. (Modified from Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81[10]:942–948.)

ACE Inhibitors and ARBs

Initiation of therapy with an ACE inhibitor or an ARB is commonly associated with a functional decrease in GFR that is not considered AKI. Indeed, it is well established that use of these medications is associated with improved kidney outcomes despite the initial drop in GFR that is often seen. ACE inhibitors and ARBs may also cause hemodynamically induced AKI in the setting of reduced kidney perfusion by impairing compensatory vasoconstriction of the efferent arteriole. These drugs may directly impair kidney perfusion by their antihypertensive effects. Patients in whom kidney perfusion is compromised due to dehydration, renovascular disease, or functionally impaired autoregulation are at particular risk for developing AKI after initiation of therapy. Patients chronically treated with ACE inhibitors or ARBs have an increased risk for postoperative kidney dysfunction, probably as a consequence of intraoperative hypotensive episodes.

Aminoglycosides

Aminoglycoside toxicity may occur if the dose is not adjusted to the GFR. Cationic amino groups (NH_3^+) on the drugs bind to anionic megalin on the brush border of proximal tubular epithelial cells. Following endocytosis aminoglycosides accumulate in proximal tubular cell lysosomes and can reach 100 to 1000 times their serum concentration. These drugs interfere with cellular energetics, impair intracellular phospholipases, and induce oxidative stress.10

A

B

C

D

Fig. 70.9 Imaging Showing Bilateral Acute Cortical Necrosis of the Kidneys. (A–B) Contrast-enhanced computed tomography (CT) scanning coronal images disclose remarkable distortion of the anatomic appearance of both kidneys, including irregular margins, presence of hypodensity of the renal cortices and patchy medullary enhancement. (C–D) After 60 days, repeat CT scanning (coronal view) shows complete resolution of previously observed kidney abnormalities. (From Luo X, Cielo AG, and Velez JCQ. Abnormal imaging findings of the kidneys in a patient with shock. Kidney360. 2020;1[12]:1462–1463.)

Nonoliguric AKI usually occurs after 5 to 10 days of treatment with gentamicin. Involvement of distal tubular segments may produce polyuria, potassium, and magnesium wasting. The risk for AKI correlates with the accumulation of gentamicin in proximal tubular cells and is related to the daily dose and duration of therapy. Prolonged accumulation in proximal tubular cells may allow development of AKI even after the drug has been discontinued. Additional risk factors for gentamicin toxicity include increasing age, preexisting kidney disease, hypotension, concurrent liver disease, sepsis, coadministration of vancomycin, and concurrent nephrotoxins. Aminoglycoside serum levels should be monitored to minimize nephrotoxicity. When possible, the drug should be administered in a single daily total dose, which leads to lower renal proximal tubular cell accumulation. Gentamicin, tobramycin, and netilmicin appear to have similar nephrotoxic effects. Amikacin, which has fewer amino groups per molecule, and plazomicin, a next-generation aminoglycoside, may be less nephrotoxic.

Vancomycin

The extent to which vancomycin is directly nephrotoxic is controversial.[11] The recommendation for higher vancomycin trough levels to target methicillin-resistant Staphylococcus aureus has led to recognition that vancomycin can be nephrotoxic. Vancomycin is excreted primarily by glomerular filtration, but accumulation in proximal tubule cells via basolateral secretion is thought to underlie nephrotoxicity. Experimentally, high-dose vancomycin causes oxidative stress and triggers intrarenal apoptotic pathways. In humans, high initial vancomycin trough levels greater than 15 µg/mL have been associated with nephrotoxicity in a graded fashion. Additional risk factors include total dose of more than 4 g daily, long duration of therapy, concurrent nephrotoxin or diuretic exposure, and critical illness. Vancomycin coadministration with piperacillin-tazobactam appears to increase risk for AKI, though the mechanism for this is unclear.[12] A precipitous rise in serum creatinine could be observed in a subset of cases of vancomycin-associated AKI.[13] ATN is the predominant lesion seen in experimental models of vancomycin nephrotoxicity, but case reports of human biopsies have shown both interstitial nephritis and ATN. Vancomycin can cause a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) with inflammatory kidney injury. Treatment is generally conservative. High-flux hemodialysis can be used for drug removal when levels are very high. Kidney injury from vancomycin is generally reversible.

Amphotericin B

This polyene macrolide antibiotic binds to sterols in the cell membranes of both fungal walls (ergosterol) and mammalian (cholesterol) cell membranes, resulting in the formation of aqueous pores that increase membrane permeability. Within the renal tubular cell, the subsequent sodium influx leads to increased Na+,K+-ATPase activity and depletion of cellular energy stores.14 Additionally, the standard amphotericin B formulation is suspended in the bile salt deoxycholate, which has a detergent effect on cell membranes. Nephrotoxicity relates to cumulative dosage, usually occurring after administration of 2 to 3 grams.

Early signs of nephrotoxicity include a loss of urine-concentrating ability, followed by a decrease in GFR. Hypokalemia and hypomagnesemia due to distal tubular wasting are common. A distal renal tubular acidosis may be present due to proton back-leak in the cortical collecting duct.

Prevention of nephrotoxicity requires the maintenance of high urine flow rates by saline loading during amphotericin administration.

The more expensive liposomal amphotericin B preparations reduce the incidence of AKI by approximately 50%. As amphotericin B binds more avidly to fungal ergosterol than to cholesterol, delivering the drug as a cholesterol liposome diminishes binding to tubular epithelial cell membranes without altering fungicidal activity. Additionally,

Nephrotoxic Agents Leading to Acute Kidney Injury
3. Small vessel disease
Renal vasoconstriction
NSAIDs
ACE inhibitor or ARB
Radiocontrast agents
Calcineruin inhibitors
Norepinephrine
Cocaine

2. Renal artery

1. Prerenal azotemia
Antihypertensive agents
Diuretics

Thrombotic microangiopathy
Gemcitabine,VEGF inhibitors
Calcineurin inhibitors
Mitomycin C
Clopidogrel
Quinine
Oral contraceptives

9. Renal vein

4. Glomerular disease
Rapidly progressive glomerulonephritis
Hydralazine
Propylthiouracil
Organic solvents
Levamisole adulterated cocaine

8. Postrenal obstruction
Papillary necrosis (NSAIDs, compound analgesics)
Urinary retention (anticholinergics, tricyclic antidepressants)

7. Intratubular obstruction
Crystal formation
Acyclovir
Atazanivir
Ethylene glycol
Methotrexate
Triamterene
Sulfonamide antibiotics
High-dose oral phosphate

5. Acute tubular necrosis
Amphotericin
Aminoglycosides
Foscarnet
Tenofovir, cidofovir, adefovir
Cisplatin
Ifosfamide
Acetaminophen
Heavy metals
Herbal remedies
Radiocontrast agents
Pentamidine
Organic solvents

Herbicides (paraquat)
Intravenous immunoglobulin

6. Acute interstitial nephritis
Antibiotics (penicillins, cephalosporins, rifampicin, sulfamethoxazole, ciprofloxacin)
NSAIDs
Loop and thiazide diuretics
Allopurinol
Cimetidine
Mesalazine
Proton pump inhibitors
Phenytoin

Fig. 70.10 Common nephrotoxic agents leading to acute tubular necrosis. ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal antiinflammatory drug; VEGF, vascular endothelial growth factor.

liposomal preparations do not contain deoxycholate. Amphotericin B–induced AKI is usually reversible with discontinuation of the drug, although distal tubular injury as manifested by magnesium wasting may persist.

Antiviral Therapy

Acyclovir

Nephrotoxicity is typically seen after intravenous (IV) acyclovir administration and may be due to direct tubular cell toxicity and the formation of intratubular, birefringent needle-shaped acyclovir crystals. However, kidney biopsy data suggest that AIN may be the predominant mechanism of toxicity.

Oliguric AKI typically occurs within a few days of treatment and may be associated with abdominal or loin pain. High serum levels of acyclovir due to decreased kidney clearance may produce neurologic toxicity. The AKI is usually mild and recovers on stopping the drug. Maintaining a high urine flow rate and avoiding IV bolus administration of acyclovir may be preventative.

Tenofovir

Tenofovir is a nucleoside reverse transcriptase inhibitor used to treat both HIV and hepatitis B infection. The prodrug, tenofovir disoproxil fumarate (TDF), is the most widely used therapy for HIV in the world. Tenofovir is secreted into proximal tubule cells via organic anion transporters (OATs), where it can interfere with mitochondrial DNA synthesis and upset the energy supply, resulting in characteristic enlarged, dysmorphic mitochondria. Manifestations of tenofovir nephrotoxicity include subclinical tubular defects (e.g., normoglycemic glycosuria), Fanconi syndrome, ATN, and CKD.15 Kidney manifestations can develop within weeks of drug initiation or can occur after years, but reversibility is common. Risk factors include preexisting CKD, advanced age, low CD4 count, and total dose and duration of TDF use. HIV patients exhibit a variety of kidney diseases (see Chapter 58), and biopsy should be strongly considered when kidney dysfunction does not improve after drug cessation or when resistance patterns make tenofovir critical for patient care. Tenofovir alafenamide (TAF) is a newer prodrug of tenofovir, the use of which has increased in recent years such that it is now included in many first-line drug regimens. TAF concentrates in mononuclear cells, resulting in lower plasma concentrations and reduced drug delivery to the kidney. TAF is less nephrotoxic than TDF, but cases of TAF-associated AKI have been reported.16

Other Antiviral Agents

Among antivirals used to treat HIV infection, both cobicistat and dolutegravir inhibit proximal tubular secretion of creatinine, causing a false elevation in serum creatinine. A small rise in creatinine is considered acceptable and generally occurs within 2 weeks of starting these drugs. Atazanavir, a protease inhibitor, can cause urolithiasis, crystalline-induced kidney injury, AIN, or a granulomatous interstitial nephritis. Acute presentations are largely reversible, but long-term use can lead to CKD.17 Adefovir, a second-line drug used to treat hepatitis B, was frequently nephrotoxic when prescribed at high doses, but current lowdose regimens appear safe for most patients. Foscarnet and cidofovir are well-recognized nephrotoxic antivirals.

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors can be associated with a functional decrease in GFR that is likely the result of direct renovascular effects, similar to that seen with initiation of ACE inhibitors and ARBs, and is not considered to represent AKI. In fact, the risk of AKI as a direct result of treatment with SGLT2 inhibitors is low.18 There are rare case reports of AKI due to osmotic nephrosis following initiation of an SGLT2 inhibitor. The use of SGLT2 inhibitors in CKD is covered in Chapters 32 and 33.

Immunosuppressive Agents

Calcineurin Inhibitors

Cyclosporine and tacrolimus may cause AKI due to afferent arteriolar vasoconstriction, partly mediated by endothelin. This is usually reversible upon dose reduction. Persistent injury may lead to chronic interstitial fibrosis in a striped pattern along medullary rays reflecting both the ischemic nature of the insult, as well as the development of arteriolar hyalinosis. Associated clinical features include hypertension, hyperkalemia, hyperuricemia, and wasting of phosphorus and magnesium from tubular injury. Calcineurin inhibitors also cause reversible tubular dysfunction, and are associated with the development of thrombotic microangiopathy, likely due to their effects on the endothelium (see Chapter 30).

Other Immunosuppressive Agents

The monoclonal anti-CD3 antibody (OKT3) or polyclonal antilymphocyte and antithymocyte preparations (ALG, ATG) may cause a first-dose cytokine release syndrome and prerenal azotemia secondary to capillary leak. Intravenous immunoglobulin (IVIG) can cause AKI, which may be partly mediated by the high sucrose concentration in these products. Tubular uptake of sucrose may result in osmotic cell swelling and injury. Although it does not typically cause AKI, sirolimus delays the recovery from AKI in kidney transplant patients with delayed graft function.

Anticoagulation-Related Nephropathy

AKI has been described in patients taking anticoagulants who develop an acute rise in the international normalized ratio (INR), usually to greater than 3. Most cases of anticoagulation-related nephropathy (ARN) appear within the first 8 weeks of initiating therapy in patients with underlying CKD. AKI results from glomerular hematuria with obstruction of renal tubules by red blood cell casts. The risk of ARN is thought to be highest in patients treated with warfarin, but cases in patients treated with direct acting oral anticoagulants have also been reported.19

Acute Phosphate Nephropathy

Oral sodium phosphate has been widely used as a bowel preparation for colonoscopy procedures, but recent cases of AKI have limited the use of this purgative.20 AKI associated with oral sodium phosphate is believed to be caused by phosphaturia and acute calcium-phosphate deposition within the renal tubules. Risk factors for this condition include older age, volume depletion, and underlying CKD. A similar phenomenon has been reported with use of sodium phosphate–containing enemas.

Drugs of Abuse

AKI is a common condition in those who abuse drugs and may be due to nephrotoxicity of the drug, coexistent viral infection (HIV, HCV), sepsis, infective endocarditis, or rhabdomyolysis.21

Cocaine induces intense vasoconstriction, which may lead to AKI due to severe hypertension or rhabdomyolysis. Mechanisms for rhabdomyolysis include coma and pressure necrosis, vasospasm leading to ischemic muscle injury, and adrenergic stimulation with hyperpyrexia leading to increased cellular metabolism. Cocaine may also exert direct toxic effects on the myocyte.22 Most cocaine entering the United States is contaminated by levamisole, an immunomodulator and antihelminthic agent. In humans, levamisole has been reported to cause an antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis with a necrotizing crescentic glomerulonephritis and prominent skin lesions.

Other illicit drugs associated with AKI include opiates (comaassociated, pressure-induced rhabdomyolysis); phencyclidine (rhabdomyolysis secondary to hyperpyrexia and vasoconstriction); and methamphetamines (AKI secondary to rhabdomyolysis, AIN, or acute necrotizing angiitis). Recently, synthetic cannabinoids have been implicated as a cause of AKI, although the culprit component is unclear. When available, kidney biopsy has shown ATN and more rarely AIN. In most cases, no other cause for AKI could be identified.21

Ethylene Glycol

Ethylene glycol, found in antifreeze, is a cause of both deliberate and accidental overdose. It is rapidly metabolized by alcohol dehydrogenase to glycoaldehyde and glyoxylate, which are toxic to tubular cells. Further metabolism generates oxalic acid, which can precipitate, leading to intratubular obstruction.

The diagnosis is suggested by the presence of a severe anion gap metabolic acidosis and an elevated serum osmolal gap. Calcium oxalate crystals are often seen on the urine microscopy (see Chapter 4, Fig. 4.4). Management includes inhibition of alcohol dehydrogenase with fomepizole, or IV ethanol if this agent is not available. Although there is no specific ethylene glycol level above which extracorporeal removal is mandated, hemodialysis is the quickest way to remove both parent alcohol and toxic metabolites. Methanol intoxication may present with similar metabolic abnormalities but rarely causes AKI (see Chapter 13).

Occupational Toxins

Heavy Metals

Lead intoxication usually causes a chronic nephropathy (see Chapter 65). Rarely, ATI occurs that may be associated with Fanconi syndrome. AKI may also occur in cadmium and mercury poisoning.

Organic Solvents

Organic solvents may cause ATI due to peroxidation of membrane lipids. Subacute kidney failure due to anti–glomerular basement membrane (anti-GBM) antibody disease has also been reported with exposure to halogenated hydrocarbons.

Herbal Remedies

AKI has been reported with the use of herbal remedies; however, nephrotoxicity is most often due to impurities found in unregulated formulations of these substances (e.g., lead, NSAIDs) and not the herbs specifically. Some herbs used in traditional African medicine (e.g., Cape aloes, Callilepis laureola) are common causes of AKI in parts of Africa. Aristolochic acid (found in certain traditional Chinese medicines) can cause subacute kidney failure (see Chapters 65 and 79).

Contrast-Induced Nephropathy

It is generally agreed that iodinated contrast can be nephrotoxic but that the risk of AKI with contrast administration is frequently overstated. AKI typically occurs in patients with underlying CKD and is rarely seen in patients with preserved estimated glomerular filtration rate (eGFR). In hospitalized patients, it is often difficult to determine whether a contrast CT is the primary cause of AKI, as imaging is often obtained in the setting of other potential kidney insults (e.g., infection, antibiotics). Recent studies have questioned the link of IV contrast CT with nephrotoxicity, suggesting minimal risk of AKI when low or isoosmolar contrast is administered intravenously to patients with eGFR greater than 30 mL/min/1.73 m2 23-25 Indeed, in these studies, the risks of AKI associated with contrast administration were similar among well-matched hospitalized patients who received noncontrast CT scans.

Intraarterial contrast administration, required for cardiac catheterization or renal angiography, poses a greater risk for AKI because a larger dose of iodinated material is required and is then delivered to the renal arteries in a concentrated manner. Risk factors for the development of AKI from contrast nephropathy include diabetic nephropathy, advanced age (>75 years), congestive heart failure, volume depletion, hyperuricemia, and high or repetitive doses of radiocontrast agents. Concurrent use of NSAIDs, ACE inhibitors, or diuretics may increase the risk (see Chapter 74).

TABLE 70.1

Muscle injury/ischemia

Both kidney ischemia and direct tubular epithelial cell toxicity are implicated in the pathogenesis of contrast nephrotoxicity. Typically, a biphasic hemodynamic response is seen. Initial vasodilation (lasting a few seconds to minutes) is followed by more prolonged renal vasoconstriction.

The resultant medullary hypoxia may be exacerbated by low flow in the vasa recta as a result of a contrast-induced rise in blood viscosity. An osmotic diuresis, leading to increased sodium delivery to the medullary thick ascending loop, may result in increased oxygen consumption for sodium reabsorption. Uricosuria, as well as a hyperosmolar activation of the aldose reductase-fructokinase system in the kidney, has also been proposed to play a role. Radiocontrast agents also cause direct tubular epithelial cell injury. Human studies have demonstrated low-molecular-weight proteinuria, suggestive of proximal tubular injury, partly mediated by ROS. The administration of antioxidants ameliorates contrast nephrotoxicity in animals.

OTHER SPECIFIC ETIOLOGIES OF AKI

Heme Pigment Nephropathy

Heme pigment nephropathy is a common cause of AKI and is usually secondary to the breakdown of muscle fibers (rhabdomyolysis), which release potentially nephrotoxic intracellular contents (particularly myoglobin) into the systemic circulation. Less commonly, heme pigment nephropathy may occur due to massive intravascular hemolysis. Prevention and therapy of heme pigment nephropathy are discussed in Chapter 74

Causes of Rhabdomyolysis

Muscle trauma is the most common cause of rhabdomyolysis. The initial description was by Bywaters and Beall during the bombing of London in World War II.[26] Other common causes of muscle injury include marked exercise, seizures, pressure necrosis secondary to coma, substance abuse, and limb ischemia (Table 70.1). In skeletal muscles confined to rigid compartments, cell swelling after injury may result in increased intracompartmental pressures that can impair local microvascular circulation and lead to compartment syndrome (Fig. 70.11). In the patient with substance or alcohol abuse, rhabdomyolysis is often multifactorial. Contributing causes include pressure necrosis from coma (“found down”), direct myotoxicity from ethanol, seizures, and electrolyte abnormalities (hypokalemia and hypophosphatemia). Therapy with statins may be associated with rhabdomyolysis, especially when fibrates, cyclosporine, or erythromycin are used concurrently. The risk of rhabdomyolysis appears to be highest with simvastatin and lower with newer statins such as atorvastatin and rosuvastatin. Familial myopathies such as McArdle syndrome and carnitine palmitoyl transferase deficiency should be suspected in patients with

Causes of Rhabdomyolysis

Trauma; pressure necrosis, electric shock, burns, acute vascular disease

Myofiber exhaustion

Seizures, excessive exercise, heat exhaustion

Toxins

Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snakebite

Drugs

Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics

Electrolyte disorders

Hypophosphatemia, hypokalemia, hyperosmolar states

Infections

Viral: Influenza, HIV, coxsackievirus, Epstein-Barr virus, COVID-19

Bacterial: Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus

Familial

McArdle disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia

Other

Hypothyroidism, polymyositis, dermatomyositis

A

B

Fig. 70.11 Compartment Syndrome. (A) Severe calf swelling due to anterior and posterior compartment syndromes after ischemia-reperfusion. (B) Appearance after emergency fasciotomy: note edematous muscle and hematoma. (Courtesy Mr. M.J. Allen, FRCS.)

Pathophysiology of Heme Pigment Nephropathy
Compartment syndrome

Fluid sequestration

Severe
hemolysis

Muscle injury

Inflammatory
cascade

Myoglobin
(?other toxins)

Scavenging
of nitric oxide

Volume
depletion

Renal
vasoconstriction
Renal
hypoperfusion

Hemoglobin

Reactive oxygen
species
Intraluminal
cast
obstruction

Heme-protein–mediated
tubular toxicity

ATN

Fig. 70.12 Pathophysiology of Heme Pigment Nephropathy. ATN, Acute tubular necrosis.

recurrent episodes of rhabdomyolysis associated with muscle pain, positive family history, onset in childhood, and the absence of other identifiable causes. In developing countries, ingestion of hair dye containing paraphenylene-diamine as a means of self-harm may cause AKI secondary to rhabdomyolysis. Snake and spider bites, bee stings and venomous caterpillar bites may all cause rhabdomyolysis (see Chapter 71). There have been several reports of rhabdomyolysis associated with COVID-19 infection and recreational exposure to bath salts (3,4-methylenedioxypyrovalerone).

haptoglobin. With massive hemolysis, however, haptoglobin stores become exhausted. Hemoglobin (69 kDa) then dissociates into α β dimers (34 kDa), which are small enough to be filtered, resulting in hemoglobinuria, hemoglobin cast formation, heme uptake by proximal tubular cells, ATN, and filtration failure. Causes of hemoglobinuric AKI include incompatible blood transfusion, autoimmune hemolytic anemia, malaria (blackwater fever), glucose-6-phosphate dehydrogenase deficiency, paroxysmal nocturnal hemoglobinuria, march hemoglobinuria, and toxins (dapsone, venoms).

Causes of Hemoglobinuria

Pathogenesis of Heme Pigment Nephropathy

Intravascular hemolysis results in circulating free hemoglobin. If the hemolysis is mild, the released hemoglobin is bound by circulating

The kidney injury is due to a combination of factors including volume depletion, renal vasoconstriction, direct heme-protein–mediated cytotoxicity, and intraluminal cast formation (Fig. 70.12).27 Volume depletion is often prominent in patients with rhabdomyolysis owing to the sequestration of up to 15 to 20 L of fluid in injured muscle. Volume depletion activates the sympathetic nervous system and reninangiotensin system, resulting in renal vasoconstriction. This may be exacerbated by the scavenging of nitric oxide by circulating heme proteins.

Myoglobin (17 kDa) is freely filtered at the glomerulus and is toxic to tubular epithelial cells. The heme center of myoglobin may directly induce lipid peroxidation and kidney injury, and liberated free iron catalyzes the formation of hydroxyl radical through the Fenton reaction, inducing free radical–mediated injury. It has recently been demonstrated that myoglobin released from damaged skeletal muscle activates platelets, which, in turn, induce macrophages in the kidney to produce macrophage extracellular traps (METs).28 METs have been implicated in the development of kidney injury in mice, though it remains unclear exactly which components of METs are responsible. Renoprotection has been demonstrated in animal models with free iron scavengers and various antioxidants. Finally, the precipitation of myoglobin with uromodulin (Tamm-Horsfall protein) and sloughed proximal tubular cells may result in obstructing casts in the distal nephron, especially when tubular flow rates are low due to volume depletion. The binding of myoglobin to uromodulin is enhanced in acidic urine.

Atheroembolic Kidney Disease

This underrecognized condition occurs predominantly in older patients with atherosclerotic vascular disease (see also Chapter 43). It can occur spontaneously but is most commonly precipitated by arteriography, vascular surgery, thrombolysis (streptokinase and tissue plasminogen activator), or anticoagulation. Destabilization of atherosclerotic plaques primarily in the aorta above the level of the renal arteries results in showers of cholesterol that lodge in small arteries in the kidneys (see Fig. 43.12) and the lower extremities (see Fig. 43.11). Characteristic needle-shaped clefts may be seen on kidney or skin biopsy, denoting the localization of cholesterol plaques before dissolution during tissue fixation (Fig. 43.12). The cholesterol emboli produce an inflammatory reaction and occlusion of the vasculature.

Renal Artery or Vein Occlusion

AKI can be caused by bilateral renal artery occlusion, or unilateral occlusion in the setting of a single functioning kidney (see also Chapter 43). Thrombosis or embolization (noncholesterol) of the renal artery or its intrarenal branches are more common in elderly patients. Atrial fibrillation is an important risk factor for renal emboli. Aortic dissection may also progress to occlude the renal arteries. Renal vein thrombosis most commonly occurs in the setting of nephrotic syndrome and rarely may cause AKI if bilateral.

Acute Interstitial Nephritis

This is most commonly a drug-induced phenomenon and is an important differential diagnosis in AKI because removal of the offending agent can result in reversal of the condition. Less commonly, interstitial nephritis may be due to infection or immune-mediated diseases (see Chapter 64).

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) should be considered when a patient presents with AKI and thrombocytopenia, although the condition may occur in the absence of a low platelet count (see also Chapter 30).

TABLE 70.2

Syndrome

Causes of Pulmonary-Renal

Anti-GBM Disease (Goodpasture)
Systemic vasculitis
ANCA associated:
- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis
- Drugs (penicillamine, hydralazine, propylthiouracil)

Immune complex disease:
- Lupus
- IgA vasculitis
- Mixed cryoglobulinemia
- Rheumatoid vasculitis

Infection

Severe bacterial pneumonia, postinfectious glomerulonephritis, legionella, leptospirosis, hantavirus, infective endocarditis

Pulmonary edema
and AKI

Volume overload in severe left ventricular failure

Multiorgan failure

Acute respiratory distress syndrome and AKI

Other

Paraquat poisoning, renal vein or inferior vena cava thrombosis with pulmonary emboli

AKI, Acute kidney injury; anti-GBM, anti–glomerular basement membrane; ANCA, antineutrophil cytoplasmic antibody; IgA, immunoglobulin A.

Glomerular Disease
All types of glomerular disease (see Section 4) may present with AKI, but it is more commonly seen with forms of acute glomerulonephritis such as postinfectious glomerulonephritis, ANCA-associated small-vessel vasculitis, anti-GBM disease, lupus nephritis, and immunoglobulin A nephropathy. In nephrotic syndrome, AKI may occur due to volume depletion from diuretic use, superimposed ATN, renal vein thrombosis, or rarely from superimposed acute glomerulonephritis (e.g., anti-GBM disease in membranous nephropathy). Minimal change disease in adults is the most common nephrotic disorder associated with AKI.

Pulmonary-Renal Syndromes
The term pulmonary-renal syndrome usually describes the presence of pulmonary hemorrhage in a patient with acute glomerulonephritis. It can be caused by anti-GBM disease (Goodpasture syndrome), systemic vasculitis, or systemic lupus erythematosus (see Chapters 25–27). Patients with pulmonary-renal syndrome require urgent evaluation, and specific testing for these diseases should be pursued.

A similar clinical presentation may occur in patients with pulmonary infection and AKI, or in the setting of pulmonary edema secondary to volume overload from AKI. Other conditions that may masquerade as a pulmonary-renal syndrome are outlined in Table 70.2

SPECIFIC CLINICAL SITUATIONS

AKI in the Patient With Sepsis

Sepsis accounts for up to 50% of cases of AKI in intensive care unit patients, and septic AKI requiring renal replacement therapy is associated with mortality rates as high as 50% to 60%.[29] The traditional model of hypotension and vasoconstriction leading to ischemic ATN has been challenged because in early sepsis, renal blood flow is often normal or even increased. Moreover, the severe drop in GFR observed with sepsis is out of proportion to the relatively mild histologic injury seen on kidney biopsies, and on autopsy only 22% of patients with sepsis-associated AKI had histologic features of ATN.30

The pathogenesis of sepsis-associated AKI is mediated by molecules released from pathogens (lipopolysaccharide, flagellin, lipoteichoic acid, DNA), or injured cells, which activate the innate immune system.31,32 This leads to the activation of a wide range of cellular and humoral mediator systems, including the cytokine cascade (TNF-a, IL-1β, IL-6); the complement, coagulation, and fibrinolytic systems; increased oxidative stress; and the release of mediators such as eicosanoids, platelet-activating factor, endothelin-1, and nitric oxide.

Renal endothelial cells can be damaged in the procoagulant milieu and upregulate their expression of adhesion molecules, further amplifying the immune response. Disruption of the renal microcirculation ensues, with local areas of cortical ischemia despite maintenance of normal renal arterial blood flow. Ligation of toll-like receptors on tubular cells (TLR-4) leads to mitochondrial dysfunction, oxidative stress, and severe apoptosis. The mechanism for the abrupt GFR decline in early sepsis likely involves efferent arteriolar vasodilation. Therapies that promote efferent arteriolar vasoconstriction may be beneficial. Treatment with arginine vasopressin, which constricts the efferent more than the afferent arteriole, was associated with reduced progression to the most severe category of AKI in patients with septic shock.33 Administration of large volumes of IV fluid is common in the early resuscitation phase of sepsis. Isotonic crystalloid solutions with supraphysiologic concentrations of chloride (e.g., normal saline) are associated with an increased incidence of AKI compared with balanced crystalloid solutions (e.g., lactated ringers and plasmalyte), likely due to intense afferent arteriolar vasoconstriction resulting from increased chloride delivery to the macula densa. Sepsis may lead to multiorgan failure, and affected patients may experience repeated episodes of AKI due to nephrotoxic drug exposure or hospital-acquired infections. Maladaptive repair processes can lead to CKD following AKI in sepsis.

AKI in COVID-19

AKI is a common complication of COVID-19; ATN is the predominant mechanism of injury. Cases of collapsing focal segmental glomerulosclerosis have also been reported; these patients typically present with AKI in addition to nephrotic range proteinuria. Kidney disease in COVID-19 is discussed further in Chapter 59.

AKI in the Trauma Patient

AKI significantly increases mortality among those with severe trauma.34 Mechanisms for kidney injury include rhabdomyolysis (earthquake victims, crush injuries, burns), ATN from hypovolemic shock, or abdominal compartment syndrome due to massive hemorrhage or aggressive hydration. Direct kidney injury may result from penetrating (gunshot, stab wound) or more commonly blunt trauma (fall, motor vehicle collision, assault, sports injury). Proper diagnosis of these injuries requires a contrast-enhanced CT with delayed imaging, otherwise late extravasation from the kidney pelvis or ureters may be missed. Management is generally conservative, but emergent nephrectomy may be required.

AKI in the Postoperative Patient

Postoperative AKI is commonly due to perioperative hemodynamic instability, volume depletion, and/or nephrotoxin exposure.

After Cardiac Surgery

Risk factors for postoperative AKI include duration of cardiac bypass, preoperative kidney function, hyperuricemia, age, diabetes, valvular surgery, blood transfusions, and poor cardiac function.35 The surgery is often performed with the patient cooled to less than 30°C to protect cells against ischemic injury; however, systemic hypothermia may cause intravascular coagulation. Aortic instrumentation and crossclamping may lead to renal atheroembolism. Cardiac bypass causes loss of pulsatile flow and exposure of blood to a nonendothelialized surface, resulting in activation of neutrophils, platelets, complement, and fibrinolytic systems. Significant hemolysis and hemoglobinuria may also occur. Perioperative myocardial infarction or left ventricular dysfunction may impair kidney perfusion postoperatively, although the low cardiac output is often transient (myocardial stunning) and recovers within 24 to 48 hours. Atrial fibrillation is common and may be associated with peripheral embolization. Off-pump coronary artery bypass operations may have a lower risk of AKI than surgeries involving cardiopulmonary bypass.

After Vascular Surgery

AKI is common after abdominal aortic aneurysm repair. The risk appears to be lower with endovascular versus open repair.36 Mechanisms for AKI include ischemic ATN due to prolonged aortic cross-clamping, renal artery thromboembolism or dissection, and cholesterol atheroemboli. Additional complications specific to endovascular repair include contrast nephropathy and kidney ischemia due to endograft malpositioning or migration. In patients with peripheral vascular disease, there is often ischemic kidney disease. Preoperative reduction in eGFR is the strongest predictor of the risk for postoperative AKI.

Abdominal Compartment Syndrome

Markedly raised intraabdominal pressures (>20 mm Hg) may occur after trauma, after abdominal surgery, or secondary to massive fluid resuscitation and can cause AKI. Particularly vulnerable are patients with low mean arterial pressures, as this further compromises abdominal perfusion pressure.37 The multifactorial mechanisms of AKI likely include increased kidney venous pressure and vascular resistance, as well as a drop in cardiac output from decreased venous return and reduced ventricular compliance. Intraabdominal pressures are best estimated by measurement of intravesical (bladder) pressures. Efforts to reduce intraabdominal pressures, including paracentesis, nasogastric suction, ultrafiltration, or surgical decompression, may improve kidney function.

AKI and Liver Disease

AKI is common in patients with cirrhosis. The differential diagnosis is typically between prerenal AKI, ATN, and hepatorenal syndrome. The pathophysiology of hepatorenal syndrome is discussed in Chapter 76. Assessment of intravascular volume status can be difficult, and a therapeutic trial of volume replacement is typically undertaken. Risk factors for AKI in this population include hypovolemia, GI bleeding, and infection (particularly spontaneous bacterial peritonitis). Severe malnutrition and decreased muscle mass may be masked by the presence of edema; in these settings, a normal serum creatinine can represent a significant loss of GFR. Rarely, the same etiologic agent may be responsible for both the liver and kidney injury. This occurs with certain infections (e.g., leptospirosis, hantavirus) and nephrotoxic agents (Table 70.3). Cholemic nephropathy, AKI secondary to bile cast mediated tubular injury, has been described in obstructive jaundice.

AKI in Heart Failure (Cardiorenal Syndrome)

The development of AKI in patients with decompensated heart failure is common and is associated with poor prognosis. Reduced kidney perfusion secondary to decreased cardiac output has long been considered the primary cause; however, there are important contributions from right ventricular dysfunction leading to kidney venous hypertension and from activation of renin angiotensin and sympathetic nervous systems.38

AKI in the Cancer Patient

Patients with cancer are prone to AKI due to the underlying malignancy and its treatment (see Chapter 67). In a large European population, the incidence of AKI was 18% in the year following cancer diagnosis, and AKI occurs commonly in critically ill cancer patients.[39] Prerenal azotemia is common in cancer patients due to the high frequency of vomiting and diarrhea, and urinary tract obstruction must always be ruled out (Table 70.4). More specific causes of intrarenal AKI are noted in the following sections.

Tumor Lysis Syndrome

Necrosis of tumor cells may release large amounts of nephrotoxic intracellular contents (uric acid, phosphate, xanthine) into the circulation. This usually occurs after treatment of lymphoma (particularly

TABLE 70.3

Causes of AKI and Liver

Prerenal azotemia	Diuretic use, gastrointestinal loss, large-volume paracentesis, hypoalbuminemia
Disease	Hepatorenal syndrome Acute tubular necrosis Hyperbilirubinemia (bile cast nephropathy), sepsis, GI hemorrhage
Drugs	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampin, isoniazid, anesthetic agents, sulfonamides, anticonvulsants (DRESS syndrome), allopurinol, methotrexate, aspirin (Reye syndrome)
Infections	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis
Other	Papillary necrosis, inhalation of chlorinated hydrocarbons, mushroom poisoning (Amanita phalloides), carbon tetrachloride

AKI, Acute kidney injury; DRESS, drug reaction with eosinophilia and systemic symptoms; GI, gastrointestinal; NSAID, nonsteroidal antiinflammatory drug.

TABLE 70.4

Burkitt lymphoma) and leukemia but may occur with solid tumors. Rarely, a spontaneous form of tumor lysis syndrome occurs in patients with rapidly growing tumors that have outstripped their blood supply. AKI occurs when crystals of uric acid, calcium phosphate, and xanthine precipitate in the renal tubules causing obstruction and inflammation. Hyperuricemia may also contribute to AKI by crystal-independent mechanisms including renal vasoconstriction and oxidative injury.40 Risk factors for tumor lysis syndrome include preexisting CKD, bulky and rapidly proliferating tumors, volume depletion, and acidic urine. The AKI is typically oligoanuric, and the condition should be suspected in patients with high lactate dehydrogenase levels suggestive of massive cell lysis. Markedly elevated phosphate and urate levels may be found. Hyperkalemia may be prominent and life-threatening. Prevention and therapy of tumor lysis syndrome are discussed in Chapter 67

Hypercalcemia

Hypercalcemia is common in advanced cancer and may result from lytic bone metastases, overproduction of 1,25-dihydoxyvitamin D (predominantly lymphomas), or production of parathyroid hormone–related peptide. Hypercalcemia causes nausea, vomiting, and polyuria, and AKI in this setting is often driven by volume depletion. Additional mechanisms for hypercalcemia-induced AKI include direct intrarenal vasoconstriction and intratubular obstruction.

Chemotherapeutic Agents

Cisplatin is commonly associated with nonoliguric AKI, and nephroxicity is the most common dose-limiting side effect of this drug.41 Cisplatin accumulates in mitochondria inhibiting oxidative phosphorylation, resulting in excessive reactive oxygen formation and impairment in ATP generation, leading to cell death. Tubular injury affects both the proximal and distal nephrons and clinically may be associated with magnesium wasting, impaired urinary concentration, and rarely salt wasting with volume depletion. Prophylaxis against nephrotoxicity includes volume loading and reducing the dose when possible. Although kidney impairment may persist after treatment, progressive decline in GFR is unusual. When combined with bleomycin and vinca alkaloids, cisplatin is also associated with thrombotic microangiopathy. The alternative agent carboplatin appears to be less nephrotoxic.

Ifosfamide is a cyclophosphamide analog with a nephrotoxic metabolite, chloroacetaldehyde. AKI is usually mild, although

Causes of AKI in Patients With Cancer

Prerenal

Nausea and vomiting, hypercalcemia, cardiomyopathy secondary to chemotherapy

Vascular

Thrombotic microangiopathy (adenocarcinoma of stomach; cancer of the breast, prostate, lung, or pancreas; radiation nephropathy), renal vein thrombosis secondary to hypercoagulability, DIC (acute promyelocytic leukemia)

Glomerular

Rapidly progressive glomerulonephritis

Acute tubular necrosis

Sepsis and antibiotic nephrotoxicity

Malignant infiltration

Lymphoma, acute lymphoblastic leukemia

Intraluminal obstruction

Tumor lysis syndrome, myeloma cast nephropathy

Postrenal obstruction

Transitional cell carcinoma ureters and bladder, prostatic obstruction, extrinsic ureteral compression (tumor, nodes, retroperitoneal fibrosis)

Chemotherapeutic Agents
Tubular toxicity

Cisplatin, ifosfamide, plicamycin (mithramycin), imatinib, pemetrexed, pentostatin, high-dose bisphosphonates

Thrombotic microangiopathy

Mitomycin C, gemcitabine, cisplatin, CNIs, anti-VEGF therapies

Other mechanisms

Capillary leak syndrome (IL-2 therapy), AIN (interferon α, check point inhibitors, lenalidomide), intraluminal obstruction (methotrexate)

AIN, Acute interstitial nephritis; AKI, acute kidney injury; CNI, calcineurin inhibitor; DIC, disseminated intravascular coagulation; IL-2, interleukin-2; VEGF, vascular endothelial growth factor.

proximal tubular dysfunction (Fanconi syndrome) and hypokalemia may be prominent and sometimes persistent.

High-dose methotrexate and its metabolites can precipitate within the tubular lumen and cause AKI. Risk factors for drug crystallization include acid urine, volume depletion, impaired GFR, and concurrent nephrotoxin exposure. Aggressive hydration and urinary alkalinization (pH >7) can reduce the risk for nephrotoxicity.

Gemcitabine is a nucleoside analog that causes AKI primarily by damaging the renal endothelium. The most common manifestation is a thrombotic microangiopathy that develops 1 to 2 months following drug completion. AKI is often accompanied by new onset hypertension

or worsening of existing hypertension. Laboratory evidence of systemic hemolysis is common. AKI due to thrombotic microangiopathy may also be caused by mitomycin and by drugs that inhibit vascular endothelial growth factor pathways (e.g., bevacizumab, tyrosine kinase inhibitors).42

Immune checkpoint inhibitors (e.g., ipilimumab, nivolumab, and pembrolizumab) all increase the risk of AKI. Several case series have identified AIN as the predominant mechanism of AKI, although TMA and immune complex–mediated glomerulonephritis have also been observed. Additional chemotherapeutic agents that may cause AKI are listed in Table 70.4

SELF-ASSESSMENT QUESTIONS

1. Acute tubular injury predominantly affects which segments of the nephron?
A. Proximal convoluted tubule and loop of Henle
B. Proximal tubule and distal convoluted tubule
C. Loop of Henle and distal convoluted tubule
D. Distal convoluted tubule and collecting ducts
E. All tubular segments of the nephron equally
2. What is the most likely mechanism by which nonsteroidal antiinflammatory drugs cause AKI in a patient with systolic heart failure?
A. Impaired efferent arteriole vasodilation
B. Impaired efferent arteriole vasoconstriction
C. Impaired tubuloglomerular feedback
D. Impaired afferent arteriole vasodilation
E. Impaired afferent arteriole vasoconstriction
3. Which of the following nephrotoxic agents causes AKI predominantly by the formation of intratubular crystals?
A. Cisplatin

B. Methotrexate
C. Gentamicin
D. Amphotericin
E. Tacrolimus
4. How does tubular injury (acute tubular necrosis) cause a drop in glomerular filtration rate?
A. Efferent arteriole vasoconstriction and increased hydraulic pressure in Bowman’s space
B. Afferent arteriole vasoconstriction and increased hydraulic pressure in Bowman’s space
C. Efferent arteriole vasoconstriction and decreased hydraulic pressure in Bowman’s space
D. Afferent arteriole vasoconstriction and decreased hydraulic pressure in Bowman’s space
E. Efferent arteriole vasodilation and unchanged hydraulic pressure in Bowman’s space

REFERENCES

1. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
2. Liano F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int. 1996;50(3):811–818.
3. Zuk A, Bonventre JV. Acute kidney injury. Annu Rev Med. 2016;67:293–307.
4. Schley G, Klanke B, Schodel J, et al. Hypoxia-inducible transcription factors stabilization in the thick ascending limb protects against ischemic acute kidney injury. J Am Soc Nephrol. 2011;22(11):2004–2015.
5. Havasi A, Borkan SC. Apoptosis and acute kidney injury. Kidney Int. 2011;80(1):29–40.
6. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121(11):4210–4221.
7. Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81(10):942–948.
8. Humphreys BD, Czerniak S, DiRocco DP, Hasnain W, Cheema R, Bonventre JV. Repair of injured proximal tubule does not involve specialized progenitors. Proc Natl Acad Sci U S A. 2011;108(22):9226–9231.
9. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol. 2015;11(5):264–276.
10. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79(1):33–45.
11. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. Ther Adv Endocrinol Metab. 2016;7(3):136–147.
12. Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL. Vancomycin Plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. Crit Care Med. 2018;46(1):12–20.
13. Velez JCQ, Obadan NO, Kaushal A, et al. Vancomycin-associated acute kidney injury with a Steep rise in serum creatinine. Nephron. 2018;139(2):131–142.
14. Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine (Baltim). 2010;89(4):236–244.
15. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol. 2013;24(10):1519–1527.
16. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, doubleblind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606–2615.
17. Hara M, Suganuma A, Yanagisawa N, Imamura A, Hishima T, Ando M. Atazanavir nephrotoxicity. Clin Kidney J. 2015;8(2):137–142.
18. Zhao M, Sun S, Huang Z, Wang T, Tang H. Network meta-analysis of Novel glucose-Lowering drugs on risk of acute kidney injury. Clin J Am Soc Nephrol. 2020;16(1):70–78.
19. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. J Thromb Haemost. 2016;14(3):461–467.
20. Markowitz GS, Perazella MA. Acute phosphate nephropathy. Kidney Int. 2009;76(10):1027–1034.
21. Pendergraft 3rd WF, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL. Nephrotoxic effects of common and emerging drugs of abuse. Clin J Am Soc Nephrol. 2014;9(11):1996–2005.

22. Gitman MD, Singhal PC. Cocaine-induced renal disease. Expert Opin Drug Saf. 2004;3(5):441–448.
23. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality

iodinated contrast material. Radiology. 2013;267(1):94–105.
24. McDonald RJ, McDonald JS, Carter RE, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology. 2014;273(3):714–725.
25. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol. 2016.
26. Beall D, Bywaters EGL, Belsey RHR, Miles JAR. A case of crush injury with renal failure. Brit Med J. 1941;1941:432–434.
27. Panizo N, Rubio-Navarro A, Amaro-Villalobos JM, Egido J, Moreno JA. Molecular mechanisms and Novel therapeutic Approaches to rhabdomyolysis-induced acute kidney injury. Kidney Blood Press Res. 2015;40(5):520–532.
28. Okubo K, Kurosawa M, Kamiya M, et al. Macrophage extracellular trap formation promoted by platelet activation is a key mediator of rhabdomyolysis-induced acute kidney injury. J Nat Med. 2018;24(2):232–238.
29. Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM. Sepsis-associated acute kidney injury. Semin Nephrol. 2015;35(1):2–11.
30. Langenberg C, Bagshaw SM, May CN, Bellomo R. The histopathology of septic acute kidney injury: a systematic review. Crit Care. 2008;12(2):R38.
31. Martensson J, Bellomo R. Sepsis-induced acute kidney injury. Crit Care Clin. 2015;31(4):649–660.
32. Shum HP, Yan WW, Chan TM. Recent knowledge on the pathophysiology of septic acute kidney injury: a narrative review. J Crit Care. 2016;31(1):82–89.
33. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med. 2010;36(1):83–91.
34. Stewart IJ, Sosnov JA, Howard JT, Chung KK. Acute kidney injury in critically injured Combat Veterans: a Retrospective Cohort study. Am J Kidney Dis. 2016;68(4):564–570.
35. O’Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: current understanding and future directions. Crit Care. 2016;20(1):187.
36. Schermerhorn ML, O’Malley AJ, Landon BE. Long-term outcomes of abdominal aortic aneurysm repair. N Engl J Med. 2015;373(21):2088–2089.
37. Mohmand H, Goldfarb S. Renal dysfunction associated with intraabdominal hypertension and the abdominal compartment syndrome. J Am Soc Nephrol. 2011;22(4):615–621.
38. Braam B, Joles JA, Danishwar AH, Gaillard CA. Cardiorenal syndromecurrent understanding and future perspectives. Nat Rev Nephrol. 2014;10(1):48–55.
39. Cohen EP, Krzesinski JM, Launay-Vacher V, Sprangers B. Onconephrology: Core Curriculum 2015. Am J Kidney Dis. 2015;66(5):869–883.
40. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844–1854.
41. Latcha S, Jaimes EA, Patil S, Glezerman IG, Mehta S, Flombaum CD. Long-term renal outcomes after cisplatin treatment. Clin J Am Soc Nephrol. 2016;11(7):1173–1179.
42. Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. Am J Kidney Dis. 2015;66(5):857–868.

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Acute Kidney Injury in the Tropics

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Approximately 40% of the world population lives in the tropics, and this proportion is expected to rise to 60% by 2060. Tropical countries have high sociopolitical-economic heterogeneity, which influences health care. Facilities providing sophisticated care coexist with lack of basic public sector health infrastructure.1-3

Acute kidney injury (AKI) epidemiology in the tropics reflects these inequalities. In wealthy areas of the main cities and tertiary hospitals, AKI epidemiology is similar to that found in high-income countries in nontropical areas, and AKI principal causes are ischemia and drug nephrotoxicity. In contrast, in remote small cities, in vulnerable neighborhoods of large cities, and in rural zones, AKI is frequently community acquired, affecting previously healthy younger individuals. In those settings, infectious diarrhea, tropical infectious diseases, poisonous animals, natural medicines, and poor obstetric care are common causes of AKI.1 2 Poverty, malnutrition, lack of quality sanitation, deficient public health systems, and uncontrolled urbanization are frequent and add significantly to the disease burden. Access to kidney replacement therapy (KRT) may be limited because of nonavailability and costs.2-4 Epidemiologic data for community-acquired AKI in tropical countries showed a high frequency and high early mortality.2-3

There is regional variability in the cause of AKI in the tropics. Malaria, leptospirosis, diarrheal diseases, and venomous snakebite are common causes in South Asia. Malaria, diarrheal diseases, obstetric accidents, and indigenous herbal remedies are frequent in Africa. Malaria, leptospirosis, dengue fever, animal envenomation, and obstetric complications are important in Latin America.1-4 Acute decreases in glomerular filtration rate (GFR) associated with dehydration from prolonged strenuous work in an unhealthy environment has been described in agricultural workers (see Chapter 66).5 The long-term morbidity and mortality of tropical disease–associated AKI are nearly unknown.

SNAKEBITE

Snakebite is a neglected public health occupational hazard. Economically deprived populations living in rural communities are affected disproportionately. It has been suggested that snakebite envenomation causes 120,000 global deaths annually, with the highest burden in South and Southeast Asia, Latin America, and sub-Saharan Africa.6 This is likely an underestimate because the data are based on hospital admissions. In 2019 the World Health Organization (WHO) released a strategy aiming to reduce snakebite-associated death and disability by 50% before 2030.7

Snake venoms are complex, with significant inter- and intraspecies variation. AKI is an important complication of snake venoms and may develop after bites by hemotoxic or myotoxic snakes belonging to the Viperidae and Elapidae families, such as Russell’s viper, saw-scaled viper, puff adder, rattlesnake, tiger snake, green pit viper, Bothrops, Lachesis, South American rattlesnake (Crotalus), boomslang, gwardar,

dugite, Hypnale, Cryptophis, and sea snakes. AKI is more frequent after Russell’s viper bites (Fig. 71.1) in Asia and Bothrops and Crotalus bites in Latin America.1 8-10 In a single center report from India, 21% of 866 snakebite patients over a 10-year period had developed AKI.11 AKI prevalence is higher in children, probably because of the higher venom dose in relation to the body size.1 10

Clinical and Laboratory Features

Clinical manifestations depend on the nature and injected dose of venom. Local pain, swelling, blistering, ecchymosis and tissue necrosis at the bite site, and coagulation abnormalities leading to bleeding diathesis are frequent in Russell’s viper and Bothrops bites (Figs. 71.2 and 71.3). Neurotoxicity (paralysis) and rhabdomyolysis (myalgia and cola-colored urine) may occur after sea snake and Crotalus bites 1 8-11 Other uncommon manifestations include myocardial injury and hypopituitarism.12 13

AKI develops within a few hours (snake venom concentrates in kidney minutes after the bite) to as late as 96 hours after the accident.1 8-11

The AKI is usually oliguric and catabolic. Oliguria generally lasts for 1 to 2 weeks, and its persistence suggests the likelihood of acute cortical necrosis, which can be confirmed by kidney biopsy or a contrastenhanced computed tomography scan.1 8-11 Although kidney function usually recovers, AKI-associated snakebite has been associated with chronic kidney disease (CKD) in both adults and children on longterm follow-up.14 AKI after snakebite may aggravate kidney dysfunction in CKD of unknown ethology in agricultural workers.15

Laboratory investigation may disclose hemolysis (elevated free serum hemoglobin and lactate dehydrogenase and reduced haptoglobin), along with hypofibrinogenemia, reduced factors V, X, and XIIIA, protein C and antithrombin C, and elevated fibrin degradation products. Rhabdomyolysis may be present. Other findings include leukocytosis and elevated hematocrit as a result of hemoconcentration.1 8-11

Laboratory features suggestive of thrombotic microangiopathy (TMA) were described in 19% cases,16 related with severe and prolonged AKI and more likely to be associated with acute cortical necrosis. Elevations in urinary kidney structural biomarkers can predict AKI following Russell’s viper bites.17

Pathology

Grossly, the kidneys may have petechial hemorrhages. On light microscopy, acute tubular cell injury ranging from mild changes to overt tubular necrosis, with hyaline or pigment casts, variable degree of interstitial edema and infiltration, and scattered hemorrhages are usually found. Mesangiolysis may occur (especially with Crotalid envenomation), and vessels may show fibrin thrombi. Electron microscopic findings include dense intracytoplasmic bodies representing degenerated organelles in the proximal tubules and electron-dense mesangial deposits. Less common findings are acute interstitial nephritis, necrotizing vasculitis, and proliferative and crescentic immune-complex glomerulonephritis (GN). Acute cortical necrosis is seen in about 20% to 25% of cases after Russell's viper and Echis carinatus bites and has been described after Bothrops bites.1 8-11

Pathogenesis

Fig. 71.1 Russell's Viper. This large snake is an important cause of venomous snakebite–induced acute kidney injury in Asia.

Snake venom is a mixture of enzymes, toxins, peptides, carbohydrates, lipids, metals, biogenic amines, and nucleotides. Factors potentially involved in kidney injury include direct tubular toxicity, hemodynamic instability, hemolysis, rhabdomyolysis, systemic inflammation, glomerular deposition of microthrombi, oxidative stress, hyperuricemia, release of cytochrome c, and apoptosis of tubular epithelial cells.1 8-11 18-20

Management

Key steps include early administration of specific monovalent antivenom, appropriate volume replacement, maintenance of adequate urine output, correction of electrolyte abnormalities, administration of tetanus immunoglobulin, and treatment of infections.1 8-11 Locally available polyvalent antivenom is effective against envenoming by multiple or unknown snakes.21 Nonavailability of antivenom in rural hospitals and poor infrastructure that hampers transportation to health centers delay antivenom administration and may contribute to high mortality.1 8-11 22 A recent systematic review highlighted the lack of high-quality evidence supporting the safety and efficacy of antivenom or other interventions in preventing or treating AKI.23 Limited availability and the risk for side effects have encouraged the exploration of alternatives for antivenom therapies, but none has shown efficacy.24 Therapeutic plasma exchange in cases with TMA was not effective.16

ARTHROPODS

Bees

Fig. 71.2 Necrotic Finger Injury After Bothrops Snakebite. (Courtesy Carlos A.C. Mendes, São José do Rio Preto, Brazil.)

Hundreds of simultaneous bee stings or multiple stings from wasps, yellow jackets, or hornets cause a multifaceted clinical picture comprising intravascular hemolysis; rhabdomyolysis; bleeding; cardiovascular, hepatic, and pulmonary injury; and severe AKI, with high mortality.1 25 26 The potential mechanisms include direct venom nephrotoxicity, intrarenal vasoconstriction, hemoglobinuria, myoglobinuria, hypotension, TMA, and inflammatory and oxidative stress pathways activation.27 Rarely, AKI can develop following a single sting, either due to anaphylactic reaction or secondary to TMA.28 Kidney histology shows acute tubular necrosis.1 27 The high morbidity and lethality of massive bee attacks has prompted the development of an antivenom, which was effective in protecting against rhabdomyolysis and hemolysis in mice.29

Caterpillars

Fig. 71.3 Hemorrhagic Blister Developing a Few Hours After Bothrops Snakebite. (Courtesy Carlos A.C. Mendes, São José do Rio Preto, Brazil.)

Accidents with caterpillars of the genus Lonomia produce severe hemorrhagic disorders, characterized by both fibrinolytic and disseminated intravascular coagulation–like activity.1 Severe and prolonged AKI, with some patients evolving to CKD, has been reported after Lonomia obliqua (Fig. 71.4) envenomation.1 30 Early antivenom administration in rats prevented hemorrhagic manifestations and kidney dysfunction.31 The AKI mechanisms likely involve glomerular deposition of fibrin, intravascular hemolysis, direct venom nephrotoxicity, activation of the endothelial cell inflammatory pathway, increased kidney expression of proteins involved in cell stress, heme-induced oxidative stress, coagulation, complement system activation, and kinin release.32 33 Kidney histologic findings include acute tubular necrosis, ischemia, and tubular atrophy.30 32

NATURAL MEDICINE

Herbs and indigenous remedies are widely used in poor societies living in the tropics and are an important cause of AKI, especially in subSaharan Africa. This subject is discussed in Chapter 79

MALARIA

Fig. 71.4 Lonomia obliqua Caterpillars. Each hair works as a miniature hypodermic needle to inject the hemolymph, which contains powerful venom that is able to induce severe coagulation system changes. (Courtesy Elvino J.G. Barros, Porto Alegre, Brazil.)

Five species of Plasmodium parasites (falciparum, vivax, malariae, ovale, and knowlesi) cause malaria. Globally, malaria afflicts over 200 million people annually, causing nearly 500,000 deaths, mostly in children with P. falciparum. The contribution of malaria as the cause of AKI among different geographic areas ranges from 2% to 39%. AKI frequency in P. falciparum malaria reaches 60%, and in P. vivax malaria varies from 10% to 19%.[41] P. malariae, P. knowlesi, and P. ovale–induced AKI are less common. Malaria-associated AKI frequency using Kidney Disease: Improving Global Outcomes criteria is higher than using the WHO criteria.[42] In this chapter we focus on P. falciparum malaria–associated AKI.

Pathophysiology

Fig. 71.5 Loxosceles spp. (Brown Recluse Spider). (Courtesy Katia C. Barbaro, São Paulo, Brazil.)

Loxosceles (Brown Recluse Spider)

Loxosceles genus spiders (Fig. 71.5) cause local necrosis at the bite site (Fig. 71.6), intravascular hemolysis, rhabdomyolysis, coagulation abnormalities, and AKI.[1,34] Even patients with mild cutaneous lesions may develop severe hemolysis and AKI, which is the main cause of death after these accidents. AKI pathogenesis has been related to massive intravascular hemolysis, kidney vasoconstriction, direct nephrotoxicity, and rhabdomyolysis.[1,34,35] Kidney histologic examination shows pigment-induced acute tubular necrosis.[34] Antivenom is likely the most effective therapy against AKI, but its use is frequently delayed because the bite goes unnoticed.

Scorpions

Scorpion venom causes autonomic overactivity and massive discharge of vasoactive substances and inflammatory cytokines and concentrates rapidly in kidney tissue.[36] Scorpion venom–associated AKI is rare.[37,38] AKI mechanisms are probably kidney vasoconstriction, hemodynamic instability, rhabdomyolysis, systemic inflammation, hemoglobinuria, mitochondrial dysfunction, and direct venom nephrotoxicity.[36-39] Kidney structural changes include acute tubular necrosis, glomerular changes, interstitial infiltrates, TMA, and acute cortical necrosis.[36,37,38,40]

P. vivax, P. ovale, and P. knowlesi infect young erythrocytes, and P. malariae infects aging cells. P. falciparum infects erythrocytes of all ages, producing a higher number of merozoites (Fig. 71.7). Heavy parasitemia is commonly observed in P. falciparum malaria, creating adverse effects on the microcirculation. Parasitized erythrocytes play a major role in the pathophysiologic process of the disease through decreased erythrocyte deformability and sequestration, knobs and rosette formation, cytoadherence, and changes in membrane transport and permeability (Fig. 71.8).

The presence of knobs on parasitized erythrocyte membranes and cytoadherence between parasitized erythrocytes and vascular endothelial cells are characteristic of P. falciparum malaria. Cytoadherence of mature P. vivax parasitized erythrocytes to vascular endothelial cells involves intercellular adhesion molecule-1, CD36, endothelial protein C receptor, platelet endothelial cell adhesion molecule, and chondroitin sulfate A receptors.43 P. vivax–caused cytoadherence is lower than that of P. falciparum–infected erythrocytes. Several proinflammatory cytokines (tumor necrosis factor; interleukins 1, 6, and 8; interferon-γ) and vasoactive mediators are released. The reninangiotensin-aldosterone system is also stimulated. Hemodynamic changes in malaria are similar to those of bacterial sepsis, including decreased systemic vascular resistance, hypervolemia, increased cardiac output, and increased kidney vascular resistance. Because of increased vascular permeability, the initial hypervolemia is followed by hypovolemia and decreased cardiac output, with decreased kidney blood flow and GFR. Increased blood viscosity, intravascular coagulation, hemolysis, rhabdomyolysis, jaundice, fever, lactic acidosis, complement activation, and reactive oxygen species further compromise kidney blood flow. Activation of poly (adenosine diphosphate [ADP]ribose) polymerase by peroxynitrite and free radicals decreases oxygen utilization.

AKI in malaria is ischemic and hypoxic in origin and usually occurs with heavy parasitemia, intravascular coagulation, intravascular hemolysis, or rhabdomyolysis.41 Immune responses in malaria involve Th1 and Th2 activation. Immune complex GN can occur (see Chapter 57). Tubular changes vary from cloudy swelling to tubular degeneration (Fig. 71.9). Bile and hemoglobin casts and Tamm-Horsfall protein are present in the tubular lumen. Interstitial mononuclear infiltration and edema can occur. TMA and acute cortical necrosis have been reported.44 45 Malarial antigens are occasionally seen along the glomerular endothelium and medullary capillaries. Adhesion molecules and proinflammatory cytokines are overexpressed in the vascular endothelium and proximal tubules.41

A

B

C

Fig. 71.6 Local Necrotic Injury in the Left Leg of a Female Patient After Loxosceles Bite. (A) At 4 days after the bite. (B) At 60 days after the bite. (C) At 3 months after the bite. (Courtesy Carlos A.C. Mendes, São José do Rio Preto, Brazil.)

Clinical Manifestations

Fig. 71.7 Ring form and merozoites of Plasmodium falciparum in infected erythrocytes.

Malarial AKI affects predominantly nonimmune adults, mostly infected by P. falciparum. Reports link P. vivax infection with acute respiratory distress syndrome (ARDS), severe AKI, and TMA.44 Mixed Plasmodium infections and comorbidities related to sepsis are likely important contributing factors to AKI. Symptoms include fever, chills, headache, prostration, and occasionally jaundice. The urinalysis usually shows few erythrocytes, leukocytes, and granular casts and proteinuria, often less than 1 g/24 hr. Hemoglobinuria happens in the patient with intravascular hemolysis, frequently associated with glucose-6 phosphate dehydrogenase deficiency. Rhabdomyolysis with myoglobinuria can be observed. Fluid and electrolyte changes are common in malaria.41 46 Hyponatremia, usually asymptomatic, is observed in 67% of patients, is related to the severity of malaria, and resolves within a few days after antimalarial treatment. The causes of hyponatremia are multiple, including increased antidiuretic hormone with water retention, intracellular shift of sodium as a result of decreased Na+,K+ ATPase activity, and sodium depletion. Hypernatremia is uncommon, indicates hypothalamic lesions with diabetes insipidus, and is associated with unfavorable prognosis. Hypokalemia occurs in 20% to 40%

most commonly used. The first choice in malarial AKI is artesunate, because it has high efficacy and does not need adjustment for kidney function. Early and frequent KRT (hemodialysis or peritoneal dialysis) is lifesaving.41 Continuous venovenous hemofiltration yields good results in patients with multiorgan involvement, especially those with pulmonary edema or ARDS.41 Exchange blood transfusion and erythrocytapheresis are adjunctive for the patient with heavy parasitemia.48

The mortality rate of malarial AKI ranges from 10% to 50%. Kidney function may not recover completely in severe AKI, evolving to CKD in 7% of malaria-induced AKI.

6

4

7

1
2
5
2

LEPTOSPIROSIS

1
3

Fig. 71.8 Transmission electron micrograph from the kidney in Plasmodium falciparum malaria showing sequestration of two parasitized ed blood cells (2) within a glomerular capillary. Malarial pigment (5) is seen in a phagocyte (4). (1) P. falciparum. (3) Glomerular endothelial cell. (6) Glomerular basement membrane. (7) Podocyte. (Courtesy Dr. Emsri Pongponratn, Faculty of Tropical Medicine, Mahidol University.)

Fig. 71.9 Acute tubular necrosis in Plasmodium falciparum malaria.

of patients with uncomplicated cases. Hyperkalemia is observed in patients with intravascular hemolysis, rhabdomyolysis, and/or AKI. Hypocalcemia with prolonged QTc interval occurs in 45% of severe malaria cases and resolves with infection control.46 Decreased activities of Na^+,K^+-ATPase, Ca^{2+}-ATPase, and parathyroid hormone are considered the main causes for hypocalcemia. Hypophosphatemia is observed in 6% to 30% and hypomagnesemia in 30% of patients.46 Downregulation of sodium channels on the apical membrane of alveolar epithelial cells and increased vascular permeability account for the development of pulmonary edema and ARDS.47

Malarial AKI is characterized by a rapid increase in serum creatinine and is often associated with cholestatic jaundice. Risk factors for AKI include high parasitemia, jaundice, high liver enzymes, thrombocytopenia, decreased diastolic blood pressure, retinopathy, and ARDS. Hemolytic uremic syndrome has been described. Severe acidosisassociated lactic acidemia, hypoglycemia, and central nervous system symptoms are observed in severe malaria. Malarial AKI with multiple organ involvement and papilledema carries an unfavorable prognosis. AKI duration ranges from one to several weeks and is oliguric in 60% of the patients. Quinine and artesunate are the antimalarial agents

Leptospirosis, the world’s most common zoonosis, is caused by Leptospira genus spirochetes.

The WHO included leptospirosis as a reemerging infectious disease in both higher and lower income areas, and cases have been increasingly reported in wealthy countries. Wild and domestic mammals (rodents, dogs, pigs, cattle, horses) are the disease vectors. The infection is transmitted accidently to humans through broken skin or mucosal membranes exposed to water or soil contaminated with organisms shed in the urine from the natural vectors.1 Leptospirosis is a job-related threat for rodent exterminators, slaughterhouse workers, farmers, pet traders, veterinarians, garbage collectors, and sewer workers. Human leptospirosis is endemic in many tropical countries and usually reaches epidemic levels after heavy rainfall and flooding, or natural disasters, such as hurricanes or earthquakes. A meta-analysis revealed that flooding, lacerated wounds, and history of contact with livestock were independent risk factors for human leptospirosis.49 There is an annual global estimate of 1 million cases, with 58,900 fatalities, with about half among young adult males.50 A high seroprevalence of anti-Leptospira antibodies has been found in the general asymptomatic population in tropical countries.1

Leptospira interrogans, the only parasitic species, is mobile, aerobic, and unstained by the Gram method. Its endotoxins primarily affect tubulointerstitial cells. The bacterial outer membrane contains lipopolysaccharide, cytotoxic glycolipoprotein (GLP), and lipoproteins (LipL), especially LipL 32, which is immunogenic. Because Leptospira have special tropism for the kidneys, the effect of GLPs on tubular Na+,K+-ATPase activity is potentially involved in the AKI cellular pathophysiology, in the urinary concentrating defects, and in the paradoxical hypokalemia frequently seen in these patients.1 Glycocalyx and endothelial injury caused by spirochete membrane proteins also may contribute to AKI (Fig. 71.10).

Kidney involvement is almost universal in leptospirosis but becomes relevant in Weil disease, the most severe form of leptospirosis, which is characterized by multiorgan involvement, with diffuse alveolar hemorrhage, pulmonary edema, ARDS, or a combination of these features, accompanied by AKI and a high mortality rate. Leptospirosisassociated AKI incidence varies from less than 10% to more than 80%, and its severity is associated with increasing mortality. Oliguria, jaundice, arrhythmias, thrombocytopenia, elevated baseline serum creatinine, and urinary neutrophil gelatinase–associated lipocalin levels have been associated with AKI development.51 AKI is typically nonoliguric and associated with hypokalemia.1 Tubular changes characterized by high urinary fractional excretion of sodium and potassium precede reduced GFR, which could explain the high frequency of hypokalemia. Long-term follow-up of leptospirosis-associated AKI found late development of CKD and presence of tubular function abnormalities.52

Early diagnosis and treatment are pivotal to successful leptospirosis treatment. The symptoms of leptospirosis (fever, myalgia, and headache) are nonspecific, jeopardizing its diagnosis.53 The THAI

Pathogenesis of Leptospirosis-Associated Acute Kidney Injury
Leptospiral outer membrane
protein such as LipL32, LipLoa22,
LipL41, and Lig family

Leptospirosis

Direct toxicity
Tubular epithelial cell

Tubular cell
apoptosis, necrosis

Indirect toxicity
Hemodynamic instability
Hyperbilirubinemia
Rhabdomyolysis

LipL32
Tubular epithelial cell injury
Recruit inflammatory cell
Loss of microvilli

TLR-2
NF-k
Gene expression

iNOS
MCP-1
TNF

Disease factor

Leptospirosis species:
Interrogans, Borgpetersenii
Degree of hypotension,
dehydration, rhabdomyolysis,
hyperbilirubinemia

Specific tubular proteins expression
such as NGAL
Severity of leptospirosis-AKI

Patient factors
Age, comorbidity (CKD, DM),
immune status

Fig. 71.10 Pathogenesis of leptospirosis associated acute kidney injury (AKI). CKD, Chronic kidney disease; DM, diabetes mellitus; NGAL, neutrophil gelatinase-associated lipocalin.

LEPTO score was proposed as a tool to help distinguish leptospirosis from other diseases in the inpatient setting. It includes hypotension, jaundice, muscle pain, AKI, low hemoglobin, hypokalemia with hyponatremia, and neutrophilia. The score showed a high discriminatory power with area under the curve (AUC) of 0.82.54 A subsequent report in an outpatient department setting showed that the simplified score (Lepto OPD score) comprising history of exposure to wet ground at workplace, contact with water reservoir used by animal, positive urine dipstick test for protein and blood, and neutrophil count higher than

80% had an AUC of 0.72.55 Microtranscriptome profiles of patients with severe leptospirosis versus nonsevere were different, suggesting novel biomarkers for severe leptospirosis.56

The leptospirosis diagnostic tests recommended by WHO include microscopic agglutination test, direct culture, and polymerase chain reaction technique. These techniques require advanced facilities, which are not universally available. Rapid diagnostic test kits, which mainly test serum immunoglobulin M antibodies, might be an alternative for this situation. However, different test kits have diversity of accuracy in different populations, and so their performance must be evaluated in specific populations before its use.57

Antibiotics of the penicillin group are considered the basis of treatment, but their efficacy remains unproven.58 A study exploring the role of corticosteroid and desmopressin in severe leptospirosis patients with pulmonary involvement did not demonstrate any benefit on survival.59

Current treatment recommendations include a high KRT dose, conservative fluid intake, and approaches to minimize lung injury, including extracorporeal membrane oxygenation support when indicated.60

HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) are caused by RNA viruses of four different families (Flaviridiae, Arenaviridae, Bunyaviridae, Filoviridae). Dengue, Rift Valley fever, yellow fever, and Crimean-Congo virus can be acquired by bites from infected arthropods, by inhalation of infected rodent excreta particles (Lassa, Junin, Machupo, Hantaan virus), or through contact with contaminated material (Ebola virus). The clinical picture includes fever, malaise, increased vascular permeability, and coagulation abnormalities that may lead to bleeding. Dengue and yellow fever are the most prevalent forms of VHF in the tropics.1 61 62

Dengue Fever

Dengue, which is currently the most important urban arboviral disease, is an acute febrile disease caused by an arbovirus transmitted primarily by mosquitoes, mainly the female Aedes aegypti mosquito. The number of yearly infections is estimated at 390 million.62 63

Several factors account for the rising incidence and widespread occurrence of dengue, such as climate changes (global warming, intensity and duration of rain season, hurricanes), ecosystem modifications, demographic increases, uncontrolled urbanization, and human migration. There are four serotypes of antigenically related dengue flavivirus (DEN 1 to DEN4), but immunity to one does not confer enduring immunity to another. The introduction of a new serotype in a determinate area accounts for the occurrence of epidemics and the hemorrhagic fever dengue form, which is a more severe and potentially lethal form of the disease.63

Mechansims of Dengue-Associated Acute Kidney Injury
Fluid sequestration & RAS activation
Prerenal AKI or ischemic ATN

2
Vasoactive mediators
ET-1, TXA2, TNF-α

Rhabdomyolysis

Intrarenal vasoconstriction

1
Vascular leakage

Hemoglobin or myoglobin
Direct muscle invasion
Inflammatory cytokines
IL-6
IL-17
IL-18
TNF-α

Fe

Myotoxic cytokines
TNF-α

3

Hemolysis

DENV
Subneutralizing Ab

Viral tubular invasion?
Secondary DVI

Cytokines

Nephrotoxic ATN
&
Intratubular obstruction

Immune complex
&
Autoimmunity

7

5

Antibody-dependent enhancement

Cytokines-induced ATN

6
Acute glomerulonephritis

Fig. 71.11 Summary of Mechanisms of Dengue-Associated Acute Kidney Injury (AKI).

(1) Dengue virus triggers cascades of inflammatory response, which lead to endothelial injury and vascular leakage. Reduced kidney perfusion occurs as a result. (2) Rhabdomyolysis in dengue virus is proposed to result from direct viral invasion and myotoxic inflammatory cytokines. (3) Intravascular hemolysis can be found, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. (4) Myoglobin and hemoglobin are freely filtered into urine and directly injure kidney tubular cells. In some instances, they can, together with tubular proteins, form casts in the tubular lumens. (5) Acute tubular damage can be accounted for by inflammatory cytokines or by direct viral invasion suggested by the presence of viral antigen in tubular cells of dengue patients with AKI. (6) Evidence of dengue-associated acute glomerulonephritis with glomerular immune complex deposits has been reported, as well as development of autoantibodies to glomerular basement membrane (GBM) resulting in anti-GBM disease. The latter process is thought to be mediated by molecular mimicry of viral antigens. (7) Key immunopathogenesis of severe dengue virus infection (DVI) is based on antibody-dependent enhancement, where subneutralizing antibodies acquired from past infection promote dengue virus (DENV) entry into cells and suppress the antiviral response. Ab, Antibody; ATN, acute tubular necrosis; ET-1, endothelin-1; IL, interleukin; RAS, renin-angiotensin system; TNF-α, tumor necrosis factor-α; TXA2, thromboxane A2.

Dengue infection may manifest as undifferentiated fever, dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Common clinical manifestations of dengue fever are high fever, myalgia, arthralgia, retroocular pain, headache, anorexia, nausea, vomiting, and a cutaneous rash. DHF and DSS are severe forms of the disease, characterized by fever, hemorrhage, thrombocytopenia, and evidence of plasma leakage (increased hematocrit, pleural effusion, ascites, and hypoalbuminemia), mental disorientation, shortness of breath, tachycardia, shock, and death.62 64

Kidney involvement in dengue includes AKI, proteinuria (sometimes nephrotic), GN (see Chapter 57), hemolytic uremic syndrome, and electrolyte abnormalities.62 64 65 The frequency of dengueassociated AKI varies from 1% to 30%, and its development and severity are related to poor prognosis.62 64 66 67

Dengue-induced AKI is usually associated with shock, hemolysis, and/or rhabdomyolysis but may occur without any of these triggers and is described in all forms of dengue.62 64 Risk factors for AKI comprise increased hepatic enzymes, hypoalbuminemia, reduced serum bicarbonate, other simultaneous viral or bacterial infection, multiple organ dysfunction, use of inotropic or nephrotoxic drugs, increased age, obesity, dengue severity, rhabdomyolysis, presence of diabetes mellitus, and delayed hospitalization.62 64

The pathogenesis of dengue-associated AKI has been attributed to hemodynamic instability, rhabdomyolysis, hemolysis, direct viral invasion, and immune response. Patients with severe dengue infection, mostly reinfected by another viral strain, may develop plasma leakage syndrome, which eventually results in hypotension, causing kidney hypoperfusion and AKI. Inflammatory cytokines produced by dengueinfected monocytes and mast cells probably are linked to this phenomenon.68 Rhabdomyolysis may occur rarely in dengue, and viral muscle invasion and inflammatory cytokines myotoxicity have been considered as possible agents causing muscles injury.69 Data from autopsies and from studies in rodents demonstrated the presence of dengue virus in kidney tissue, suggesting direct kidney cytopathic effects. Host immune response may be involved in the pathogenesis of dengue-associated AKI. The concept of secondary infection as the key pathogenic factor for developing DHF/DSS has been well established for decades and is explained by antibody-dependent enhancement. Previous infection by one serotype of dengue virus results in development of subneutralizing antibodies. These antibodies possess high viral attachment efficiency enhancing internalization of virus into cells. Reports of DHF and AKI associated with proteinuria, hematuria, and reduced serum C3 level without presence of hypotension, rhabdomyolysis, hemolysis, or use of nephrotoxic agents support the role of possible immunopathogenic mechanism causing glomerular and tubular damage either by immune complex–mediated mechanism or cytokine-mediated tubular injury. Autoimmunity induced by molecular mimicry is another possible mechanism for dengue-associated kidney disease (Fig. 71.11).62 64

There is no specific treatment for dengue fever. Therapy is mostly supportive, avoiding the use of aspirin and nonsteroidal antiinflammatory drugs.

Yellow Fever

Yellow fever is a noncontagious infectious disease that is endemic in tropical Africa, South America, and Panama. The yellow fever virus is part of the Flavivirus genus (Flaviviridae family).61 It is transmitted to humans by blood-eating insect bites, especially by the Aedes and Haemagogus genera. There are two cycles, termed sylvatic and urban. The sylvatic cycle affects sporadic individuals who come in contact with the vectors when performing economic or recreational activities in infested forests. The urban cycle is characterized by virus transmission through A. aegypti to individuals living in urban areas. The urban cycle was eliminated in the Americas from the 1940s to 1950s, but its resurgence was recently documented in Bolivia. The movement of viremic individuals to cities with high vector populations can potentially generate explosive urban epidemics affecting thousands of nonvaccinated people.[61] There is no evidence of yellow fever in Asia, despite an extensive presence of vectors.[70] It is possible that the hyperendemicity of dengue in Southwest Asia has afforded protection because of cross-reactive antibodies.

Yellow fever infection might be asymptomatic, cause moderate febrile disease, or be severe, causing hemorrhagic fever, liver failure, AKI, and death. Most patients (85%) fully recover after 3 to 4 days and become permanently immunized against the disease. About 20% develop the severe form, with mortality of up to 50%.[61] After 3 to 6 days of incubation, the clinical picture starts abruptly with high fever, chills, anorexia, myalgia, headache, vomiting, and bradycardia. Hemorrhagic manifestations may occur. There is then a remission period with symptom improvement, and mild cases do not have any further manifestation. In the severe forms, fever recurs followed by vomiting, epigastric pain, and jaundice—the so-called intoxication phase. There are large increases in transaminases and bilirubin, and leukopenia and ST segment abnormalities may develop. Hemorrhagic events associated with hepatic damage and consumptive coagulopathy can occur, such as hematemesis, melena, petechiae, bruises, mucosal bleeding, and metrorrhagia in women. Microcirculatory thrombosis, disseminated intravascular coagulation, tissue anoxia, oliguria, and shock may follow.[61]

Yellow fever–associated AKI occurs usually after 5 days of disease in the severe forms and may evolve to anuria and acute tubular necrosis, with increased mortality. In Africa, AKI is observed earlier, without jaundice or liver abnormalities, with higher mortality. AKI mechanisms are poorly understood. Kidney ischemia, intravascular coagulation, shock, bilirubin-induced kidney tubule cell toxicity, virus direct effect on kidney tissue, and intense inflammatory cytokine discharge are likely mechanisms of AKI.[71-73] In 2017 and 2018, outbreaks of yellow fever in Brazil AKI and increased kidney echogenicity were identified as independent factors associated to higher patient mortality.[74-75]

SELF-ASSESSMENT QUESTIONS

1. Bites from what families of snakes may lead to acute kidney injury?
A. Viperidae and Elapidae
B. Only Elapidae
C. Only Tropidophiidae
D. Colubridae and Aniliidae
E. Only Aniliidae

2. A 25-year-old farmer from northeast Thailand, without underlying diseases, presented with high fever and history of back pain for the last 3 days. His vital sign revealed heart rate 120 beats/min, blood pressure 80/40 mm Hg, body temperature 38.8°C, and respiratory rate 30 breaths/min. Initial laboratory examination showed leukocytosis with neutrophil predominate. Urinalysis showed white blood cells numbering 10 to 30/high power field (HPF) and red blood cells 5 to 10/HPF.

On the second day after admission, he was still febrile and had worsening of kidney function. Blood pressure was 120/70 mm Hg. His serum creatinine increased from 1.0 mg/dL to 4.2 mg/dL. A leptospirosis rapid test was negative. Indirect immunofluorescence assay for scrub typhus was pending. Dengue NS1 Ag was negative. Malaria thick and thin films were negative. Hemoculture was negative.

What is the most likely diagnosis?
A. Melioidosis
B. Scrub typhus
C. Dengue infection
D. Leptospirosis
E. Malaria

3. What is the correct sequence (from higher to lower frequency) of Plasmodium species associated with AKI development?
A. First vivax, then falciparum, less common malariae, ovale, and knowlesi
B. First falciparum, then vivax, less common malariae, ovale, and knowlesi

C. First falciparum and vivax similarly, then malariae, ovale, and knowlesi
D. Falciparum, vivax, malariae, ovale, and knowlesi similarly
E. First malariae, ovale, and knowlesi similarly, then falciparum and vivax

4. What kind of viral hemorrhagic fevers are more commonly associated with development of acute kidney injury?
A. Crimean-Congo hemorrhagic fever and Ebola
B. Chikungunya fever and Rift Valley fever
C. Dengue, yellow fever, and Hantavirus hemorrhagic fever
D. Malaria and leptospirosis
E. Tick-borne encephalitis and Brazilian hemorrhagic fever

REFERENCES

1. Burdmann EA, Jha V. Acute kidney injury due to tropical infectious diseases and animal venoms: a tale of 2 continents. Kidney Int. 2017;91:1033–1046.
2. Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's by 2025 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616–2643.
3. Mehta RL, Burdmann EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology by 2025 Global Snapshot: a multinational cross-sectional study. Lancet. 2016;387:2017–2025.
4. Lombardi R, Rosa-Diez G, Ferreiro A, et al. Acute kidney injury in Latin America: a view on renal replacement therapy resources. Nephrol Dial Transplant. 2014;29:1369–1376.
5. Paula Santos U, Zanetta DM, Terra-Filho M, et al. Burnt sugarcane harvesting is associated with acute renal dysfunction. Kidney Int. 2015;87:792–799.
6. Kasturiratne A, Wickremasinghe AR, de Silva N, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 2008;5:e218.
7. Minghui R, Malecela MN, Cooke E, Abela-Ridder B. WHO's Snakebite Envenoming Strategy for prevention and control. Lancet Glob Health. 2019;7:e837–e838.
8. Kanjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. Semin Nephrol. 2008;28:363–372.
9. Rodrigues Sgrignolli L, Florido Mendes GE, Carlos CP, et al. Acute kidney injury caused by bothrops snake venom. Nephron Clin Pract. 2011;119:c131–c137.
10. Pinho FM, Zanetta DM, Burdmann EA. Acute renal failure after Crotalus durissus snakebite: a prospective survey on 100 patients. Kidney Int. 2005;67:659–667.
11. George TK, Toms AG, Fenn BN, et al. Renal outcomes among snakeenvenomed patients with acute kidney injury in southern India. Natl Med J India. 2019;32:5–8.
12. Niraj M, Jayaweera JL, Kumara IW, et al. Acute myocardial infarction following a Russell's viper bite: a case report. Int Arch Med. 2013;6:7.
13. Rajagopala S, Thabah MM, Ariga KK, et al. Acute hypopituitarism complicating Russell's viper envenomation: case series and systematic review. QJM. 2015;108:719–728.
14. Herath HM, Wazil AW, Abeysekara DT, et al. Chronic kidney disease in snake envenomed patients with acute kidney injury in Sri Lanka: a descriptive study. Postgrad Med J. 2012;88:138–142.
15. Silva A, Samarasinghe R, Pilapitiya S, et al. Viper bites complicate chronic agrochemical nephropathy in rural Sri Lanka. J Venom Anim Toxins Incl Trop Dis. 2014;20:33.
16. Noutsos T, Currie BJ, Lek RA, Isbister GK. Snakebite associated thrombotic microangiopathy: a systematic review of clinical features, outcomes, and evidence for interventions including plasmapheresis. PLoS Negl Trop Dis. 2020;14:e0008936.
17. Ratnayake I, Mohamed F, Buckley NA, Gawarammana IB, et al. Early identification of acute kidney injury in Russell's viper (Daboia russelii) envenoming using renal biomarkers. PLoS Negl Trop Dis. 2019;13:e0007486.
18. Zornetta I, Caccin P, Fernandez J, et al. Envenomations by Bothrops and Crotalus snakes induce the release of mitochondrial alarmins. PLoS Negl Trop Dis. 2012;6:e1526.
19. Morais IC, Pereira GJ, Orzáez M, et al. L-Aminoacid Oxidase from Bothrops leucurus venom induces nephrotoxicity via apoptosis and necrosis. PLoS One. 2015;10:e0132569.
20. Sunitha K, Hemshekhar M, Thushara RM, et al. Inflammation and oxidative stress in viper bite: an insight within and beyond. Toxicon. 2015;98:89–97.
21. Maduwage K, Silva A, O'Leary MA, et al. Efficacy of Indian polyvalent

snake antivenoms against Sri Lankan snake venoms: lethality studies or clinically focussed in vitro studies. Sci Rep. 2016;6:26778.

22. Gutiérrez JM, Burnouf T, Harrison RA, et al. A multicomponent strategy to improve the availability of antivenom for treating snakebite envenoming. Bull World Health Organ. 2014;92:526–532.
23. Bhaumik S, Beri D, Lassi ZS, Jagnoor J. Interventions for the management of snakebite envenoming: an overview of systematic reviews. PLoS Negl Trop Dis. 2020;14:e0008727.
24. Martines MS, Mendes MM, Shimizu MH, et al. Effects of Schizolobium parahyba extract on experimental Bothrops venom-induced acute kidney injury. PLoS One. 2014;9:e86828.
25. Mejía Vélez G. [Acute renal failure due to multiple stings by Africanized bees. Report on 43 cases]. Nefrologia. 2010;30:531–538.
26. Vikrant S, Jaryal A, Parashar A. Mortality due to mass Hymenoptera attacks: a serious but underrecognized public health problem in a mountainous state of India. Indian J Public Health. 2019;63:154–156.
27. Grisotto LS, Mendes GE, Castro I, et al. Mechanisms of bee venominduced acute renal failure. Toxicon. 2006;48:44–54.
28. Kumar V, Nada R, Kumar S, et al. Acute kidney injury due to acute cortical necrosis following a single wasp sting. Ren Fail. 2013;35:170–172.
29. Santos KS, Stephano MA, Marcelino JR, et al. Production of the first effective hyperimmune equine serum antivenom against Africanized bees. PLoS One. 2013;8:e79971.
30. Burdmann EA, Antunes I, Saldanha LB, et al. Severe acute renal failure induced by the venom of Lonomia caterpillars. Clin Nephrol. 1996;46:337–339.
31. Da Silva WD, Campos CM, Gonçalves LR, et al. Development of an antivenom against toxins of Lonomia obliqua caterpillars. Toxicon. 1996;34:1045–1049.
32. Berger M, Santi L, Beys-da-Silva WO, et al. Mechanisms of acute kidney injury induced by experimental Lonomia obliqua envenomation. Arch Toxicol. 2015;89:459–483.
33. Zanon P, Pizzato SB, da Rosa RL, et al. Urine proteomic analysis reveals alterations in heme/hemoglobin and aminopeptidase metabolism during Lonomia obliqua venom-induced acute kidney injury. Toxicol Lett. 2021;341:11–22.
34. Lucato Jr RV, Abdulkader RC, Barbaro KC, et al. Loxosceles gaucho venom-induced acute kidney injury—in vivo and in vitro studies. PLoS Negl Trop Dis. 2011;5:e1182.
35. Albuquerque PLMM, Tessarolo LD, Menezes FH, et al. Acute kidney injury due to systemic Loxoscelism: a cross-sectional study in Northeast Brazil. Rev Soc Bras Med Trop. 2018;51:695–699.
36. Angsanakul J, Sitprija V. Scorpion venoms, kidney and potassium. Toxicon. 2013;73:81–87.
37. Viswanathan S, Prabhu C. Scorpion sting nephropathy. NDT Plus. 2011;4:376–382.
38. Torrez PP, Quiroga MM, Abati PA, et al. Acute cerebellar dysfunction with neuromuscular manifestations after scorpionism presumably caused by Tityus obscurus in Santarém, Pará/Brazil. Toxicon. 2015;96:68–73.
39. Saidani C, Hammoudi-Triki D, Laraba-Djebari F, et al. In vitro studies with renal proximal tubule cells show direct cytotoxicity of Androctonus australis hector scorpion venom triggered by oxidative stress, caspase activation and apoptosis. Toxicon. 2016;120:29–37.
40. Dizaji R, Sharafi A, Pourahmad J, Vatanpour S, Hosseini MJ, Vatanpour H. The effects of Hemiscorpius lepturus induced-acute kidney injury on PGC-1α gene expression: from induction to suppression in mice. Toxicon. 2020;174:57–63.
41. Mishra SK, Fas BS. Malaria and acute kidney injury. Semin Nephrol. 2008;28:395–408.
42. Mohapatra MK. Early diagnosis of acute kidney injury in falciparum malaria with KDIGO criteria and serum cystatin-C. Int J Malariol. 2016;117:230–239.
43. Carvalho BO, Lopes SC, Nogueira PA, et al. On the cytoadhesion of

Plasmodium vivax-infected erythrocytes. J Infect Dis. 2010;202:638–647.
44. Sinha A, Singh G, Bhat AS, et al. Thrombotic microangiopathy and acute kidney injury following vivax malaria. Clin Exp Nephrol. 2013;17:66–72.
45. Kumar R, Bansal N, Jhorawat R, et al. Renal cortical necrosis: a rare complication of Plasmodium vivax malaria. Indian J Nephrol. 2014;24:390–393.

References

46. Sitprija V. Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol. 2008;4:91–101.
47. Hee L, Dinudom A, Mitchell AJ, et al. Reduced activity of the epithelial sodium channel in malaria-induced pulmonary oedema in mice. Int J Parasitol. 2011;41:81–88.
48. Nieuwenhuis JA, Meertens JH, Zijlstra JG, et al. Automated erythrocytapheresis in severe falciparum malaria: a critical appraisal. Acta Trop. 2006;98:201–206.
49. Naing C, Reid SA, Aye SN, et al. Risk factors for human leptospirosis following flooding: a meta-analysis of observational studies. PLoS One. 2019;14(5):e0217643.
50. Costa F, Hagan JE, Calcagno J, et al. Global morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis. 2015;9:e0003898.
51. Srisawat N, Praditpornsilpa K, Patarakul K, et al. Neutrophil gelatinase associated lipocalin (NGAL) in leptospirosis acute kidney injury: a multicenter study in Thailand. PLoS One. 2015;10:e0143367.
52. Yang HY, Hung CC, Liu SH, et al. Overlooked risk for chronic kidney disease after leptospiral infection: a population-based survey and epidemiologic cohort evidence. PLoS Negl Trop Dis. 2015;9:e0004105.
53. Haake DA, Levett PN. Leptospirosis in humans. Curr Top Microbiol Immunol. 2015;387:65–97.
54. Sukmark T, Lumlertgul N, Peerapornratana S, et al. Thai-Lepto-onadmission probability (Thai-LEPTO) score as an early tool for initial diagnosis of leptospirosis: result from Thai-Lepto AKI study group. PLoS Negl Trop Dis. 2018;12(3):e0006319 (NR).
55. Temeiam N, Jareinpituk S, Phinyo P, et al. Development and Validation of a simple score for diagnosis of Leptospirosis at outpatient departments. PLoS Negl Trop Dis. 2020;14(1):e0007977.
56. Limothai U, Dinhuzen J, Payongsri T, et al. Circulating microtranscriptome profiles reveal distinct expression of microRNAs in severe leptospirosis. PLoS Negl Trop Dis. 2020;14(11):e0008809.
57. Dinhuzen J, Limothai U, Tachaboon S, et al. A prospective study to evaluate the accuracy of rapid diagnostic tests for diagnosis of human leptospirosis: result from Thai-LEPTO AKI study. PLoS Negl Trop Dis. 2021;15(2):e0009159.
58. Charan J, Saxena D, Mulla S, et al. Antibiotics for the treatment of leptospirosis: systematic review and meta-analysis of controlled trials. Int J Prev Med. 2013;4:501–510.
59. Niwattayakul K, Kaewtasi S, Chueasuwanchai S, et al. An open randomized controlled trial of desmopressin and pulse dexamethasone as adjunct therapy in patients with pulmonary involvement associated with severe leptospirosis. Clin Microbiol Infect. 2010;16(8):1207–1212.

60. Chaikajornwat J, Rattanajiajaroen P, Srisawat N, et al. Leptospirosis manifested with severe pulmonary haemorrhagic syndrome successfully treated with venovenous extracorporeal membrane oxygenation. BMJ Case Rep. 2020;13(1):e230075.
61. Monath TP, Vasconcelos PF. Yellow fever. J Clin Virol. 2015;64:160–173.
62. Burdmann EA. Flaviviruses and kidney diseases. Adv Chronic Kidney Dis. 2019;26:198–206.
63. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496:504–507.
64. Oliveira JF, Burdmann EA. Dengue-associated acute kidney injury. Clin Kidney J. 2015;8:681–685.
65. Vachvanichsanong P, Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever and the kidney. Arch Virol. 2016;161:771–778.
66. Mallhi TH, Sarriff A, Adnan AS, et al. Dengue-Induced Acute Kidney Injury (DAKI): a neglected and fatal complication of dengue viral infection—a

systematic review. J Coll Physicians Surg Pak. 2015;25:828–834.
67. Mallhi TH, Khan AH, Sarriff A, et al. Defining acute kidney injury in dengue viral infection by conventional and novel classification systems (AKIN and RIFLE): a comparative analysis. Postgrad Med J. 2016;92:78–86.
68. Pagliari C, Simoes Quaresma JA, Kanashiro-Galo L, et al. Human kidney damage in fatal dengue hemorrhagic fever results of glomeruli injury mainly induced by IL17. J Clin Virol. 2016;75:16–20.
69. Huang SY, Lee IK, Liu JW, et al. Clinical features of and risk factors for rhabdomyolysis among adult patients with dengue virus infection. Am J Trop Med Hyg. 2015;92(1):75–81.
70. Wasserman S, Tambyah PA, Lim PL. Yellow fever cases in Asia: primed for an epidemic. Int J Infect Dis. 2016;48:98–103.
71. Vasconcelos PF, Luna EJ, Galler R, et al. Brazilian Yellow Fever Vaccine Evaluation Group. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet. 2001;358:91.
72. Engelmann F, Josset L, Girke T, et al. Pathophysiologic and transcriptomic analyses o viscerotropic yellow fever in a rhesus macaque model. PLoS Negl Trop Dis. 2014;8:e3295.
73. Lopes RL, Pinto JR, Silva Junior GBD, Santos AKT, Souza MTO, Daher EF. Kidney involvement in yellow fever: a review. Rev Inst Med Trop Sao Paulo. 2019;61:e35.
74. de Ávila RE, José Fernandes H, Barbosa GM, et al. Clinical profiles and factors associated with mortality in adults with yellow fever admitted to an intensive care unit in Minas Gerais, Brazil. Int J Infect Dis. 2020;93:90–97.
75. Neves YCS, Castro-Lima VAC, Solla DJF, et al. Ultrasound findings and laboratory Predictors of early mortality in patients with severe yellow fever. AJR Am J Roentgenol. 2021;216:1392–1399.

72

Diagnosis and Clinical Evaluation of Acute Kidney Injury

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The term acute renal failure (ARF) describes the clinical syndrome in which an abrupt (hours to days) decrease in kidney function leads to the accumulation of nitrogenous waste products and, commonly, a reduction in urine output. Acute kidney injury (AKI) has become the consensus term for ARF.1-3 This change in terminology served to standardize a definition for the syndrome, as well as to incorporate knowledge that increases in serum creatinine as small as 0.3 mg/dL (27 μmol/L) are associated with increased morbidity and mortality.4

In 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) guideline unified the definition of AKI and included stages of severity (Table 72.1). AKI has since been defined as an increase in serum creatinine of 0.3 mg/dL or greater within 48 hours of observation or 1.5 or more times baseline, which is known or presumed to have occurred within 7 days, or a reduction in urine volume below 0.5 mL/kg/h for 6 hours.1 Subclassification of AKI based on disease severity as indicated by the level of increase in serum creatinine and reduction in urine output has been adopted as a three-stage classification by KDIGO. Increasing severity of AKI based on creatinine and urine output associates with increased risk for death.1

There are many different causes of AKI, and most are identified through clinical investigation. Globally, hypotension and volume contraction or dehydration accounted for 40% of AKI cases in both the hospital and nonhospital setting.5 In higher-income countries, hypotension and shock were the most common causes of AKI, whereas volume contraction or dehydration predominated in lower-income countries. Nephrotoxic agents were implicated in up to a quarter of AKI events across all countries.5 However, nephrotoxin administration may account for a larger proportion of hospital-acquired AKIs in older patients.6,7 Kidney biopsy is rarely performed to establish the cause of AKI. In an observational study of 745 patients with AKI in the intensive care unit (ICU), only 3% (22 patients) underwent kidney biopsy and, as expected, glomerulonephritis (GN) and acute interstitial nephritis (AIN) were each diagnosed in about a third of the biopsy specimens, and about 23% showed only acute tubular necrosis (ATN).8

EARLY DETECTION OF ACUTE KIDNEY INJURY

The definition of AKI is based on increases in serum creatinine, yet when used as a marker of kidney function, serum creatinine concentrations have multiple limitations. In addition to a steady-state balance of creatinine production and excretion being required for appropriate estimation of glomerular filtration rate (GFR), serum creatinine concentrations may not rise for subtle declines in GFR and are slow to rise for rapid falls in GFR. Furthermore, the generation of creatinine from muscle is reduced in sepsis-induced AKI, and serum creatinine concentrations may not increase proportionally to GFR decline.9

Kidney injury will initially remain undetected until serum creatinine concentrations rise (8–48 hours) (Fig. 72.1).10 Serum and urine biomarkers with potential as early indicators of AKI include tissue inhibitor of metalloproteinase 2 (TIMP-2), insulin-like growth factor–binding protein 7 (IGFBP7), hepcidin, kidney injury molecule 1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), proenkephalin A, and others. These biomarkers also may allow for improved prognostication and insight into the specific cause of AKI.11

Signifying the integration of nontraditional biomarkers in the diagnosis of AKI, the definition of AKI has been expanded to include biomarker status, including a subclinical stage (1S) where biomarkers are positive without significant changes in serum creatinine or urine output.11 Biomarkers are categorized by predictive type. The strongest predictor of AKI severity and outcome involves a combination of biomarker types and clinical judgment. For example, the combination of biomarkers reflecting kidney function (cystatin C) and kidney damage (NGAL) was superior to serum creatinine in predicting AKI severity in children undergoing cardiopulmonary bypass.12

Serum cystatin C is a 13-kDa cysteine protease inhibitor that is freely filtered at the glomerulus and normally reabsorbed by proximal tubule cells and may be more sensitive than serum creatinine concentrations for detecting small reductions in GFR,13 and thus may have advantages for diagnosing AKI and predicting AKI severity.11,14

The combination of urinary levels or IGFBP7 and TIMP outperforms all other biomarkers in the early detection of AKI in critically ill patients.15 Both proteins are expressed in tubular cells and have autocrine and paracrine effects that lead to G1 cell cycle arrest for short periods. In AKI, preventing or delaying tubular cell division may be a protective response to injury. The risk for stage 2 or 3 AKI correlated well with logarithmic values of [IGFBP7]*[TIMP-2] measured from a urine sample obtained within 12 hours of the diagnosis of AKI,15 and their combined urinary levels correlated to clinician-adjudicated AKI better than KDIGO criteria.16 The release of TGFBP7 and TIMP-2 during cell cycle arrest make their urinary levels potentially useful for predicting the development of AKI.11,17

Assessing kidney function with a loop diuretic challenge (furosemide stress test) improves prediction of kidney outcomes compared with biomarker measurement. In patients with early AKI in the ICU, urinary responses to intravenous furosemide predicted the need for dialysis better than biomarker measurement alone.18 Failure to produce more than 200 mL of urine within 2 hours of intravenous furosemide dosed at 1 to 1.5 mg/kg strongly predicted both the need for dialysis and progression to AKI stage 3.18

KIM-1, a cell membrane glycoprotein upregulated in injured proximal tubular cells, can act as a nonmyeloid phosphatidylserine receptor that transforms epithelial cells into semiprofessional phagocytes.19 The ectodomain of this membrane-associated molecule is shed into the urine of injured but not healthy kidneys. KIM-1 messenger ribonucleic acid

TABLE 72.1 Kidney Disease: Improving Global Outcomes Composite Staging of Acute Kidney Injury

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 × baseline or ≥0.3 mg/dL (≥29 µmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 × baseline or Increase in serum creatinine to ≥4.0 mg/dL (≥352 µmol/L) or Initiation of kidney replacement therapy or In patients younger than 18 yr, decrease in estimated glomerular filtration rate <35 mL/min/1.73 m2	<0.3 mL/kg/h for ≥24 h or Anuria for ≥12 h

From the Kidney Disease Improving Global Outcomes (KDIGO) Working Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.

Chronological Evolution of
Acute Kidney Injury
Detection of AKI via
novel biomarkers
Window
8–48 h

Serum creatinine

GFR

Detection of AKI via
traditional biomarkers

Initial
kidney
injury

Ongoing injury

Time

Fig. 72.1 Chronologic evolution of acute kidney injury (AKI). GFR, Glomerular filtration rate. (Modified from Ravn B, Rimes-Stigare C, Bell M, et al. Creatinine versus cystatin C based glomerular filtration rate in critically ill patients. J Crit Care. 2019;52:136–140.)

(mRNA) levels may rise more than any other gene after kidney injury, and urinary levels are increased specifically with AKI resulting from ischemia or toxin exposure.20 21 Urine KIM-1 is categorized as a damage biomarker.11

NGAL, a protein produced by neutrophils, binds and traffics free iron.20 It also mediates the tubular response to epidermal growth factor and is thereby involved in the progression of kidney disease.22 Urinary NGAL levels are increased in the setting of tubular stress or injury, but not in prerenal disease.23 A large number of studies correlated urinary NGAL levels to early detection of AKI.10 Plasma and urine levels of NGAL are categorized as a damage biomarker that may be used to diagnose and predict the severity of AKI.11

IL-18 is an inflammatory cytokine found in macrophages, monocytes, and proximal tubule cells. Urinary levels are upregulated in kidney ischemic injury in multiple clinical settings.10 Urinary IL-18 levels are used as a damage biomarker.11

Biomarkers have the potential for detecting AKI early, identifying minor kidney injuries that do not raise serum creatinine concentrations (subclinical AKI), monitoring therapeutic benefits of novel treatment interventions, and specifying the cause of AKI. However, AKI frequently occurs unobserved in the community or is present at the time of recognition. Approximately 50% of patients admitted from the emergency department with septic shock have AKI on arrival to the ICU.24 Even when computer models successfully predict hospital-acquired AKI, early interventions have had little effect on outcomes. The composite outcome of maximum change in serum creatinine level, need for dialysis, or death at 7 days did not change when primary providers were notified of AKI by an electronic alert system.25 Multicenter implementation of an AKI alert system along with an AKI care bundle and education of health care workers resulted in increased AKI recognition and more frequent assessment of patient fluid status, but the risks of 30-day mortality after AKI (24.5%) and progressive AKI were unchanged.26 Nevertheless, biomarkers remain an exciting potential tool for diagnosing, identifying a cause of, and predicting outcomes of AKI.

DIAGNOSTIC APPROACH TO ACUTE KIDNEY INJURY

The basic diagnostic approach to patients with AKI is to determine the cause (see Chapter 70). This process should start by excluding or correcting both prerenal and postrenal causes (Fig. 72.2). In hospitalized patients, making a diagnosis often involves selecting the most probable cause among many choices.27 Assessing daily urine volume can narrow the differential diagnosis, dividing AKI into oliguric (<500 mL/d) and nonoliguric causes. Acute tubular necrosis, the most common cause of hospital-acquired AKI, is oliguric, whereas AIN and glomerularrelated AKI are typically nonoliguric. A careful history and physical examination and basic laboratory tests often suffice for diagnosis (Table 72.2).27

Acute Kidney Injury Versus Chronic Kidney Disease

It can be difficult to determine whether a patient with kidney failure has AKI or AKI superimposed on chronic kidney disease (CKD).

Knowledge of prior serum creatinine concentrations is required to determine the degree of potentially reversible AKI. Ultrasound evidence of small, scarred kidneys is consistent with CKD, but even advanced diabetic nephropathy, amyloidosis, human immunodeficiency virus (HIV) infection–related nephropathy, or polycystic kidney disease can present with normal or increased kidney size. Normocytic anemia, hyperparathyroidism, peripheral neuropathy, and broad waxy casts in the urinary sediment suggest CKD. Patients with CKD are at high risk for developing AKI.28

CLINICAL ASSESSMENT

The evaluation of a hospitalized patient with AKI should begin with a complete medical history and review of the hospital records. Once the prior serum creatinine concentration or other evidence of underlying kidney disease is established, the history should be directed toward the events preceding the AKI (see Fig. 72.2). These events

Investigation and Management of Acute Kidney Injury

Elevated serum
creatinine

Assessment of baseline kidney
function (if available)

Serum creatinine elevated at baseline
or rise not meeting
KDIGO definition of AKI

Chronic kidney
disease algorithm

Serum creatinine >1.5 × baseline or
rise ≥0.3 mg/dL in 48 h

Kidney
ultrasound

Bladder
catheterization/
Urologic
evaluation

Evidence of
obstruction

No evidence
of obstruction

History, physical examination,
laboratory testing (as appropriate,
see text for details), examine urine
sediment (Fig. 72.4)

Suspected prerenal cause

Suspect intrinsic
renal cause

Acute
glomerulonephritis
- Postinfective
- RPGN
- Lupus nephritis
- Cryoglobulinemia

Acute tubular
injury
- Ischemic
- Drug
- Pigment

Acute interstitial
nephritis
- Drug
- Infection
- Autoimmune

- Malignancy

Intravenous fluid challenge

Responsive

Nonresponsive

Supportive therapy

Intratubular obstruction
- Paraprotein
- Crystals

Macrovascular
- Increased renal vein pressure
- Bilateral renal artery occlusion
- Bilateral renal vein thrombus

Microvascular
- Atheroembolic
- Thrombotic microangiopathy

Fig. 72.2 Investigation and Management of Suspected Acute Kidney Injury (AKI). The majority of AKI causes can be identified by reviewing the events that preceded the AKI. Evaluating for urinary obstruction early prevents the delay of urologic therapy, if needed; however, not all patients require a kidney ultrasound. If prerenal and postrenal causes have been excluded, the kidneys are normal size, and the diagnosis remains unclear, a kidney biopsy may be indicated. KDIGO, Kidney Disease: Improving Global Outcomes; RPGN, rapidly progressive glomerulonephritis.

may be part of a systemic disease process (e.g., sepsis, rhabdomyolysis), an inpatient event (e.g., surgery, nephrotoxic agent exposure), or an outpatient event (e.g., medication or drugs, volume contraction from diarrhea or vomiting). Particular attention should be paid to the medication record, looking for use of nonsteroidal antiinflammatory drugs (NSAIDs), renin-angiotensin-aldosterone antagonists, diuretics, antibiotics, proton pump inhibitors, chemotherapy agents (e.g., platin-based therapies and immune check point inhibitors), herbs that might contain aristolochic acid (see Chapter 65), or a synthetic cannabinoid.29 In Africa and India the ingestion of hair

dyes containing paraphenylenediamine may result in AKI. Clues to a postrenal cause (e.g., urinary hesitancy, frequent nocturia, pelvic or flank pain, overflow urinary incontinence, metastatic cancer) should be assessed early.

Physical examination may reveal reduced body weight, marked orthostatic decrease in blood pressure, an increase in pulse rate, and lack of jugular venous distention, all suggesting a reduction in extracellular fluid volume. Patients with prerenal AKI can appear volume overloaded in heart failure, cirrhosis, and nephrotic syndrome when effective arterial blood volume is reduced. In critically ill patients,

TABLE 72.2

Differential Diagnosis by Pathophysiologic Classification of AKI

Cause

Comments

Prerenal
Volume depletion
Decreased cardiac output
Systemic vasodilation
Afferent arteriolar vasoconstriction
Efferent arteriolar vasodilation

30%–60% of AKI
Renal losses, GI losses, hemorrhage
Right- or left-sided heart failure, cardiac tamponade
Sepsis, anaphylaxis, anesthetics
NSAIDs, calcineurin inhibitors, radiocontrast, hepatorenal syndrome, hypercalcemia
ACE inhibitors, ARBs

Intrinsic
Acute tubular injury
Ischemic
Nephrotoxic (drug)
Nephrotoxic (pigment)
Acute interstitial nephritis
Drug induced
Infection related
Autoimmune diseases
Malignancy
Intratubular obstruction
Paraprotein
Crystals
Acute glomerulonephritis
Macrovascular

~40% of AKI
Aminoglycosides, lithium, amphotericin, pentamidine, cisplatin, ifosfamide, radiocontrast
Rhabdomyolysis, intravascular hemolysis
Penicillins, cephalosporins, NSAIDs, PPIs, allopurinol, rifampin, sulfonamides, immune checkpoint inhibitors
Pyelonephritis, viral nephritides
Sjögren syndrome, sarcoidosis, SLE
Lymphoma, leukemia

Microvascular

Immunoglobulin light chains
Acute phosphate nephropathy, tumor lysis syndrome, ethylene glycol, acyclovir, indinavir, methotrexate
Postinfectious, cryoglobulinemia, RPGN, SLE
Increased renal vein pressure from increased intraabdominal pressure, bilateral renal vein thrombosis, bilateral renal artery
emboli
Atheroembolic disease, HUS, TTP, scleroderma renal crisis, malignant hypertension

Postrenal (Obstruction)
Intrinsic
Extrinsic

Approximately 10% of AKI
Bilateral ureteral stones, bladder outlet obstruction (prostatic enlargement or blood clot), neurogenic bladder
Retroperitoneal fibrosis, metastatic cancer

ACE, Angiotensin-converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; GI, gastrointestinal; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal antiinflammatory drugs; PPIs, proton pump inhibitors; RPGN, rapidly progressive glomerulonephritis; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

hemodynamic measurement by right heart catheterization may be necessary to differentiate volume overload from noncardiogenic pulmonary infiltrates. Trends in daily intake and output volumes also assist in determining the extracellular fluid volume of the critically ill patient. Monitoring urine output in the ICU is associated with improved detection of AKI, as well as reduced 30-day mortality in patients with AKI.30

Examination of the abdomen may reveal a tender, distended bladder in a lower urinary tract obstruction, and, when this is present, sterile postvoid bladder catheterization should be performed. A distended, tense abdominal wall may represent ascites, aggressive intravenous fluid resuscitation, or recent abdominal surgery. Intraabdominal pressure can be measured in the ICU to distinguish AKI from abdominal compartment syndrome, defined as intraabdominal pressure exceeding 20 mm Hg.31

Fever, skin rash, and arthralgias may be signs of systemic lupus erythematosus, vasculitis, endocarditis, or drug allergy with AIN. A history of recent aortic catheterization (e.g., cardiac catheterization) and the findings of livedo reticularis or a discolored toe are diagnostic clues for cholesterol or atheromatous emboli. Painless hematuria suggests acute GN or genitourinary malignancy, whereas painful hematuria is more consistent with obstruction.27

DIAGNOSTIC EVALUATION

Differentiating the two most common causes of AKI in hospitalized patients, prerenal AKI and ATN, may be difficult when both the effective arterial blood volume and the time course of the kidney injury are unknown.32 Here the term acute tubular injury may more accurately describe the pathology involved in intrinsic AKI from ischemic or toxic insults.33 Evaluation of urine volume, urinary sediment, and urinary indices (the last is useful only in patients with oliguria) is helpful in making the correct diagnosis (Table 72.3 and Fig. 72.2). Initial laboratory tests include a urinalysis, blood urea nitrogen (BUN), serum sodium, potassium, bicarbonate, and creatinine levels not only for the diagnosis but also for assessment of complications of AKI.27 The dipstick urinalysis, a low-cost test that provides rapid information about urinary protein and cellular content, is commonly underutilized. Among 3 tertiary care hospitals, a urinalysis was obtained less than half the time in patients diagnosed with AKI.34

Results from initial laboratory testing may prompt further evaluation. For example, in the absence of treatment with a sodium-glucose cotransporter-2 inhibitor, glycosuria occurring with a normal plasma glucose level offers evidence for proximal tubular dysfunction. The presence of amino acids and bicarbonate in the urine and/or elevated urinary fractional excretion of phosphate and uric acid can be used to confirm Fanconi syndrome (see Chapter 50).

Ratio of Blood Urea Nitrogen to Creatinine

The ratio of BUN to creatinine in healthy individuals is 10:1 to 15:1 (when both are expressed in mg/dL, or 40:1 to 60:1 when expressed in mmol/L). In prerenal AKI the ratio may exceed 20:1 because of a disproportionate increase in urea reabsorption resulting from elevated serum vasopressin levels. However, BUN-to-creatinine ratio has limited value in differentiating the type of AKI. Upper gastrointestinal tract bleeding, impaired protein anabolism (e.g., systemic corticosteroid administration), increased catabolism (e.g., sepsis), and increased

TABLE 72.3 Clinical and Laboratory Variables in the Differential Diagnosis Between Prerenal and Intrarenal Acute Kidney Injury

	Prerenal	Intrarenal
History	Volume loss from GI, urinary, skin, or blood or reduced EABV (e.g., heart failure, pancreatitis)	Drugs or toxin exposure, hemodynamic change
Clinical presentation	Hypotension or volume depletion	No specific symptoms or signs
Laboratory studies		
BUN/SCr	>20	<20
Sediment	Normal to few hyaline casts	Muddy brown casts
Uosm (mmol/kg)	>500	<350
Proteinuria	None to trace	Mild to moderate
UNa (mmol/L)	<20	>40
FENa (%)	<1	>1
FEUrea (%)	<35	>35
Novel biomarkers	None	IGFBP7*TIMP-2, KIM-1, cystatin C, NGAL, CYR61, others

BUN, Blood urea nitrogen; CYR61, cysteine-rich protein 61; EABV, effective arterial blood volume; FENa, fractional excretion of sodium; FEUrea, fractional excretion of urea; GI, gastrointestinal; IGFBP7*TIMP-2, insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinase 2; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase–associated lipocalin; SCr, serum creatinine; UNa, urinary sodium; Uosm, urinary osmolality.

protein intake all raise BUN levels. Furthermore, diminished urea production from decreased protein intake or underlying liver disease are associated with lower BUN levels. Also, elevations in serum creatinine levels may exceed BUN levels in patients with creatinine release from muscle breakdown, as in rhabdomyolysis.

Urine Volume

In AKI, urine volume directly correlates with residual GFR.35 Urine volume can indicate the severity of AKI and also provide important diagnostic information. Oliguric AKI (<500 mL/d) is typically associated with worse outcomes than AKI with preserved urine volume, especially with a positive fluid balance in the critical care setting.36-39 Oliguria commonly occurs in AKI caused by ATN, although it can be seen in early prerenal AKI or AIN. Wide variations in daily urine output suggest obstruction. Anuria (urine output <100 mL/d) suggests obstruction or a bilateral acute vascular catastrophe (renal vein or renal artery occlusion), shock, rarely kidney cortical necrosis, hemolytic uremic syndrome, or anti–glomerular basement membrane (GBM) antibody disease.27

Urinalysis and Urine Microscopy

In the setting of AKI, a dipstick urinalysis may reveal microhematuria or proteinuria but must be interpreted in conjunction with more specific tests such as a ratio of spot urinary protein or albumin to creatinine and urine microscopy. Dipstick urinalysis may not detect immunoglobulin free light chains (FLCs) or may be falsely positive for protein in the setting of radiographic contrast or alkaline urine. In conjunction with urine microscopy, the presence of urinary hemoglobin or myoglobin by dipstick can be further differentiated. Urine microscopy has been validated as a diagnostic and prognostic tool in hospitalized patients with AKI.32 A fresh urine sample is centrifuged, and the sediment is examined for the presence of cells, casts, and crystals (Figs. 72.3 and 72.4) (see also Chapter 4). Urine microscopy in early prerenal AKI is typically normal with occasional hyaline casts. “Muddy brown” granular casts and renal tubular epithelial cells in the urine support ATN-related AKI. In hospitalized patients with AKI, the presence of more than 10 granular casts per low-power field had a positive predictive value of 100% for a final diagnosis of ATN, and a urine sediment score based on granular casts and renal tubular epithelial cells was directly associated with worsening AKI. Thus, urine microscopy

is useful for distinguishing ATN-related AKI from prerenal AKI and predicting the severity of AKI.32

Findings on urinalysis and urine microscopy (see Chapter 4) may suggest CKD (broad, waxy casts), but, more important, they may be diagnostic clues to a rare cause of AKI. Proliferative GN may be characterized by considerable microhematuria and proteinuria by dipstick and an active urinary sediment consisting of red blood cells (RBCs) and RBC casts. In this setting the history and physical examination findings should be supported by serologic testing and a kidney biopsy, if the kidneys are normal in size. The presence of white blood cells (WBCs) in clumps and casts, in the absence of bacteria, suggests AIN.27 Renal tubular epithelial cells, granular casts, RBCs and, rarely, even RBC casts can occur in patients with AIN, whereas urinary eosinophils are no longer considered helpful in diagnosing AIN (see Chapter 64).40 A urine sediment with abundant uric acid crystals accompanying high serum phosphorus levels in a patient undergoing chemotherapy may indicate tumor lysis syndrome (TLS).

Fractional Excretion of Sodium and Urea

The urine-serum concentrations of sodium in relation to the urineserum concentrations of creatinine (fractional excretion of sodium [FENa]) have been used to approximate kidney tubular function:

$$FENa = \frac{[U/S]Na}{[U/S]Cr} \times 100\%$$

where U is urine, S is serum, Na is sodium, and Cr is creatinine. The basic premise is that renal tubular cells will reabsorb sodium in the prerenal setting, whereas tubules damaged by ATN will not.41 FENa less than 1% is consistent with prerenal AKI, and FENa greater than 3% is typical of ATN. However, FENa may be less than

1% despite ATN in the setting of sepsis, hemoglobinuria or myoglobinuria, radiocontrast exposure, nonoliguria, heart failure, and advanced cirrhosis. Underlying CKD, diuretic use, recent intravenous fluid administration, glycosuria, bicarbonaturia, and saltwasting disorders may be associated with elevated FENa despite the presence of prerenal AKI.41 Therefore, FENa has significant limitations in the setting of hospital-acquired AKI, yet may be helpful in differentiating prerenal AKI from ATN in specific patient populations with oliguria.

B
A

D

C

F

E

G

Fig. 72.3 Examples of Urinary Sediments Seen in Acute Kidney Injury (AKI). (A) Epithelial cell aggregate. (B) Hyaline cast as can be seen in prerenal AKI. (C) Epithelial cast as can be seen in early acute tubular necrosis (ATN; arrows indicate epithelial cells). (D) Muddy brown cast, typical of established ATN. (E) Erythrocyte cast as seen in glomerulonephritis and vasculitis. Inset: Hemoglobin cast. (F–G) Two forms of indinavir crystals.

Urea reabsorption, primarily occurring in proximal tubules, is less affected by loop and thiazide diuretics, and the fractional excretion of urea (FEUrea) may be an alternative to FENa in patients receiving diuretics. The calculation of FEUrea is identical to that of FENa, and values less than 35% favor prerenal AKI over ATN.

Laboratory Evaluation of Acute Kidney Injury in Systemic Illnesses

In the presence of systemic illness, additional laboratory evaluation may narrow the differential diagnosis of AKI. Serum complement levels of C3 and C4 are useful in differentiating causes of GN, particularly when a kidney biopsy is not feasible. Postinfectious GN, infective endocarditis, lupus nephritis, mixed cryoglobulinemia, and membranoproliferative GN are typically associated with low levels of serum C3 and/or C4 (see Chapter 22), whereas serum complement levels are normal in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti–glomerular basement antibody disease, and immunoglobulin A (IgA) vasculitis (HenochSchönlein purpura). Despite activation of the complement system in thrombotic microangiopathy (see Chapter 30), serum C3 and C4 can be maintained at normal levels through increased hepatic production.[42] Alternatively, when liver synthesis is impaired, low

Urinary Sediment in Acute Kidney Injury (AKI)
Normal or few RBCs or WBCs
or hyaline casts

Prerenal
Postrenal
Arterial
thrombosis or
embolism
Preglomerular
vasculitis
HUS or TTP
Scleroderma crisis

Abnormal

RBCs
RBC casts

WBCs
WBC casts

GN
Vasculitis
Malignant
hypertension
Thrombotic
microangiopathy

Interstitial
nephritis
GN
Pyelonephritis
Allograft
rejection
Malignant
infiltration of the
kidney

RTE cells
RTE casts
Pigmented
casts

ATN
Tubulointerstitial
nephritis
Acute cellular
allograft rejection
Myoglobinuria
Hemoglobinuria

Granular
casts

Eosinophiluria

Crystalluria

ATN

GN
Vasculitis
Tubulointerstitial nephritis

Allergic interstitial nephritis
Atheroembolic disease

Acute uric acid nephropathy
Calcium oxalate (ethylene glycol intoxication)
Drugs or toxins (acyclovir, indinavir, sulfadiazine, amoxicillin)

Fig. 72.4 Urinary sediment in acute kidney injury (AKI). ATN, Acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; RBC, red blood cell; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBC, white blood cell.

serum levels of C3 and/or C4 are less reliable in differentiating the type of acute GN.

In the right clinical setting, laboratory studies may support a specific cause of AKI. For example, AKI with thrombocytopenia, schistocytes on peripheral blood smear, and an elevated blood lactate dehydrogenase level would be consistent with thrombotic microangiopathy from atypical hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. However, these laboratory findings may also be present in sepsis with disseminated intravascular coagulation (DIC). AKI in sepsis with DIC typically results from ATN or antibiotic-related AIN and not thrombotic microangiopathy.

In the appropriate clinical setting, the following laboratory tests can help identify a cause: complete blood count with differential/platelet count, serum albumin, creatine kinase, uric acid, phosphorus, urine myoglobin, HIV antibody, hepatitis C antibody, cryoglobulins, rheumatoid factor, hepatitis B virus studies, antinuclear antibody, anti–double-stranded DNA antibody, ANCA, anti-GBM antibody, and serum FLC with ratio.

Imaging Studies

Kidney imaging may not be necessary if the explanation for AKI is apparent (e.g., prerenal AKI or ATN). However, when the diagnosis is uncertain, and especially if urinary obstruction or renal vascular occlusion are suspected, imaging is indicated.27 Risk factors associated with hydronephrosis include history of prior hydronephrosis, current urinary tract infection, abdominal or pelvic cancer, and neurogenic bladder.43 Point-of-care ultrasound is an emerging tool for assessing volume responsiveness in critically ill and ventilated patients, but it may also be a rapid and relatively low-cost option for excluding urinary obstruction in AKI (see Chapter 5).44 A dedicated kidney ultrasound can identify urinary obstruction, polycystic kidney disease, and the size and number of kidneys. When Doppler flow is used, renal arteries and veins can be assessed. Highresolution, noncontrast computed tomographic imaging is the preferred test for the detection of urinary tract calculi. Radionuclide renography using radiolabeled mercaptoacetyltriglycine (MAG3) may be used to estimate the kidney plasma flow in a transplanted kidney with AKI but is increasingly replaced by Doppler ultrasound. Other radionuclide methods are less useful in AKI (e.g., tagged WBC scan for AIN). Magnetic resonance imaging without contrast is now recommended to evaluate renal arterial or venous thrombosis.27

Kidney Biopsy

Kidney biopsy is reserved for patients in whom prerenal and postrenal AKI have been excluded and the cause of intrinsic AKI remains unclear (see Fig. 72.2). Kidney biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to diseasespecific therapy (e.g., vasculitis, systemic lupus erythematosus, and AIN).

Electronic Health Record to Predict Acute Kidney Injury

Computer-based models have been used to develop AKI electronic alerts.45 46 In one study, real-time alert of worsening of AKI by an AKI “sniffer” increased the timeliness of early therapeutic intervention.47 However, in a large randomized controlled study, an electronic alert system for AKI in hospitalized patients did not demonstrate any improvements in clinical outcomes and rather increased the use of health care resources.25 Further studies are needed to further define the utility of such AKI alerts.

ACUTE KIDNEY INJURY IN SPECIFIC SETTINGS

Acute Tubular Necrosis

ATN is a clinical syndrome of abrupt and sustained decline in GFR that is triggered by an acute ischemic or nephrotoxic event and develops within minutes to days after the insult.27 Apart from kidney biopsy, no definitive test can diagnose ATN. The diagnosis is suggested by a history of recent hypotension, volume depletion, sepsis, or nephrotoxic exposure. Muddy brown, coarse, granular casts are present on urine microscopy in the majority of patients with ATN, particularly those who are oliguric.27 Other laboratory findings consistent with the diagnosis of ATN are shown in Table 72.3.

The pathophysiology of ATN involves multiple pathways (see Chapter 70). Obstruction of flow within the tubule by cellular debris, disruptions of tubular cell polarity and cytoskeleton, loss of the lining epithelium with resulting backleak of glomerular filtrate into the kidney interstitium, and afferent arteriolar constriction all may play pathophysiologic roles in ATN. ATN has been described as a (mal)adaptive response of the kidney—“trading away” GFR for the preservation of medullary oxygenation and tubular integrity.33

ATN after ischemia/reperfusion injury is usually most severe within the outer medulla of the kidney (see Chapter 70).48 The typical histologic features of human proximal tubular injury include vacuolation, loss of brush border, disruption of the epithelial cells lining the tubule, and presence of intratubular casts. Necrosis of tubular cells is typically focal and may be missed in a biopsy specimen because most biopsies contain cortex and the outer medulla is not sampled adequately. Apoptosis of tubular cells is present in kidney biopsy specimens from humans with ATN, and evidence of cellular regeneration is often seen, most commonly in areas of greatest tubular cell loss. Regenerative changes and fresh epithelial injury are often observed in the same biopsy specimen, suggesting that recurrent episodes of tubular ischemia continue to occur during the maintenance phase of ATN. The morphologic appearance of the common forms of nephrotoxin-induced ATN is similar to that of ischemic ATN, with loss of microvasculature and immune cell infiltration. Correlations of morphologic findings to functional endpoints have been difficult.

Acute Interstitial Nephritis

AIN is characterized by the presence of inflammatory infiltrates and edema within the interstitium, with an acute deterioration in GFR (see Chapter 64).49 It is a relatively common cause of AKI, accounting for 15% to 27% of kidney biopsies performed because of AKI, yet AIN may be overlooked as a cause of AKI in settings in which ATN is common (e.g., sepsis). Drug use, in particular antimicrobials, proton pump inhibitors, and NSAIDs, is the most common cause of AIN (see Table 72.2).49

The diagnosis of AIN generally requires kidney biopsy. The clinical presentation of drug-induced AIN is variable, with a mean delay between drug exposure and the appearance of kidney manifestations of 10 days, although the latent period can be as short as 1 day with some antibiotics or as long as several months with NSAIDs.49 In AIN the reported frequency of symptoms included arthralgias (45%), fever (36%), and skin rash (22%). In the same analysis, urinary findings included nonnephrotic proteinuria (93%), leukocyturia (82%), and microscopic hematuria (67%).49 The classic clinical presentation of maculopapular rash, peripheral eosinophilia, and arthralgias may not be present in drug-induced AIN and is uncommon in infectionrelated or idiopathic AIN (see Table 72.2). Although the presence of urine eosinophils is not sensitive or specific for AIN, urinary levels of tumor necrosis factor α and interleukin-9 show promise as biomarkers of AIN.50

Acute Kidney Injury From Intratubular Obstruction

Several endogenous and exogenous molecules can precipitate in the tubular lumen to produce AKI, including uric acid, calcium phosphate, calcium oxalate, immunoglobulin FLCs, myoglobin, and medications (e.g., acyclovir, indinavir, methotrexate, sodium phosphate–containing cathartics, and sulfadiazine).27 Medication-induced crystal

nephropathy occurs more commonly when high doses of medication are combined with low tubular flow rates from volume contraction or underlying CKD.

Ethylene glycol ingestion from solvents and antifreeze may result in AKI from calcium oxalate crystal deposition. Patients with ethylene glycol poisoning typically have high anion gap metabolic acidosis because the ethylene glycol is metabolized into glycolic acid. The glycolic acid is converted to oxalic acid, which binds free calcium to form calcium oxalate crystals. Crystal deposition resulting in AKI typically manifests 48 to 72 hours after ingestion; oxalate crystals can be readily identified in the urine soon after exposure.

Intratubular obstruction from calcium phosphate and urate crystals contribute to AKI in TLS, which is characterized by a constellation of metabolic derangements caused by massive and abrupt release of intracellular components in the blood after rapid lysis of malignant cells. It is typically seen after initiation of cytotoxic therapy for hematologic malignancies with large tumor burden or cell counts.51 Clinical features of TLS result from the effects of the metabolic derangements. Nucleic acids released during cell lysis are metabolized to hypoxanthine and then xanthine, which is converted by xanthine oxidase to uric acid. With significant tumor lysis, severe hyperuricemia and intratubular obstruction from urate crystals may result. Hyperkalemia may induce cardiac arrhythmias, weakness (“spaghetti legs”), and paresthesias. Hyperphosphatemia initially produces muscle cramps and lethargy but also can promote nausea, vomiting, diarrhea, and seizure. Hypocalcemia, primarily caused by phosphorus binding, causes similar symptoms with muscle cramps, tetany, cardiac arrhythmias, and seizures.51 Hyperkalemia and hypocalcemia associated with AKI in a patient receiving cytotoxic chemotherapy may be the only initial clues to the syndrome because blood uric acid and phosphate levels are not routinely monitored. Urine microscopy can assist in the diagnosis by revealing the presence of many urate crystals.

Rhabdomyolysis

Rhabdomyolysis is characterized by the leakage of muscle-cell contents, including myoglobin, electrolytes, creatine kinase, aldolase, lactate dehydrogenase, nucleic acids, and aspartate aminotransferase into the circulation.52 AKI, occurring primarily in severe rhabdomyolysis, results from renal vasoconstriction, proximal tubular cell injury from oxidant stress, and intranephronal obstruction. Both myoglobin, a heme pigment protein that contains iron in the ferrous (Fe^{2+}) state, and uric acid have less nephrotoxicity in alkaline urine. Intravascular volume contraction and acidic urine promote distal tubule obstruction from myoglobin and uric acid precipitation.

A recent study showed that macrophages activated by platelets are able to form macrophage extracellular traps that are pathogenic in rhabdomyolysis-induced kidney injury.53 See Table 72.4 for common causes of rhabdomyolysis.52

Patients with acute rhabdomyolysis often present with muscle pain and reddish-brown urine. The presence of pigmented granular casts and the lack of RBCs on urine microscopy coupled with a blood-positive urinary dipstick are important diagnostic clues for rhabdomyolysis-related AKI. However, the diagnosis must be confirmed by elevated serum creatine kinase levels and the presence of urinary myoglobin.27 A weak correlation exists between creatine kinase values and the incidence of AKI. The risk for AKI is lower when creatine kinase levels are less than 20,000 U/L. Rhabdomyolysis may contribute to AKI with creatinine kinase levels as low as 5000 U/L when coexisting conditions such as sepsis, intravascular volume contraction, and acidosis are present.52

TABLE 72.4

Trauma[a]
Crush injury
Prolonged immobilization
Limb compression from loss of consciousness
[a]Most

Causes of Rhabdomyolysis 52
Increased
Exertion
Seizure
Alcohol withdrawal
Strenuous exercise

Genetic Defects Infections
Disorders of glycolysis or gluconeogenesis
Disorders of lipid metabolism
Mitochondrial disorders

Influenza A and B
Coxsackievirus
Epstein-Barr virus
Streptococcus pyogenes
Pyomyositis (Staphylococcus aureus)
Clostridioides

Body Temperature Changes

Drug or Toxin Exposure

Heat stroke
Neuroleptic malignant syndrome
Hypothermia
Malignant hyperthermia

Lipid-lowering drugs
Alcohol[a]
Quetiapine
Cocaine[a]
Heroin[a]

Metabolic and Electrolyte Disorders
Hypokalemia
Hypophosphatemia
Hypocalcemia
Nonketotic

hyperosmotic
conditions
Diabetic ketoacidosis

commonly associated with acute kidney injury.

Acute Kidney Injury in Myeloma

Monoclonal immunoglobulin FLCs are responsible for the majority of severe AKI in patients with myeloma. In such patients, monoclonal FLCs are overproduced, often with circulating levels hundreds of times higher than normal.54 Unlike most endogenously produced proteins, monoclonal FLCs have a strong propensity to cause tubular damage (see Chapter 28).54 Some κ monoclonal FLCs are cytotoxic and promote proximal tubular cell injury, with one mechanism resulting in a defect in sodium-coupled cotransport processes producing type II renal tubular acidosis, aminoaciduria, phosphaturia, and glycosuria (i.e., Fanconi syndrome).55 A separate mechanism of FLC-mediated AKI is intratubular obstruction from precipitation of monoclonal FLCs in the distal nephron, that is, cast nephropathy.27 Cast formation occurs under specific conditions mediated by the ionic composition of tubule fluid, tubule fluid flow rates, the concentration of Tamm-Horsfall glycoprotein and FLCs, the strength of the binding interaction between TammHorsfall glycoprotein and FLC, and the presence of furosemide.54

AKI attributed to cast nephropathy occurs in approximately onethird of patients with multiple myeloma and AKI. Other causes of AKI include extrarenal obstruction (e.g., nephrolithiasis, amyloid deposition in the ureters), hypercalcemia, hyperviscosity syndrome, and non–myeloma-related causes (e.g., AIN or contrast-associated AKI).27 56

Cast nephropathy should be considered, particularly in older patients with unexplained AKI. Predisposing conditions may include hypercalcemia, intravascular volume contraction, furosemide use, exposure to radiocontrast, and/or NSAID use. AKI may be the presenting event in patients with an undiagnosed plasma cell dyscrasia. Because FLC may not be detected on dipstick analysis, urinalysis in cast nephropathy will often show no or trace protein and the urinary sediment is typically bland. Assay of serum FLC levels is critical in assisting in the differential diagnosis of unexplained AKI (Chapter 68), but kidney biopsy may be needed to diagnose cast nephropathy. A low urinary albumin excretion

(<10%) assessed with 24-hour urine electrophoresis was found useful in distinguishing cast nephropathy from ATN and less acute causes of kidney injury in multiple myeloma (e.g., amyloid lightchain [AL] amyloidosis and monoclonal immunoglobulin deposition disease).57

Contrast-Associated AKI

Historically, AKI occurring shortly after exposure to intravenous radiocontrast was termed contrast-induced nephropathy. However, iodinated contrast exposure may be one of multiple causes of AKI following a radiographic study or procedure. In a retrospective analysis with statistical adjustment, incidence rates of AKI were similar between contrast and noncontrast groups (5.5% vs. 5.6%, respectively).58 The broader term, contrast-associated AKI, has gained favor in describing the pathophysiology of an AKI after contrast exposure.56 The incidence of contrast-associated AKI is low (<1%) in patients with normal kidney function and no other risk factors for AKI.27 Risk factors for contrast-associated AKI include CKD, diabetic nephropathy, advanced heart failure, states of reduced kidney perfusion, high total dose of contrast, and concomitant exposure to other nephrotoxins. Data from animal models suggest that both renal vasoconstriction from direct effects of the contrast media and toxic injury of tubular cells (likely from activation of osmolality-sensitive aldose reductase in the proximal tubule) are the main factors in the pathophysiology of contrast-associated AKI.59 Emerging data suggest a role for contrast-induced uricosuria in the pathogenesis of contrastassociated AKI.60 The kidney injury likely occurs within minutes of contrast exposure; however, the detection of AKI is typically delayed by 24 to 48 hours after contrast exposure. The timing of AKI in relation to contrast exposure and the exclusion of other causes of AKI generally suffice for diagnosis. Urinalysis and urine sediment findings are typically consistent with ATN. Kidney biopsy is generally not helpful in the setting of contrast-associated AKI because the expected findings of ATN are nonspecific, no specific treatment exists, and the kidney injury is typically short lived.

SELF-ASSESSMENT QUESTIONS

A 20-year-old man with Marfan syndrome is admitted to the hospital for elective aortic valve replacement and endovascular repair of a distal (type B) thoracic aortic dissection. On postoperative day 4, his urine output decreases to 420 mL over a 24-hour period and the urine appears dark in his Foley catheter collection bag. He requires mechanical ventilation and pressor support, with a mean arterial blood pressure of 70 mm Hg. There is no rash visible on examination. Available laboratory data are as follows.

Preoperation Blood

Postoperation Day 4 Blood

Postoperation Day 4 Blood

Sodium	140 mEq/L
Potassium	4.0 mEq/L
Chloride	108 mEq/L
Bicarbonate	24 mEq/L
BUN	12 mg/dL
Creatinine	0.6 mg/dL

Sodium	141 mEq/L
Potassium	6.1 mEq/L
Chloride	106 mEq/L
Bicarbonate	14 mEq/L
BUN	24 mg/dL
Creatinine	4.4 mg/dL

Arterial Blood Gas

pH	7.27
P_{CO_2}	31 mm Hg
P_{O_2}	97 mm Hg
HCO_3	14 mEq/L

Glucose	100 mg/dL

Glucose
Calcium
Phosphate
Albumin
Osmolality
Lactate

98 mg/dL
5 mg/dL
10.2 mg/dL
3.8 g/dL
294 mOsm/kg
Normal

Urinalysis
Specific gravity
pH
Protein
Blood
Ketones
Red blood cells

1.028
6.0
Negative
Positive
Negative
None

1. What is the most appropriate next diagnostic test?
A. Serum creatine kinase level
B. Kidney ultrasound with Doppler
C. Kidney biopsy
D. Serum antineutrophil cytoplasmic antibody
E. Fractional excretion of urea

2. Which test result is most consistent with preserved kidney tubular function in a person who is volume contracted and has healthy kidneys?
A. Urine osmolality of 300 mOsm/kg
B. Fractional excretion of urea of 45%
C. BUN of 34 mg/dL
D. Spot urine sodium of 40 mEq/L
E. None of the above

3. A 78-year-old man is brought to the emergency department by his family because of worsening confusion throughout the day. One week ago the patient fell and fractured his distal radius, necessitating splinting and pain medication. His medical history was pertinent with chronic kidney disease stage 3 (baseline serum creatinine 1.4 mg/dL), longstanding hypertension, chronic obstructive pulmonary disease, osteopenia, and benign prostatic hypertrophy. Current medications included lisinopril 20 mg/d, amlodipine 5 mg/d, hydrochlorothiazide 25 mg/d, doxazosin 4 mg nightly, oxycodone 5 mg every 8 hours as needed for arm pain, vitamin D 2000 U/d, and ipratropium bromide–albuterol inhaled 4 times per day. Arrival vital signs include blood pressure 176/92 mm Hg, pulse 114/min, respirations 18/min, weight 55 kg, and temperature 98.5°F. Physical examination revealed an agitated older man with flat neck veins, reduced air movement on chest auscultation, a large and tender abdomen, a right forearm cast, and trace lower extremity edema. No skin lesions were seen or palpated. Initial laboratory test results were as follows: sodium 138 mEq/L, potassium 5.2 mEq/L, chloride 110 mEq/L, bicarbonate 20 mEq/L, BUN 54 mg/dL, serum creatinine 2.6 mg/dL, leukocyte count 7500 cells/mL, hemoglobin 11.2 g/dL, platelet count 150,000 cells/µmol, alanine aminotransferase 28 U/L

(normal 15–58 U/L), aspartate aminotransferase 36 U/L (normal 15–40 U/L), and prothrombin time 14 seconds. Urinalysis with microscopy: specific gravity 1.010, no blood or protein, and a bland sediment with no casts and few cells. What is the most appropriate next diagnostic test?

A. Kidney ultrasound with Doppler
B. Peripheral blood smear
C. Kidney biopsy
D. Postvoid bladder catheterization
E. None of the above

REFERENCES

1. Group TKDIGOKW. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Supp. 2012;2:1–138.
2. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care.2004;8:R204-R212.
3. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
4. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16:3365–3370.
5. Mehta RL, Burdmann EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. Lancet. 2016;387:2017–2025.
6. Kohli HS, Bhaskaran MC, Muthukumar T, et al. Treatment-related acute renal failure in the elderly: a hospital-based prospective study. Nephrol Dial Transplant. 2000;15:212–217.
7. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. Am J Kidney Dis. 2015;65:860–869.
8. Bouchard J, Acharya A, Cerda J, et al. A prospective International Multicenter study of AKI in the intensive care Unit. Clin J Am Soc Nephrol. 2015;10:1324–1331.
9. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. J Am Soc Nephrol. 2009;20:1217–1221.
10. Koyner JL. Assessment and diagnosis of renal dysfunction in the ICU. Chest. 2012;141:1584–1594.
11. Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open. 2020;3:e2019209.
12. Basu RK, Wong HR, Krawczeski CD, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. J Am Coll Cardiol. 2014;64:2753–2762.
13. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40:221–226.
14. Ravn B, Rimes-Stigare C, Bell M, et al. Creatinine versus cystatin C based glomerular filtration rate in critically ill patients. J Crit Care. 2019;52:136–140.
15. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17:R25.
16. Liu KD, Vijayan A, Rosner MH, Shi J, Chawla LS, Kellum JA. Clinical adjudication in acute kidney injury studies: findings from the pivotal TIMP-2*IGFBP7 biomarker study. Nephrol Dial Transplant. 2016;31:1641–1646.
17. Joannidis M, Forni LG, Haase M, et al. Use of cell cycle arrest biomarkers in conjunction with classical markers of acute kidney injury. Crit Care Med. 2019;47:e820–e826.
18. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol. 2015;26:2023–2031.
19. Ichimura T, Asseldonk EJ, Humphreys BD, Gunaratnam L, Duffield JS, Bonventre JV. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest. 2008;118:1657–1668.
20. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. Nephrol Dial Transplant. 2014;29:1301–1311.

21. Vaidya VS, Ozer JS, Dieterle F, et al. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. Nat Biotechnol. 2010;28:478–485.

22. Viau A, El Karoui K, Laouari D, et al. Lipocalin 2 is essential for chronic kidney disease progression in mice and humans. J Clin Invest. 2010;120:4065–4076.
23. Nejat M, Pickering JW, Devarajan P, et al. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney Int. 2012;81:1254–1262.
24. Kellum JA, Chawla LS, Keener C, et al. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med. 2016;193:281–287.
25. Wilson FP, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet. 2015;385:1966–1974.
26. Selby NM, Casula A, Lamming L, et al. An Organizational-Level Program of Intervention for AKI: a pragmatic stepped wedge cluster randomized trial. J Am Soc Nephrol. 2019;30:505–515.
27. Sanders PW AA. Acute Kidney Injury. In: N E, ed. Canada: Decker Intellectual Properties; 2010.
28. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74:101–107.
29. Bhanushali GK, Jain G, Fatima H, Leisch LJ, Thornley-Brown D. AKI associated with synthetic cannabinoids: a case series. Clin J Am Soc Nephrol. 2013;8:523–526.
30. Jin K, Murugan R, Sileanu FE, et al. Intensive monitoring of urine output is associated with increased detection of acute kidney injury and improved outcomes. Chest. 2017;152:972–979.
31. De Waele JJ, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal hypertension and abdominal compartment syndrome. Am J Kidney Dis. 2011;57:159–169.
32. Perazella MA, Coca SG, Hall IE, Iyanam U, Koraishy M, Parikh CR. Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients. Clin J Am Soc Nephrol. 2010;5:402–408.
33. Rosen S, Stillman IE. Acute tubular necrosis is a syndrome of physiologic and pathologic dissociation. J Am Soc Nephrol. 2008;19:871–875.
34. Moledina DG, Belliveau O, Yamamoto Y, et al. Variation in best practice measures in patients with severe hospital-acquired acute kidney injury: a multicenter study. Am J Kidney Dis. 2020.
35. Rahman SN, Conger JD. Glomerular and tubular factors in urine flow rates of acute renal failure patients. Am J Kidney Dis. 1994;23:788–793.
36. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12:R74.
37. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76:422–427.
38. Bellomo R, Cass A, Cole L, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Crit Care Med. 2012;40:1753–1760.
39. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011;6:966–973.
40. Perazella MA, Bomback AS. Urinary eosinophils in AIN: farewell to an old biomarker? Clin J Am Soc Nephrol. 2013;8:1841–1843.
41. Perazella MA, Coca SG. Traditional urinary biomarkers in the assessment of hospital-acquired AKI. Clin J Am Soc Nephrol. 2012;7:167–174.
42. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371:654–666.
43. Licurse A, Kim MC, Dziura J, et al. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification

framework. Arch Intern Med. 2010;170:1900–1907.
44. Nepal S, Dachsel M, Smallwood N. Point-of-care ultrasound rapidly and reliably diagnoses renal tract obstruction in patients admitted with acute kidney injury. Clin Med. 2020;20:541–544.
45. Sutherland SM, Chawla LS, Kane-Gill SL, et al. Utilizing electronic health records to predict acute kidney injury risk and outcomes: workgroup statements from the 15(th) ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:11.

References

46. Selby NM, Crowley L, Fluck RJ, et al. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. Clin J Am Soc Nephrol. 2012;7:533–540.
47. Colpaert K, Hoste EA, Steurbaut K, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. Crit Care Med. 2012;40:1164–1170.
48. Lieberthal W, Nigam SK. Acute renal failure. I. Relative importance of proximal vs. distal tubular injury. Am J Physiol. 1998;275:F623-F631.
49. Praga M, González E. Acute interstitial nephritis. Kidney Int. 2010;77:956–961.
50. Moledina DG, Wilson FP, Pober JS, et al. Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. JCI Insight. 2019;4.
51. Judd EMS, Tolwani A. Specific Etiologies of Acute Kidney Injury. In: EVRM L, ed. Clinical Decisions in Nephrology, Hypertension, and Renal Transplantation. New York: Springer; 2013:199–236.
52. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62–72.
53. Okubo K, Kurosawa M, Kamiya M, et al. Macrophage extracellular trap formation promoted by platelet activation is a key mediator of rhabdomyolysis-induced acute kidney injury. Nat Med. 2018;24:232–238.

54. Hutchison CA, Batuman V, Behrens J, et al. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. Nat Rev Nephrol. 2011;8:43–51.
55. Sanders PW. Mechanisms of light chain injury along the tubular nephron. J Am Soc Nephrol. 2012;23:1777–1781.
56. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. N Engl J Med. 2019;380:2146–2155.
57. Leung N, Gertz M, Kyle RA, et al. Urinary albumin excretion patterns of patients with cast nephropathy and other monoclonal gammopathyrelated kidney diseases. Clin J Am Soc Nephrol. 2012;7:1964–1968.
58. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol. 2017;28:653–659.
59. Persson PB, Hansell P, Liss P. Pathophysiology of contrast mediuminduced nephropathy. Kidney Int. 2005;68:14–22.
60. Kanbay M, Solak Y, Afsar B, et al. Serum uric acid and risk for acute kidney injury following contrast. Angiology. 2017;68:132–144.

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Epidemiology and Prognostic Impact of Acute Kidney Injury and Acute Kidney Disease

Neesh Pannu, Marcello Tonelli

INCIDENCE OF ACUTE KIDNEY INJURY

Epidemiologic studies have primarily identified acute kidney injury (AKI) through administrative data or changes in serum creatinine without specifying etiology. These studies have primarily focused on acute tubular necrosis in hospitalized populations and may not be generalizable to other forms of AKI. The incidence of AKI in unselected hospitalized patients is between 0.4% and 18%, depending on the definition used, and accounts for 1% to 4% of all hospital admissions.1 Large studies using administrative data suggest that the incidence of AKI in hospitalized patients has increased by approximately 13% per year over the last 3 decades.2 In these studies, incidence was identified by diagnostic codes that are highly specific for AKI (97%) but are relatively insensitive (35% sensitivity).3 The findings of such studies may be influenced by increasing clinical recognition of less severe AKI, leading to increased coding of AKI without a change in true incidence. In addition, there may be financial incentives to code patients as having AKI to increase reimbursement. However, similar increases have been observed in the incidence of AKI requiring kidney replacement therapy (KRT): in general, populations of hospitalized patients, as well as in specific settings including surgery, sepsis, stroke, cardiovascular events, and liver disease.4 Although more objective and clinically relevant than diagnostic codes, dialysis utilization may also be influenced by increased availability of KRT or changing trends in medical practice rather than true changes in the burden of disease.

The incidence of AKI can be estimated using consensus definitions based on serum creatinine and urine output (Table 73.1) and has been best characterized in critically ill populations. Despite using standardized definitions for AKI, multicenter studies of critically ill patients have reported the incidence of AKI to be between 10% and 67%, likely reflecting differences in case mix between health care systems and countries.5

Less is known about AKI in the community; there is significant etiologic and geographic variation in the reported incidence and risk factors for AKI in outpatient settings, where serum creatinine is infrequently measured. The concept of acute kidney disease (AKD) was proposed in the 2012 Kidney Disease: Improving Global Outcomes guidelines in recognition that subacute kidney injury may not meet criteria for AKI or chronic kidney disease (CKD) despite being clinically relevant (Fig. 73.1). AKI is recognized as a subset of AKD; the relationships between AKI, AKD, CKD, and the absence of kidney disease are shown in Fig. 73.2. A population-based study in Alberta, Canada (n = 921,116) compared the incidence and prognosis of AKD compared with AKI and CKD. AKD was 2.7-fold more prevalent than AKI, affecting 4.4% of the cohort, and was primarily identified in outpatients (77%).6

RISK FACTORS FOR AKI

Risk factors for AKI have been determined in a variety of clinical settings including cardiac surgery, contrast-induced AKI, and critically ill populations. However, risk prediction models that accurately predict the occurrence of AKI have been elusive. Nonmodifiable risk factors common to all populations are presented in Box 73.1

Age

Multiple studies show that AKI is more common in older individuals, and many have shown an independent association between AKI and older age.7 In a community-based prospective study, patients aged 80 to 89 years were 55 times more likely to develop AKI than adults younger than 50 years.8 Possible explanations for this association include (1) structural and functional changes associated with age that lead to diminished nephron reserve and reduced capacity for kidney autoregulation, (2) accumulation of comorbidity that increases susceptibility to AKI (vascular disease, diabetes, hypertension, CKD), and (3) increased exposure among older persons to medications and procedures that predispose to AKI.7

Reduced Estimated Glomerular Filtration Rate

Preexisting reduction in estimated glomerular filtration rate (eGFR) is a potent risk factor for AKI after exposure to radiocontrast,9 major surgery, and medical illness,10 although the pathophysiology underlying this association is poorly understood. It has been reported that the odds of developing dialysis requiring AKI are increased at lower baseline eGFR; the excess risk compared with normal eGFR was approximately twofold in patients with baseline eGFR 45 to 60 mL/min/1.73 m2, but more than 40-fold for patients with baseline eGFR less than 15 mL/min/1.73 m2 11 These associations were confirmed in several systematic reviews that demonstrate strong independent associations between risk for AKI and lower baseline eGFR12-14 (see Fig. 73.3). Although these analyses support a causal association between CKD and in-hospital AKI, little is known about how this association may be modified by the presence of one or more comorbidities, such as heart failure, or whether all causes of CKD confer similar risk for AKI.

Albuminuria

Albuminuria is also strongly associated with AKI risk. A case-control study of over 600,000 patients identified proteinuria as an independent predictor for AKI,11 which was replicated in multiple settings, including after cardiac surgery in Taiwan and in general population studies from the United States and Canada15-17 (Fig. 73.4).

Hyperuricemia

Two prospective randomized trials18 19 also found allopurinol plus hydration to be superior to hydration alone in preventing AKI following radiocontrast administration. Nevertheless, uric acid can also be a biomarker for other risk factors (e.g., mild CKD, cancer), and although the two studies are interesting, more data is needed before this intervention is recommended. A recent systematic review and meta-analysis

TABLE 73.1

Recent Consensus Definitions of Acute Kidney Injury

Definitions	Serum Creatinine Criteria	Urine Output Criteria
RIFLE (2003)	Increase in serum creatinine × 1.5 or decrease in GFR by 25% within 48 hr	Urine volume <0.5 mL/kg/hr for 6 hr
AKIN (2007)	Increase in serum creatinine × 1.5 or by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hr	Urine volume <0.5 mL/kg/hr for 6 hr
KDIGO (2012)	Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hr Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days Severity staging after initial criteria met	Urine volume <0.5 mL/kg/hr for 6 hr

GFR, Glomerular filtration rate.

AKI

AKI
stage 3

AKI
stage 2

AKD

1
2
3

4
5

‡

AKI
stage 1
Subacute
AKI and
normal
renal
function

*
Rapid reversal

0

2

7

14
Days

28

Fig. 73.1 Hypothetical Trajectories of Acute Kidney Disease (AKD). AKD follows on from acute kidney injury (AKI) in those patients who do not fully recover within 7 days. The trajectory of AKD can take many forms, largely depending on the severity of the initial AKI episode. Here, a series of hypothetical scenarios representing typical trajectories of the AKI-AKD continuum are depicted. Stage 3 AKI might slowly improve to stage 2 AKI and then progress to AKD (1). Stage 1 AKI might progress to stage 3 AKI, then improve rapidly to stage 1 AKI before progressing to stage 1 AKD (2). An episode of persistent AKI (>48 hr) might be followed by a period of sustained reversal, then a second episode of AKI leading to AKD (3). Stage 2 AKI might rapidly reverse (4). Subacute AKD might occur wherein the first 7 days are marked with slowly worsening kidney function that does not technically meet the criteria for AKI, and progress to stage 3 AKD (5). This trajectory can be seen in patients treated with chronic nephrotoxic medications (e.g., aminoglycosides). (From Chawla LS et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative [ADQI] 16 Workgroup. Nat Rev Nephrology. 2017;13[4]:241–257.)

(n = 13,084) of 18 studies also found that that the presence of hyperuricemia was independently associated with increased risk of contrastrelated AKI (adjusted odds ratio [OR], 1.68; 95% confidence interval [CI], 1.38–2.04).20 21

system inhibitors in decompensated heart failure and hypertension have shown that medication-associated increases in serum creatinine are associated with decreased mortality.22 These findings speak to the need for more precise definitions for AKI.

ASSOCIATION BETWEEN AKI AND ADVERSE OUTCOMES

Mortality

AKI is associated with high costs and adverse clinical outcomes, including excess mortality, increased length of hospital stay, development and/or progression of CKD, and requirement for chronic dialysis in survivors (Box 73.2). However, not all transient changes in serum creatinine are associated with kidney injury or poor outcomes. Randomized trials of diuretics and renin-angiotensin-aldosterone

Multiple observational studies demonstrate increased mortality among patients who develop AKI in hospital. In its most severe form (requirement for acute dialysis), AKI is associated with mortality ranging from 15% (AKI only) to 80% (AKI in critically ill patients).23 However, comparing patients with AKI to those without AKI does not distinguish between the increased risk for death caused by kidney disease per se and the increased risk associated with the underlying illness that was sufficiently severe to result in

Relationships of AKI, AKD, CKD, and the Absence of Kidney Disease
AKD staging
based on
GFR and
albuminuria

AKI staging
during AKI event

AKD

AKI

AKD and CKD staging based on
GFR and albuminuria

CKD

CKD staging is
“suspended” during AKI

Fig. 73.2 Relationships of AKI, AKD, CKD, and the absence of kidney disease according to KDIGO definitions. AKD, Acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NKD, no kidney disease; SCr, serum creatinine. (From Lameire NH, Levin A, Kellum JA et al. Haromizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes [KDIGO] Consensus Conference. Kidney Int. 2012;100[3]:516–526.)

Patient-Specific Risk Factors for Acute Kidney Injury

BOX 73.1

- Age
- Sex (male)
- Chronic kidney disease
- Proteinuria
- Diabetes
- Congestive heart failure
- Sepsis
- Volume depletion
- Chronic liver disease
- Hyperuricemia

AKI. Therefore, there is uncertainty about whether the association between AKI and mortality is truly independent. Nonetheless, the development of AKI signifies a poor prognosis in individual patients.

Small changes in serum creatinine of as little as 25% above baseline are a significant predictor of all-cause short-term mortality.24 A meta-analysis of eight studies of hospitalized patients (most of whom were critically ill or had heart failure) confirmed a graded relationship between increasing severity of AKI and short-term mortality.25 Most importantly, it confirmed that even mild forms of AKI are clinically relevant; an increase in serum creatinine of 0.3 mg/dL (26 μmol/L) was associated with a 2.3-fold increase in the relative risk for death. After adjustment for comorbidities, the ORs or hazard ratios (HRs) for death associated with AKI ranged from 1.7 to 1.92. Similar findings were reported in several population-based studies of unselected hospitalized patients.26

The association between AKI and mortality is likely influenced by several factors, including the presence of underlying CKD, the duration and severity of AKI, and the degree of recovery of kidney function. A population-based study of hospitalized AKI patients in Canada found that the relation between AKI and in-hospital mortality was strongest in those with severe AKI and baseline eGFR greater than 60 mL/min/1.73 m2, for whom the adjusted HR suggested a more than tenfold increase in the risk of death compared with those without AKI.26,27 The presence of CKD modifies this association; by comparison, in patients with a baseline eGFR less than 30 mL/min/1.73 m2, the adjusted HR of in-hospital mortality was increased fivefold compared with those without CKD or AKI. An analysis of postoperative AKI comparing kidney and survival outcomes in those with and without preexisting CKD (eGFR <45 mL/min/1.73 m2) found a lower attributable mortality rate because of AKI (HR 1.26, 95% CI 1.09–1.78) when subjects with prior CKD but no AKI were used as the reference.28

Although the incidence of AKI continues to climb, there has been a corresponding improvement in survival. A recent analysis reported a 19% decrease in mortality between 2000 and 2009 in patients who required acute dialysis. Whether this represents a trend toward earlier use of dialysis (rather than a true improvement in survival) requires further investigation.

Chronic Kidney Disease

Until recently, it was accepted that AKI survivors generally recovered kidney function and remained independent from dialysis. This assumption was supported by the findings of small cohort studies of predominantly critically ill patients. One recent study described longterm outcomes of 226 critically ill patients with previously normal eGFR who required acute dialysis for AKI and reported that 86% of survivors had “normal” kidney function at 5 years.29

However, an increasing number of recent studies have linked AKI survivorship to the development of CKD or end-stage kidney disease (ESKD). For example, in one study AKI (defined using ICD-9 codes)

Risk of Acute Kidney Injury as a Function of
Baseline Kidney Function (Albuminuria and eGFR)
for People With and Without Diabetes
32
No Diabetes

16

Diabetes

Adjusted HR

8
4
2
1
.5
.25
15

30

45

60
75
90
105
120
eGFR, mL/min/1.73 m2
Fig. 73.3 Hazard ratio (HR) of acute kidney injury for people with and without diabetes according to baseline
estimated glomerular filtration rate. eGFR, Estimated glomerular filtration rate.
32
No Diabetes
Diabetes

16

Adjusted HR

8
4
2
1
.5
.25
2.5

5

10

30
100
300
1,000
UACR (mg/g)
Fig. 73.4 Hazard ratio (HR) of acute kidney injury for people with and without diabetes according to the ratio

of urine albumin to creatinine. UACR, Urine albumin/creatinine ratio.

was associated with an eightfold increase in the risk for ESKD compared with subjects without AKI or CKD.30 A second cohort study evaluated the risk for progressive CKD after AKI in subjects with baseline eGFR greater than 45 mL/min/1.73 m2, finding that survivors of dialysis-dependent AKI had a 28-fold increased risk for developing stage 4 CKD (eGFR <30 mL/min/1.73 m2) or greater, compared with those without AKI.31

Since then, multiple studies have demonstrated an association between AKI and initiation or progression of CKD and/or ESKD in a variety of clinical settings, including cardiac surgery, cardiac catheterization, and in unselected hospitalized patients. A meta-analysis of 13 cohort studies reported that the HRs for CKD and ESKD were 8.8 (95% CI 3.1–25.5) and 3.1 (95% CI 1.9–5.0), respectively, compared with subjects without AKI. Kidney recovery after AKI appears to be

an important determinant of future kidney function;32 a Canadian population-based study showed that AKI that failed to return to within 25% of baseline kidney function was associated with a fourfold risk of CKD/ESKD.33 National kidney registry data from the United States shows that approximately 2% to 3% of patients with AKI requiring dialysis will fail to recover kidney function and/or progress to ESKD within 1 year.34 Recurrent episodes of AKI further increase the risk for progressive CKD; each additional AKI event after the first episode appears to double the risk for progression to stage 4 CKD.

It is possible that the apparent association between AKI and CKD is confounded by age, frailty, and unmeasured comorbidity. Also, it is sometimes difficult to distinguish AKI from progressive CKD, and there is the possibility that the observed associations are due to misclassification. However, AKI also has been linked to the development

Risk Factors for Chronic Kidney Disease After Acute Kidney Injury

BOX 73.2

- Age
- Baseline eGFR
- Congestive heart failure
- Hypertension
- Recurrent AKI
- Serum albumin during hospitalization
- Severity of AKI (AKI stage, requirement for dialysis)
- eGFR at hospital discharge

AKI, Acute kidney injury; eGFR, estimated glomerular filtration rate.

of CKD in children, in whom these potential confounders are less likely.35 A prospective single-center study of 126 critically ill pediatric AKI survivors who fully recovered kidney function reported that 10% of patients developed CKD (albumin-to-creatinine ratio ≥30 mg/g or eGFR <60 mL/min/1.73 m2) over 3 years of follow-up.36 Importantly, 38% of the cohort had mildly decreased eGFR (60–90 mL/min/1.73 m2), 3.2% had hypertension, and 8.7% had hyperfiltration—all risk factors for future CKD. Given that the median age of these patients at the time of the AKI episode was 0.5 years, these numbers likely underestimate the long-term risk for CKD for these children. Similar findings were reported in a meta-analysis of outcomes after pediatric hemolytic uremic syndrome.37

Cardiovascular Risk

Contrast-induced nephropathy after cardiac catheterization is known to be associated with excess risk for subsequent cardiovascular events; however, there are conflicting data about whether AKI is associated with an increased risk for cardiovascular events in patients without preexisting cardiovascular disease. Several large retrospective cohort studies of patients undergoing both vascular and nonvascular major surgery have recently confirmed an association between postoperative AKI and cardiovascular mortality.38 39 Further, a recent systematic review analyzed data from 25 cohort studies of patients (n = 254,408) with and without AKI and reported that AKI is associated with an 86% increased risk for cardiovascular mortality, a 38% increased risk for major adverse cardiovascular events, and a 40% increased risk for heart failure.40 The pathophysiology of this association remains unclear.

In summary, the development of AKI during hospitalization identifies a cohort of patients at high risk for adverse outcomes. Recognition of AKI therefore presents an opportunity to mitigate

future risk through appropriate monitoring and implementation of evidence-based care for CKD. However, US data suggest that only 5% of AKI survivors saw a nephrologist after hospital discharge,34 and AKI survivors with CKD and proteinuria often do not receive treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after discharge from hospital.41 This treatment gap is undoubtedly larger in patients with AKI from lower-income countries.

Health Care Costs

A single-center study of AKI in hospitalized patients demonstrated a direct relationship between severity of AKI and associated hospital length of stay and hospital costs.24 When defined as a 0.3 mg/dL (26 µmol/L) increase in serum creatinine, AKI was associated with an incremental hospitalization cost of $4886; a doubling of serum creatinine was associated with an incremental cost of $9000. Studies of specific populations of hospitalized patients support these findings; a recent study of the cost of AKI after cardiac surgery suggests that the average difference in postoperative costs ranges between $9000 and $14,000 depending on AKI severity. Postoperative AKI in noncardiac surgery is associated with an $11,308 increase in the median cost compared with patients who do not experience postoperative AKI.42 In multivariable analysis, AKI was the most costly postoperative complication for these patients and resulted in the largest proportion of resource use compared with all other complications. Another study of 5875 surgical patients found severe AKI requiring KRT to be the second most costly postoperative complication, with an estimated mean increase in hospital expenditures of $28,359 compared with an uncomplicated postoperative course, and resulted in almost twice the excess cost compared with cardiac arrest.43 However, none of these studies accounted for the impact of CKD on AKI and attendant costs, which is likely to be significant.

AKI AS A PUBLIC HEALTH ISSUE

Conservative population-based estimates of AKI incidence in hospitalized adults are in the range of 3000 per 100,000 person-years;44 the majority of these patients will survive to hospital discharge. The incidence of stage 4 CKD or greater in AKI survivors is approximately 120 per 100,000 person-years,45 and the number of adults developing new CKD after AKI may be as high as 100,000 per year in the United States alone. Extrapolated to a global scale, AKI is likely responsible for hundreds of thousands of new CKD cases each year. Given this tremendous burden of morbidity and mortality, strategies that mitigate the progression of CKD after AKI should be a public health priority.

SELF-ASSESSMENT QUESTIONS

1. All of the following are risk factors for AKI except:
A. age.
B. CKD.
C. congestive heart failure.
D. thyroid disorders.
E. diabetes.
2. The incidence of AKI in hospitalized patients has:
A. decreased by more than 10% annually over the past decade.
B. decreased by 1% over the past decade.
C. increased by more than 10% annually over the past decade.
D. increased by 1% annually over the past decade.
E. stayed the same.

3. AKI is associated with:
A. higher health care costs.
B. increased risk for CKD.
C. increased risk for chronic dialysis.
D. all the above.
4. The incidence of stage 4 CKD (eGFR < 30 mL/min/1.73 m^2) or greater in AKI survivors is approximately:
A. 1200 per 100,000 person-years.
B. 120 per 100,000 person-years.
C. 12 per 100,000 person-years.

D. 1.2 per 100,000 person-years.

REFERENCES

1. Lameire N, Van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. Nat Clin Pract Nephrol. 2006;2(7):364–377.
2. Waikar SS, Curhan GC, Wald R, et al. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17(4):1143–1150.
3. Waikar SS, Wald R, Chertow GM, et al. Validity of international classification of diseases, ninth revision, clinical modification codes for acute renal failure. J Am Soc Nephrol. 2006;17(6):1688–1734.
4. Sawhney S, Fraser D. Epidemiology of AKI: utilizing large databases to determine the burden of AKI. Adv Chron Kid Dis. 2017;24(4):194–204.
5. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–1423.
6. James MT, Levey A, Tonelli M, et al. Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. JAMA. 2019;2(4).
7. Coca SG. Acute kidney injury in elderly persons. Am J Kidney Dis. 2010;56(1):122–131.
8. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. BMJ. 1993;306(6876):481–483.
9. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy 1. JAMA. 2006;295(23):2765–2779.
10. Mehta RL, Pascual MT, Gruta CG, et al. Refining predictive models in critically ill patients with acute renal failure. J Am Soc Nephrol. 2002;13(5):1350–1357.
11. Hsu CY, Ordonez JD, Chertow GM, et al. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74(1):101–107.
12. James MT, Grams ME, Woodward M, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis. 2015;66(4):602–612.
13. Grams ME, Sang Y, Ballew SH, et al. A meta-analysis of the association of estimated GFR, albuminuria, age, race, and sex with acute kidney injury. Am J Kidney Dis. 2015;66(4):591–601.
14. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011;80(1):93–104.
15. Huang TM, Wu VC, Young GH, et al. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. J Am Soc Nephrol. 2011;22(1):156–163. PubMed PMID: 21115618.
16. Grams ME, Astor BC, Bash LD, et al. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21(10):1757–1764.
17. James MT, Hemmelgarn BR, Wiebe N, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376(9758):2096–2103.
18. Erol T, Tekin A, Katircibasi MT, et al. Efficacy of allopurinol pretreatment for prevention of contrast-induced nephropathy: a randomized controlled trial. Int J Cardiol. 2013;167(4):1396–1399.
19. Kumar A, Bhawani G, Kumari N, et al. Comparative study of renal protective effects of allopurinol and N-acetyl-cysteine on contrast induced nephropathy in patients undergoing cardiac catheterization. J Clin Diagn Res. 2014;8(12):HC03–HC07.
20. Zuo T, Jiang L, Mao S, et al. Hyperuricemia and contrast-induced acute kidney injury: a systematic review and meta-analysis. Int J Cardiol. 2016;224:286–294.
21. Kaushik M, Choo JC. Serum uric acid and AKI: is it time? Clin Kidney J. 2016;9(1):48–50.
22. McCoy I, Chertow GM. AKI-A relevant safety end point? Am J Kidney Dis. 2020;75(4):508–512.

23. Liano F, Pascual J, Madrid Acute Renal Failure Study Group. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Kidney Int. 1996;50(3):811–818.
24. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365–3370.
25. Coca SG, Peixoto AJ, Garg AX, et al. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis. 2007;50(5):712–720.
26. Pannu N, James M, Hemmelgarn BR, et al. Modification of outcomes after acute kidney injury by the presence of CKD. Am J Kidney Dis. 2011;58(2):206–213.
27. Pannu N, James M, Hemmelgarn BR, et al. Modification of outcomes after acute kidney injury by the presence of CKD. Am J Kidney Dis. 2011.
28. Wu VC, Huang TM, Lai CF, et al. Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. Kidney Int. 2011;80(11):1222–1230.
29. Schiffl H, Fischer R. Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. Nephrol Dial Transplant. 2008;23(7):2235–2241.
30. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223–228.
31. Lo LJ, Go AS, Chertow GM, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76(8):893–899.
32. Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury. Intensive Care Med. 2017;43(6):855–866.
33. Pannu N, James M, Hemmelgarn B, et al. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol. 2013;8(2):194–202.
34. United States Renal Data System. USRDS Annual Data Report; 2015. Ann Arbor, MI. https://render.usrds.org/2015/view/Default.aspx.
35. Askenazi DJ, Feig DI, Graham NM, et al. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006;73(1):184–189.
36. Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis. 2012;59(4):523–530.
37. Garg AX, Suri RS, Barrowman N, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. JAMA. 2003;290(10):1360–1370.
38. Ozrazgat-Baslanti T, Thottakkara P, Huber M, et al. Acute and chronic kidney disease and cardiovascular mortality after major surgery. Ann Surg. 2016;264(6):987–996.
39. Huber M, Ozrazgat-Baslanti T, Thottakkara P, et al. Cardiovascularspecific mortality and kidney disease in patients undergoing vascular surgery. JAMA Surg. 2016;151(5):441–450.
40. Odutayo A, Wong CX, Farkouh M, et al. AKI and Long-term risk for cardiovascular events and mortality. J Am Soc Nephrol. 2016.
41. Leung KC, Pannu N, Tan Z, et al. Contrast-associated AKI and use of cardiovascular medications after acute coronary syndrome. Clin J Am Soc Nephrol. 2014;9(11):1840–1848.
42. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Complications and costs after high-risk surgery: where should we focus quality improvement initiatives? J Am Coll Surg. 2003;196(5):671–678.
43. Davenport DL, Henderson WG, Khuri SF, Mentzer Jr RM. Preoperative risk factors and surgical complexity are more predictive of costs than postoperative complications: a case study using the National Surgical Quality Improvement Program (NSQIP) database. Ann Surg. 2005;242(4):463–468; discussion 8–71.
44. Hsu CY, McCulloch CE, Fan D, et al. Community-based incidence of acute renal failure. Kidney Int. 2007;72(2):208–212.
45. Amdur RL, Chawla LS, Amodeo S, et al. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 2009;76(10):1089–1097.

74

Prevention and Nondialytic Management of Acute Kidney Injury

Josée Bouchard, Etienne Macedo

Acute kidney injury (AKI) often results from a combination of insults. The most commonly associated causes are failure of kidney autoregulation, direct nephrotoxicity, ischemia/reperfusion, and inflammatory states. AKI severity predicts adverse outcomes, including requirement for kidney replacement therapy (KRT), length of hospital stay, and mortality. Studies using the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE); Acute Kidney Injury Network (AKIN); and Kidney Disease Improving Outcomes (KDIGO) classification systems (see Chapter 72) have shown that even small changes in creatinine levels are associated with short-term and longterm mortality.[1,2] Furthermore, the distant effects of AKI contribute to dysfunction of other organs, such as the heart, lungs, brain, and liver.[3] Consequently, primary prevention and early diagnosis of AKI are of primary importance. Once AKI has been detected, efforts to attenuate the effects of injury and treatment of its consequences are necessary.

RISK ASSESSMENT

Considering the conceptual model of AKI illustrated in Fig. 74.1, the first step in preventing AKI is an adequate risk assessment. The initial care of patients at risk should focus on identification and, if possible, reversal of the risk factors. Several factors are associated with AKI (Box 74.1). Risk scores are also available to help predict AKI development; most of them focus on specific situations (see Box 74.2).

However, in most clinical settings, there are scarce data to evaluate the potential impact of modifiable risk factors on AKI development and progression.

The most common identifiable risk factor is chronic kidney disease (CKD), and thus adequate determination of baseline kidney function is fundamental. Because 40% to 50% of patients do not have a baseline kidney function available, and the first creatinine measured in the hospital may be affected by the disease process occurring before hospital admission, CKD status is sometimes difficult to determine. In addition to the damage biomarkers, markers of kidney stress such as TIMP2*IGFBP7 have been shown to be helpful in identifying ongoing injury and enabling early assessment. For a further discussion of risk factors and scoring systems, see Chapters 72 and 73

PRIMARY PREVENTIVE MEASURES

Optimizing Volume and Hemodynamic Status

To prevent AKI, ensuring adequate kidney perfusion is essential. Prompt resuscitation of patients with hypoperfusion was shown to improve outcomes twenty years ago. Means of optimizing perfusion pressure include administration of fluid and the improvement of hemodynamic status and cardiac output. Common reasons for fluid administration and/or use of vasopressors to prevent AKI include hypovolemia, hypotension, and sepsis. However, assessment of volume status can be challenging, particularly in patients in the intensive care unit (ICU). In addition, studies in ICU patients or patients undergoing surgery have shown that only about half of hemodynamically unstable patients respond to fluid administration. There are no guidelines for optimizing hemodynamic and fluid status for kidney function preservation. Too often, the effect of fluid expansion on hemodynamic status and kidney function is retrospective and evaluated by trial and error. However, dynamic measures such as the passive leg raising maneuver and the fluid bolus test coupled with real-time stroke volume monitoring can determine fluid responsiveness accurately.[4,5] Unfortunately, these are rarely performed even in ICUs. On the ward, volume status assessment and response to fluid administration most often relies on blood pressure, heart rate, oxygen saturation, central venous pressure, and urine output. These parameters are not specific or sensitive, and thus better simple tools are urgently needed to assess volume status and fluid responsiveness outside ICUs. In emergency settings, pointof-care ultrasound can be useful. For example, a collapsing inferior vena cava at the end of expiration is suggestive of hypovolemia.

Four phases of fluid therapy have been conceptualized, including rescue, optimization, stabilization, and deescalation.[6] Rescue implies the “administration of fluid for immediate management of life-threatening conditions associated with impaired tissue perfusion.” Optimization refers to the “adjustment of fluid type, rate, and amount based upon context to achieve optimization of tissue perfusion.” Fluid boluses are used during the rescue phase, whereas fluid challenges are administered during the optimization phase. Fluid bolus in an adult typically includes the infusion of 500 mL of isotonic fluids over 15 minutes or less without close monitoring. Fluid challenge involves the administration of 250 mL or 3 mL/kg of isotonic fluids over 5 to 10 minutes with stroke volume (SV) reassessment. Some studies have defined fluid responders as an increase of 10% to 15% of SV or cardiac output after fluid challenge. These two phases are essential in preventing AKI secondary to hypoperfusion.

Stabilization aims for achieving a neutral or slightly negative fluid balance to favor organ support, and de-escalation is defined by the “minimization of fluid administration, mobilization of extra fluid to optimize fluid balance.” In the stabilization and de-escalation phases, clinicians should target a neutral and then a negative fluid balance if fluid overload is present. To obtain a neutral or negative fluid balance, fluid administration should be minimized and oral or intravenous (IV) diuretics or even ultrafiltration may be required depending on the clinical scenario and underlying kidney and cardiac function.

Adverse outcomes associated with fluid overload include cardiopulmonary complications, delayed wound healing and kidney function recovery, and increased mortality.[7,8] A meta-analysis has confirmed an association between elevated central venous pressure most often measured within 24 hours of ICU admission and AKI, suggesting a role of venous congestion in the development of AKI.[9]

Conceptual Model for AKI

Complications

Normal

Increased
risk

Risk assessment

Damage
Primary
prevention

↓ GFR

Secondary prevention

Kidney
failure

Death

Therapy

Fig. 74.1 Conceptual model for acute kidney injury (AKI). GFR, Glomerular filtration rate. (Modified from Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.)

Major Risk Factors for Acute Kidney Injury

BOX 74.1

Patient Factors
- Older age (>75 years)
- Diabetes
- Liver failure
- Chronic kidney disease
- Atherosclerosis
- Kidney artery stenosis
- Hypertension
- Hypotension
- Hypercalcemia
- Hyperuricemia
- Sepsis
- Perioperative cardiac dysfunction
- Rhabdomyolysis
- Tumor lysis syndrome

Medications and Agents
- Nonsteroidal antiinflammatory drugs
- Cyclooxygenase-2 inhibitors
- Cyclosporine or tacrolimus
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Iodinated radiocontrast agent
- Hydroxyethyl starch
- Aminoglycosides

- Amphotericin

Procedures

- Cardiopulmonary bypass procedures
- Surgery involving aortic clamp
- Increased intra-abdominal pressure
- Large arterial catheter placement with risk for atheroembolization
- Liver transplantation
- Kidney transplantation

There is controversy about the optimal fluid to use for resuscitation. The 2012 KDIGO AKI guideline suggests that isotonic crystalloids should be used instead of synthetic (hydroxyethyl starch [HES]) and nonsynthetic (albumin) colloids for intracellular volume expansion in patients at risk or presenting with AKI, in the absence of hemorrhagic shock.10 Large studies have clearly demonstrated that HES solutions increase the risk for AKI. A randomized controlled trial (RCT) in 7000 ICU patients has shown that even solutions with lower molecular weight such as 6% HES 130/0.4 increased the need for KRT compared with 0.9% sodium chloride (normal saline).11 Another large RCT including 804 patients with severe sepsis has shown that 6% HES 130/0.4 is detrimental to kidney function and also survival compared with Ringer acetate.12 The mechanism of HES-induced AKI may be because of proximal kidney epithelial cell uptake of HES causing an acquired lysosomal storage disease. Therefore, HES should be avoided in patients at risk for and with AKI.

For albumin, the Saline Versus Albumin Fluid Evaluation (SAFE) trial of 6997 critically ill patients found that fluid resuscitation with saline or albumin resulted in similar relative risks for death.13 In addition, no significant differences were found in new single-organ and multiple-organ failure or days on KRT. Two subgroup analyses from this study showed that use of albumin may be deleterious in patients with traumatic brain injury and potentially beneficial in sepsis.

Albumin can be considered when substantial amounts of crystalloids (e.g., 2 L) are required to maintain adequate mean arterial pressure (MAP), especially in septic patients. However, its effect must be balanced against its potential risks; that is, it is possibly deleterious in patients with trauma and has low potential for transmission of infectious diseases.

The type of crystalloids used can also influence kidney outcomes.

When comparing kidney artery flow velocity and cortical tissue perfusion, there was a significant reduction in artery flow and cortical tissue perfusion with isotonic saline but not with the use of chloriderestrictive fluids. Indeed, greater chloride delivery to the macula densa may activate tubuloglomerular feedback, triggering kidney vasoconstriction and reduced glomerular filtration rate (GFR). Two large single-center RCTs have shown beneficial effects of chloride-restrictive

BOX 74.2

Situations

Specific Risk Factors for the Development of Acute Kidney Injury in Common Clinical

Cardiac Surgery
Female sex
COPD
Proteinuria
Preoperative SCr >2.1 mg/dL
Anemia
Insulin-dependent diabetes
ACE inhibitor therapy
Heart failure
LV ejection fraction < 35%
Preoperative IABP
Hyperglycemia
Hyperuricemia
Emergency surgery
Valve Surgery only
Previous cardiac surgery
Other cardiac surgery
Combination of CABG + valve surgery
Blood transfusion
Critically Ill
High A–a gradient
Low serum albumin
Proteinuria
Hyperglycemia
High intra-abdominal pressure
Active cancer
Age
SCr >1.3 mg/dL
Serum bilirubin > 1.5 mg/dL
Elevated CVP > 8 cm
Hemodynamic instability
Sespsis
Gastrointestinal and Endocrine
Cirrhosis/biliary surgery
Obstructive jaundice
Diabetes mellitus
Hyperglycemia

Hemodynamic
Congestive heart failure
Aortic cross-clamping
Cardiac instability
Major vascular surgery
Infection/sepsis
Multiorgan failure
Iodinated Contrast Administration
Age > 75 yr
Heart failure
Diabetes mellitus
SCr > 1.5 mg/dL or eGFR < 60 mL/min/1.73 m2
History of pulmonary edema
Anemia/blood loss (Hct < 395 for men, < 36% for women)
Hyperuricemia

Volume of contrast > 100 mL
Intra-arterial injection
Systolic BP < 80 mm Hg for > 1 hour and need for inotropic support or IABP 24 hours after procedure
Use of IABP
Nephrotoxic Antibodies
Volume depletion
Older age
Chronic kidney disease
Amphotericin
Aminoglycosides
Duration of therapy > 7 days
Volume depletion
Divided dose regimens
Liver disease
Miscellaneous
Age
Proteinuria
Hypertension
Massive blood transfusion

aA–a

gradient is the alveolar-arterial oxygen gradient calculated with the sea level standard formula (713 × Fi o2) − (Pco2/0.8) − Pao2, where Fio2 is fractional inspired oxygen concentration, Pao2 is arterial partial oxygen pressure, and Pco2 is partial carbon dioxide pressure.
ACE, Angiotensin-converting enzyme; BP, blood pressure; CABG, coronary arterial bypass graft; COPD; chronic obstructive pulmonary disease;
CVP, central venous pressure; Hct, hematocrit; IABP: intra-aortic balloon pump; LV, left ventricular; SCr, serum creatinine.

fluids.14 15 In critically ill adults, chloride-restrictive fluids (lactated Ringer's solution or Plasma-Lyte) compared with isotonic saline decreased major kidney events (MAKE), defined as the composite outcome of death from any cause, new kidney replacement therapy, or persistent kidney dysfunction (14.3% vs. 15.4%; odds ratio [OR], 0.91; 95% confidence interval [CI], 0.84–0.99; P = .04).14 In noncritically ill adults, chloride-restrictive fluids (lactated Ringer's solution or Plasma-Lyte) also decreased the incidence of MAKE compared with isotonic saline (4.7% vs. 5.6%; OR, 0.82; 95% CI, 0.70–0.95; P = .01).15
A meta-analysis in critically ill patients has found that resuscitation with chloride-restrictive fluids decreased 30-day mortality and need for KRT compared with isotonic saline.16 Other RCTs are underway to confirm these findings (PLUS and BASICS trials). The choice of chloride-rich (isotonic saline) versus low-chloride solutions (lactated

Ringer's solution or Plasma-Lyte) should be based on the patient's clinical condition, including electrolyte and acid-base balance. Physicians must also remember that the sodium content of isotonic saline is 154 mEq/L, whereas it is 130 mEq/L for lactated Ringer's and 140 130 mEq/L for Plasma-Lyte. Of note, normal saline should be used in head-injured patients and patients with severe liver disease or other conditions imposing risk of worsening cerebral edema.
There is no consensus on how to use vasopressors to prevent AKI or avoid further deterioration of kidney function. According to international guidelines for sepsis management, after initial fluid resuscitation with 30 mL/kg of crystalloids and addition of albumin in patients requiring substantial amounts of crystalloids to maintain adequate MAP, vasopressors should be initiated targeting a MAP above 65 mm Hg.17 In sepsis, norepinephrine is the first-choice

vasopressor. In addition, angiotensin II and vasopressin are noncatecholamine options that may improve glomerular flow through several mechanisms. With regard to the kidney, one RCT showed that vasopressin is equivalent or may be better than norepinephrine to improve kidney outcomes in patients with septic shock.18 KRT was required in 25% of patients in the vasopressin group and in 35% of the norepinephrine group; however, rates of KRT were comparable among survivors from each group, and the overall mortality rate was also similar between groups.

Inotropic agents such as dobutamine should be administered if myocardial dysfunction or ongoing signs of hypoperfusion are present.

The optimal MAP values to prevent AKI need to be better delineated. One study has found that in hypertensive patients with septic shock, targeting MAP between 80 to 85 mm Hg instead of 65 to 70 mm Hg reduced the risk for AKI and KRT, whereas the risk for atrial fibrillation seemed to be heightened.19 Therefore, target MAP values may need to be individualized depending on age, hypertension status, and degree of peripheral artery and renovascular disease and are likely to be between 60 and 80 mm Hg.

Prevention of Contrast-Induced Acute Kidney Injury

The concept of contrast-induced AKI (CI-AKI) has been recently questioned. However, physicians are less likely to prescribe contrast to patients with lower estimated GFR (eGFR) and more likely to prescribe IV fluids when contrast is administered, which may affect results from observational studies.

According to the KDIGO guideline, measures to reduce the risk of AKI should be implemented in patients with a baseline eGFR below 45 mL/min/1.73 m2 for IV iodinated contrast administration. For prevention of CI-AKI, patients at risk should receive IV hydration (Fig. 74.2). Hydration with isotonic saline is superior to half-isotonic (0.45%) saline. When comparing the effectiveness of sodium bicarbonate with isotonic sodium chloride and oral N-acetylcysteine (NAC) with placebo in 8680 high-risk patients scheduled to undergo coronary or noncoronary angiography, the PRESERVE trial showed no difference in terms of AKI or mortality between the use of sodium bicarbonate and isotonic sodium chloride.20 Therefore, because of the risks of compounding errors with sodium bicarbonate, isotonic sodium chloride should be used. The use of NAC is discussed later in this chapter. Ringer’s lactate is another option because it contains less chloride than isotonic sodium chloride, possible decreasing kidney vasoconstriction and causing less hyperchloremic acidosis. In addition, it causes alkalization of renal tubular fluid, which is a suggested mechanism to decrease the damages caused by free radicals. Studies are needed to determine whether the use of balanced solutions compared with normal saline would lower AKI incidence.

Iodinated contrast can be categorized according to osmolality into high-osmolar contrast medium (approximately 2000 mOsm/kg), low-osmolar contrast medium (600–800 mOsm/kg), and iso-osmolar contrast medium (290 mOsm/kg). The KDIGO AKI guidelines recommend either iso-osmolar (preferred) or low-osmolar iodinated contrast for patients at risk for CI-AKI because the risk for nephrotoxicity is higher with increasing osmolarity.

The volume of contrast administered is also an independent predictor of CI-AKI and should be reduced as much as possible. Based on the volume (V) of contrast given (in mL) and the creatinine clearance (CrCl; mL/min), a V:CrCl ratio above 3.7 independently predicts CIAKI. Administration of iodinated contrast more than once over 48 to 72 hours should be avoided. The drugs used for CI-AKI prevention are included in the section on pharmacologic approaches.

Prevention of Drug-Induced and Nephrotoxin-Induced Acute Kidney Injury

Drug-induced nephrotoxicity often can be predicted because it is more common in certain patient populations and clinical situations. Prevention involves the knowledge of mechanisms of kidney injury, patient-related risk factors, and drug-related risk factors. The most important patient-related factors are older age (60 years or older), CKD, diabetes, heart failure, volume depletion, and sepsis. Preventive

Management of Patients Receiving Iodinated Contrast Media
Measure or estimate GFR

If <60 mL/min/1.73 m2 for
arterial administration,
<45 mL/min/1.73 m2
for intravenous administration, or AKI

Drugs to stop 48 h before
and reassess 48 h after
procedure based on creatinine:
-NSAIDs
-Metformin
-Diuretics if feasible
-ACEI? ARB?
Avoid iodinated contrast for
next 72 h if feasible

If >60 mL/min/1.73 m2 for
intraarterial administration or more
than 45 mL/min/1.73 m2
for intravenous administration

Hydration with
1. Isotonic saline 3 mL/kg/h × 1 h
before exam then 1 mL/kg/h × 6 h
or
2. Isotonic saline 1 mL/kg/h ×
12 h before exam then
1 mL/kg/h × 12 h

No further
measures required

Fig. 74.2 Management of patients receiving iodinated contrast media. ACEI, Angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal antiinflammatory drugs.

measures include correctly estimating the GFR before initiating therapy, adjusting the dosage, monitoring kidney function and drug dosage during therapy, and administering administration IV saline before exposure if possible. Alternative nonnephrotoxic drugs should be used, and nephrotoxic drug combinations should be avoided whenever feasible.

can decrease tubular cell toxicity. In the general population, extended intervals between doses maintains the target dose while decreasing the risk for nephrotoxicity compared with multiple daily doses; therefore, in patients with normal eGFR who are not at risk for AKI, aminoglycosides should be administered daily if possible, with serum concentrations measured as recommended.

Amphotericin

Tumor Lysis Syndrome

Amphotericin-associated nephrotoxicity can occur in as many as one-third of treated patients, and the risk for AKI increases with higher cumulative doses. Lipid formulations cause less nephrotoxicity compared with the standard formulation, and therefore liposomal amphotericin is preferred over conventional amphotericin; however, it is significantly more expensive. Recently, alternative antifungal agents such as itraconazole, voriconazole, and caspofungin have been more commonly used in patients at high risk for AKI because of their absence of nephrotoxicity and should be used rather than conventional amphotericin when appropriate antifungal coverage is provided.

Tumor lysis syndrome (TLS) is caused by uric acid and calciumphosphate precipitation in the tubules. Identification of patients at high risk is fundamental to prevent AKI in this setting. The most common hematologic malignancies associated with TLS are aggressive lymphomas and acute lymphoblastic leukemia. Rare cases of a TLStype of AKI have also been reported in other catabolic states, such as after heart surgery. The risk factors for TLS are related to patient (age, baseline kidney function) and tumor characteristics (cell turnover rate, growth rate, extensive bone marrow involvement, tumor bulk, and chemosensitivity).22 Baseline uric acid higher than 7.5 mg/dL, lactate dehydrogenase levels higher than 1500 U/L, and white blood cells greater than 25 × 109/L are also risk factors. The diagnosis is based on two simultaneous laboratory abnormalities occurring within 3 days before or 7 days after chemotherapy: uric acid greater than 8 mg/dL, potassium greater than 6 mEq/L, phosphate greater than 4.5 mg/dL, calcium less than 7 mg/dL, and at least one clinical complication among AKI defined as an increase in baseline creatinine by 1.5 times or greater, cardiac arrhythmia, or seizure.

In patients at low risk for developing TLS as defined in an expert consensus, management includes hydration and close monitoring of volume status and kidney function.22 The use of urine alkalinization to promote elimination of urate is not recommended because it can induce calcium phosphate deposition and therefore aggravate TLS.

In patients at intermediate and high risk, aggressive hydration with isotonic saline 2 to 3 L/m2 per day aiming for urine output between 80 and 100 mL/m2/hr should be initiated. Hydration should be continued until there is no significant evidence of tumor lysis, as shown by uric acid and phosphorus levels. If urine output decreases despite adequate fluid administration, a loop diuretic should be added, and KRT will be required if oliguria persists. In patients at intermediate risk with uric acid levels up to 8 mg/dL, a xanthine oxidase inhibitor such as allopurinol also should be started 2 days before chemotherapy,

whereas rasburicase should be used in patients with uric acid levels greater than 8 mg/dL or with concomitant cardiac or kidney diseases limiting hydration. The risk of severe cutaneous adverse events associated with allopurinol appears higher in some Asian populations.
Rasburicase should not be used in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. For high-risk patients, a single dose of rasburicase (up to 0.2 mg/kg, although a lower dose such as 3 mg is usually prescribed) is recommended, followed by close monitoring of uric acid levels. If uric acid normalizes, allopurinol treatment can be started.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) cause vasodilation of the efferent glomerular arteriole, further reducing intraglomerular pressure already compromised by the blood pressure–lowering effect of these agents. After the initiation of an ACE inhibitor or ARB, if creatinine increases by more than 30%, bilateral kidney artery stenosis, stenosis of the kidney artery in a solitary kidney, diffuse intrakidney small-vessel disease, or generalized volume depletion should be suspected, and these drugs should be discontinued. It remains unclear whether withdrawing an ACE inhibitor or ARB before iodinated contrast administration is beneficial.

Nonsteroidal AntiInflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided if possible in CKD and intravascular volume depletion because they inhibit cyclooxygenase, which blocks prostaglandin-induced vasodilation of the afferent arteriole, potentially reducing GFR and kidney blood flow. The risk of NSAIDs must be balanced against their benefit, and patients should be instructed about increased risk situations and advised on when to hold these drugs during sick days. Clinicians may also decide to temporarily stop ACE inhibitors or ARBs in patients with high-normal potassium or more severe CKD. In critically ill patients, kidney hypoperfusion caused by decreased effective circulating volume is relatively common and inhibition of prostaglandin-induced vasodilation may further compromise kidney blood flow and exacerbate ischemic injury.

Aminoglycosides

AKI caused by aminoglycoside nephrotoxicity (AG-AKI) usually occurs 5 to 10 days after initiation of the treatment. AG-AKI is typically nonoliguric and associated with decreased urine concentrating ability and urinary magnesium wasting. Aminoglycoside toxicity can also result in vestibular toxicity that can lead to tinnitus or difficulty ambulating. A large population-based study in adults undergoing surgery receiving antibiotic prophylaxis found an association between one dose of gentamicin (4 mg/kg) and AKI that challenges the notion that AG-AKI only occurs after a few days of treatment.[21] The KDIGO guideline recommends against using aminoglycosides in patients with or at risk for AKI unless no other alternative is available. With multiple daily administration schedules, elevated aminoglycoside peak levels appear to correlate with nephrotoxicity. Because aminoglycoside uptake by proximal tubular cells is saturable, once-daily administration

Secondary Prevention

After the kidney insult has occurred, secondary preventive measures should be directed to avoid further injury, facilitate repair and recovery, and prevent complications. The timeliness of interventions is crucial to their effectiveness. Various approaches have been applied but are best appreciated in the context of specific clinical scenarios.

Traumatic and Nontraumatic Rhabdomyolysis

The main step in preventing AKI after traumatic rhabdomyolysis and crush syndrome is early and aggressive fluid therapy.23 IV isotonic saline should be initiated even before the crushed limb is relieved to prevent precipitation of the pigment in the tubular lumen. Nontraumatic rhabdomyolysis can be caused by ischemia, bacterial or viral infections, severe heat, prescribed medications (statins), drugs of abuse (cocaine or heroin), inflammatory or metabolic myopathies, and electrolyte disorders (hypokalemia or hypophosphatemia). Plasma creatine kinase (CK) levels greater than 5000 U/L have been associated with AKI. In patients with CK levels above 10,000 U/L or with severe crush injury, aggressive IV fluid administration should be considered to correct hypovolemia and target urine output of 200 to 300 mL/h to reduce kidney injury. In patients with less severe rhabdomyolysis with no rapid increase in CK levels (i.e., peak 5000–10,000 U/L) and in those with underlying CKD or heart failure, less aggressive fluid infusion can be targeted. Fluid composition is controversial because no direct comparative trials have been performed. Recommendations to use sodium bicarbonate intend to maintain alkaline urine and decrease precipitation of myoglobin and arteriolar vasoconstriction. However, sodium bicarbonate also can precipitate calcium phosphate deposition and worsen hypocalcemia and should be avoided in severe hypocalcemia or metabolic alkalosis. On the other hand, large volumes of normal saline can cause hyperchloremic metabolic acidosis. Some experts use both normal saline and sodium bicarbonate. For example, if urine pH is less than 6.5, each liter of normal saline can be alternated with 850 mL of 5% dextrose plus 150 mmol of sodium bicarbonate. Bicarbonate should not be administered if there is concomitant hypocalcemia or metabolic alkalosis. Mannitol has been suggested to be beneficial because of its diuretic, antioxidant, and vasodilatory properties. Mannitol could prevent kidney tubular cast deposition, expand extracellular volume, and reduce intracompartmental pressure, muscle edema, and pain. However, mannitol may exacerbate heart failure and nephrotoxicity, requires close monitoring, and is contraindicated in oliguria, hypervolemia, hypertension, and heart failure. Mannitol may be considered in patients with CK levels greater than 30,000 U/L who have a urine flow greater than 20 mL/hr at a rate of 5 g/hr added to each liter of infusate not to exceed 1 to 2 g/kg/day.

Muscle damage induces stretch-activated ion channels, allowing for influx of calcium into cells after reperfusion. The resulting hypocalcemia is usually asymptomatic but can lead to cardiac dysrhythmias. Hence, care must be taken to avoid sodium bicarbonate–induced hypocalcemia, which can trigger tetany, seizures, and cardiotoxicity and worsen muscle damage. During AKI recovery, hypercalcemia is frequent, mainly in patients who received calcium infusion, as a result of the mobilization of previously precipitated calcium. Thus, hypocalcemia should be treated only if symptomatic.

In treating patients with rhabdomyolysis, it is important to consider when to stop fluid resuscitation. A general recommendation is to stop when CK levels decrease to less than 5000 U/L and myoglobinuria disappears, as shown by a negative urine dipstick for blood. However, the risk for fluid accumulation and compartmental expansion always should be evaluated. Frequent assessment of serum creatinine and CK also help the clinician determine the appropriate volume expansion. KRT should be considered in resistant hyperkalemia or metabolic acidosis, rapidly rising serum potassium, oliguria, anuria, or volume overload.

Hyperglycemia

It remains uncertain whether strict control of blood glucose reduces AKI incidence and mortality. In a large RCT in ICU patients, intensive glucose control (glucose of 81–108 mg/dL [4.5–6.0 mmol/L]) increased the risk for death at 90 days compared with conventional glucose control (<180 mg/dL [<10 mmol/L]). Intensive glucose control also increased the risk for severe hypoglycemia. There was no change in the incidence of AKI or use of KRT. Other studies have not found an increase in mortality with intensive glucose control. In summary, intensive glucose control in ICU patients increased the incidence of severe hypoglycemia and either increased or had no effect on mortality compared with blood glucose ranges of 140 to 180 mg/dL (7.8–10 mmol/L) and 180 to 200 mg/dL (10–11 mmol/L). We recommend maintaining glucose concentration in the range of 110 to 149 mg/dL (6.1–8.3 mmol/L).

Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) is performed by applying inflation of a blood pressure cuff for four or five short cycles in the upper or lower limb. RIPC aims to create brief ischemia and reperfusion in the arm or leg to provide protection in distant organs, such as heart, kidney, lung, and brain. The underlying mechanisms include activation of humoral factors, including adenosine, bradykinin, and cannabinoids, in addition to subcellular modulators, nuclear factor-κB (NF-κB), and nitric oxide (NO). A meta-analysis including 28 studies, which randomized a total of 6851 patients, concluded that RIPC does not confer a benefit over sham conditioning (placebo) to prevent AKI or reduce mortality in cardiac or vascular surgery.24

Pharmacologic Approaches

Because of the multiple different causes of AKI, various pathways have been targeted in studies to prevent or alter the course of AKI. These pathways include inflammation, oxidative and mitochondrial stress, cellular metabolism and repair, apoptosis, and hemodynamics. Most of these preventive strategies were successful in animal models but did not translate into beneficial effects in patients. Only a few have shown benefits (Table 74.1).

N-Acetylcysteine

N-Acetylcysteine (NAC) is a tripeptide analogous to glutathione and is able to cross cellular membranes. NAC may reduce vasoconstriction and oxygen free radical generation after the administration of contrast material. Because an increased production of free radicals by the kidneys is partly responsible for their cellular damage in postischemic and nephrotoxic AKI, several clinical studies have attempted to use NAC to prevent AKI, mainly in CI-AKI and during cardiac surgery.

In the initial study, NAC at a dose of 600 mg orally twice daily the day before and the day of the procedure prevented AKI after iodinated contrast administration. The multicenter PRESERVE trial has shown that the use of NAC does not provide any benefit to prevent CI-AKI.20 Therefore, NAC is no longer recommended to prevent CI-AKI.

Allopurinol

Hyperuricemia has been associated with the development of AKI. There are retrospective observational studies showing a reduced incidence of AKI in patients treated with allopurinol compared with those who were not. Animal models of heat stress and rhabdomyolysis with hyperuricemia have also demonstrated that allopurinol administration could prevent AKI. Allopurinol may also help in reducing AKI after iodinated contrast administration. Additional studies are required.

Loop Diuretics and Natriuretics

Diuretics are often used to manage fluid in patients who develop AKI. Although nonoliguric AKI has been associated with better outcomes than oliguric AKI, diuretics have been shown to be ineffective in the prevention of AKI or for improving outcomes once AKI occurs. In addition, diuretics should be avoided when AKI is attributed to prerenal causes. Meta-analyses have confirmed that the use of diuretics to prevent AKI did not reduce in-hospital mortality or need for KRT.25

TABLE 74.1

Drugs Used in Prevention of Acute Kidney Injury

Drug

Level of Evidence

Results

Dopamine
Fenoldopam
Norepinephrine vs. vasopressin

RCTs
Small RCTs
One meta-analysis
RCT in septic shock

Loop diuretics
Nesiritide

RCTs and meta-analysis
RCTs in cardiac surgery

N-Acetylcysteine
Allopurinol

RCTs and meta-analysis
Observational studies and small pilot studies
RCTs in perioperative period (cardiac surgery)
RCTs in CI-AKI

No effect on kidney function
No effect on kidney function
Beneficial effect on kidney function
Tendency toward less kidney replacement therapy with vasopressin
No effect on kidney function
Decreased incidence of AKI
Controversial effect on kidney replacement therapy requirement
No effect in CI-AKI
Possible beneficial effect on kidney function
No effect on kidney function

Statins

Insulin

Meta-analyses

Calcium channel blockers
Levosimendan

RCT in peritransplant period
RCT in cardiac surgery

Adenosine antagonists
Alpha-melanocyte-stimulating
hormone analog (ABT-719)
Alpha-2 adrenergic agonist
(dexmedetomidine)
Antioxidative enzyme heme
oxygenase-1
Propofol

RCTs
Phase IIb study in cardiac surgery

Small interfering RNA targeting p53

Phase II RCT in cardiac surgery

Peroxisome proliferator-activated
receptor
Nicotinamide riboside and
pterostilbene
Hepatocyte growth factor (HGF)-like
peptide (ANG-3777)
THR-184a
Mesenchymal stem cells

Phase I clinical trials

Meta-analysis in cardiac surgery
Small RCT in aortic surgery
Small phase III trial
RCTs

Possible beneficial effect on kidney
function
Controversial effect

No effect on kidney function
No effect on need for kidney
replacement therapy
Controversial effect on kidney function
No effect on kidney function
Might decrease AKI
Decreased incidence of AKI
Trend toward lower levels of the
urinary AKI biomarkers
Controversial results on kidney
function

Beneficial effect on kidney function

Phase I clinical trials

Phase II RCT
Phase I clinical trial

No effect on kidney function
Decreased incidence of AKI

Comments
Further studies required
Further studies required

Further studies required

Further studies required
Patients not receiving statins who need this drug for other indications may receive statins before their angiography
KDIGO recommends targeting blood glucose 110–149 mg/dL (6.1–8.3 mmol/L)
Further studies required

Further studies required

Ongoing phase III in kidney transplantation (NCT03646344)
Current RCTs in kidney transplantation (NCT02727296), after nephrectomy (NCT04474600), orthopedic surgery (NCT03336801)
Phase III trial ongoing in cardiac surgery (NCT03510897)
Phase II RCT in cardiac surgery (NCT03941483)
Phase II RCT in complex aortic surgery (NCT04342975)
Phase II RCT in cardiac surgery (NCT02771509)
Further studies required

aA

bone morphogenetic protein-7 agonist.
AKI, Acute kidney injury; CI-AKI, contrast-induced acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial; RNA, ribonucleic acid.

An RCT including 94 patients undergoing high-risk cardiac surgery showed that prophylactic nesiritide (β-type natriuretic peptide) did not reduce the KRT requirement or lengths of stay, although AKI rates were lower with nesiritide. Conversely, a Japanese RCT including 303 patients with CKD who underwent coronary artery bypass graft (CABG) surgery showed that human atrial natriuretic peptide (hANP, carperitide) decreased postoperative serum creatinine and need for dialysis,26 although other studies using the same medication have shown increased mortality in patients with acute heart failure. Further studies are required.

Vasoactive Agents: Vasopressors, Inotropes, and Vasodilators

Kidney-dose dopamine 0.5 to 3 μg/kg/min given as a kidney vasodilator increases urine output, but several studies have confirmed that this drug does not affect AKI outcome or mortality.27 Dopexamine, a synthetic dopamine analog, is a dopamine type-1 and less potent dopamine type-2 receptor agonist. Small studies performed in patients undergoing liver transplant surgery have not found a beneficial effect of dopexamine in preventing AKI.

Fenoldopam is a pure dopamine type-1 receptor agonist with hemodynamic kidney effects similar to those of low-dose dopamine, without systemic α- or β-adrenergic stimulation. In meta-analyses, fenoldopam was shown to reduce the risk for AKI in postoperative or critically ill patients (OR, 0.43–0.46).28,29 Intrakidney administration of fenoldopam allows the use of a substantial dose of fenoldopam mesylate while avoiding systemic adverse effects, such as hypotension. Data from experimental models suggest that fenoldopam may have additional anti-inflammatory effects. We do not recommend use of fenoldopam to prevent AKI because no high-quality data support use of this agent.

A meta-analysis on the use of levosimendan, a calcium-sensitizing agent with inotropic and vasodilatory effects, has demonstrated reduced AKI after cardiac surgery, KRT requirement, and mortality. However, a large RCT showed that levosimendan did not reduce mortality or need for KRT.30

Calcium channel blockers (CCBs) have been shown to reverse the afferent arteriolar vasoconstriction induced by a variety of stimuli and also have an independent natriuretic effect. These drugs have been evaluated in the prevention of delayed graft function (DGF). A large multicenter RCT did not find any benefit on the incidence and severity of DGF. A systematic review did not find strong evidence that CCBs reduce the incidence of DGF after transplantation.

Theophylline, a nonselective adenosine receptor antagonist, prevents adenosine-mediated vasoconstriction of the afferent arteriole.

Adenosine is released in response to increased luminal chloride concentrations in the distal tubules as part of the tubuloglomerular feedback. Meta-analyses have found a significant reduction in CI-AKI with theophylline.31 However, there is insufficient evidence to recommend theophylline monotherapy, and the KDIGO AKI guideline does not suggest using theophylline to prevent CI-AKI.

Selective adenosine blocking agents, such as rolofylline, have been used in trials for prevention and treatment of cardiorenal syndrome. In a small double-blind RCT in decompensated heart failure with AKI, the coadministration of adenosine A1 antagonist with furosemide increased diuresis and prevented further decrease in GFR.

Statins

Although the pathogenesis of CI-AKI is not completely known, multiple mechanisms may be involved. Statins induce downregulation of angiotensin receptors, decrease endothelin synthesis, decrease inflammation, improve endothelial function by inhibiting NF-κB, decrease expression of endothelial adhesion molecules, increase NO bioavailability, attenuate production of reactive oxygen species, and protect against complement-mediated injury. Those mechanisms may be involved in CI-AKI. A number of observational studies and some but not all RCTs support the potential for kidney protection with statin before an intra-arterial administration of iodinated contrast. The statins most commonly studied in this setting were rosuvastatin and atorvastatin. Therapy should continue in patients who are already receiving a statin, and those who need statins for another indication such as myocardial infarction may receive statins before their angiography. It is currently unclear whether statins should be specifically initiated to prevent CI-AKI. A recent meta-analysis suggested that CKD patients may benefit more from statins in this setting.32 Regardless, according to the KDIGO lipid guideline, CKD patients aged 50 or older with eGFR less than 60 mL/min/1.73 m^2 should be treated with a statin. A large recent retrospective study failed to show any benefit of statins for preventing AKI related to administration of IV iodinated contrast.33

Statins were associated with lower risk of AKI after elective surgery in observational studies. However, RCTs did not confirm these findings. In the largest RCT, the incidence of AKI after cardiac surgery was similar between atorvastatin and placebo groups among all participants (20.8% vs. 19.5%; risk ratio [RR], 1.06; 95% CI, 0.78–1.46; P = .75).34 Similar results were observed when stratifying for statinnaïve patients or statin users.

Antiinflammatory Agents

An alpha-melanocyte-stimulating hormone analog, ABT-719, inhibits inflammatory, cytotoxic, and apoptotic pathways. In a phase IIb study, patients with CKD who underwent cardiac surgery did not have a lower incidence of AKI compared with placebo.

Dexmedetomidine, an alpha-2 adrenergic agonist used for its sedative properties, also has hemodynamic and antiinflammatory effects.

A recent meta-analysis in cardiac surgery found that dexmedetomidine might reduce the incidence of AKI.35 A small RCT after aortic surgery has also shown a decreased incidence of AKI.36

Antioxidants

The endogenous antioxidative enzyme heme oxygenase-1 (HO-1) is a stress-inducible enzyme and has important antiapoptotic and antiinflammatory functions. Preliminary data suggest that the induction of HO-1 may be protective in several forms of injury, including AKI. A phase III RCT including 600 patients is currently determining whether this drug reduces the incidence of DGF after kidney transplantation (HOT 2 Trial, NCT03646344).

Propofol, which has antioxidant and anti-inflammatory properties, can also increase levels of bone morphogenetic protein-7 (BMP-7), a potential tubular repair agent.37 Propofol has previously shown conflicting results on kidney function. There are ongoing RCTs assessing the effect of propofol on kidney function, including one in kidney transplantation (VAPOR-2 Trial, NCT02727296), one after nephrectomy (NCT04474600), and another one in orthopedic surgery patients (NCT03336801).

Apoptosis p53 Inhibitor

In a phase II trial, patients treated with small interfering ribonucleic acid targeting p53 had a reduced AKI rate compared with those treated with placebo. Because p53 has, among other activities, a tumor suppression function, one of the major drawbacks to the use of an inhibitor of p53 is its potential carcinogenic effect. A phase III trial is underway to assess the efficacy of teprasiran to prevent AKI in cardiac surgery (NCT03510897).

Targeting Mitochondrial Stress and Cell Metabolism

ASP1128, a peroxisome proliferator-activated receptor (PPAR) delta modulator, is currently studied in a phase II trial in patients undergoing cardiac surgery (NCT03941483). A phase II trial is ongoing targeting metabolic pathways related to cellular protection using NAD+ supplementation with nicotinamide riboside and pterostilbene to prevent AKI in patients undergoing complex aortic surgery (NCT04342975).

Tubular Repair Agents

In a recent phase II RCT in patients at risk for AKI undergoing cardiac surgery, THR-184, a peptide that activates the bone morphogenetic protein pathway, did not reduce AKI over the postoperative week.38

ANG-3777, a hepatocyte growth factor (HGF)-like peptide, is evaluated in a phase II trial in patients having cardiac surgery.

Mesenchymal stem cells (MSCs) were shown to prevent ischemia/reperfusion–induced AKI in rats. A phase I clinical trial evaluated the feasibility and safety of suprakidney aorta infusion of allogeneic MSCs in patients undergoing on-pump cardiac surgery.39 No adverse events were associated with the MSC infusion, and lengths of hospital stay and readmission rates were decreased by 40% compared with matched historical controls. Postoperative kidney function remained at baseline

levels and no patients in the treatment group required hemodialysis (HD), whereas 20% of controls developed AKI. In addition, kidney function in the treatment group was stable for up to 16 months in patients with CKD, whereas matched controls showed progressive deterioration in kidney function.39 The long-term safety of MSC is unknown.

Sodium-Glucose Transporter Inhibitors

Sodium-glucose transporter (SGLT2) inhibitors have shown beneficial cardiovascular and kidney effects in patients with diabetic nephropathy. However, after approval, there were several reports of severe AKI. In recent RCTs and meta-analysis, SGLT2 inhibitors reduced the incidence of AKI by 25%, without heterogeneity across studies. These findings were replicated in real-world analyses. The reasons why these drugs may reduce AKI remain to be determined, and there is no current recommendation to use them to reduce the risk of AKI. Importantly, patients should be instructed to temporarily withhold these agents during sick days.

Summary

To prevent AKI, hypovolemia, hypotension, and sepsis should be quickly addressed. Isotonic fluids and vasopressors can be administered depending on the clinical scenario. Preference should be given to balanced solutions, especially if high volumes will be given in patients at high risk for AKI. HES and other nephrotoxins should definitively be avoided. For prevention of CI-AKI (see Fig. 74.2), patients with eGFR less than 45 mL/min/1.73 m2 receiving IV contrast or those with eGFR less than 60 mL/min/1.73 m2 receiving intra-arterial contrast should receive IV hydration with crystalloid solution. The benefit of statins and RIPC is controversial. To prevent TLS, patients at intermediate and high risk should receive aggressive hydration with crystalloid solutions. A xanthine oxidase inhibitor or rasburicase should be administered depending on the underlying risk and uric acid levels. For rhabdomyolysis, normal saline is preferable. Additional studies are required to assess whether fenoldopam, certain vasopressors, nesiritide, and statins are beneficial to prevent AKI.

TREATMENT OF ACUTE KIDNEY INJURY

Once measures to prevent AKI have failed, a key question is whether AKI can be managed with nondialytic therapy alone or if KRT is necessary (see Chapter 75). Management of AKI in liver failure is discussed in Chapter 76.

General Management

Appropriate management requires timely diagnosis of the clinical condition. Considerable effort and investment have been directed in the search for a more sensitive and specific biomarker to diagnose AKI. Initial management of AKI includes assessment of the cause and volume status. Adequate hemodynamic status should be maintained to ensure kidney perfusion and avoid further kidney injury. In the injured kidney, autoregulation of blood flow, the mechanism responsible for maintaining a constant flow during fluctuations in BP, is lost. This loss increases the susceptibility to develop AKI after episodes of hypotension. Therefore, fluid and vasoactive drug management is needed in both patients at risk for AKI and with AKI. In patients with AKI attributed to dehydration only, it is expected that the serum creatinine decreases after the administration of 1 to 3 L of isotonic fluid over 24 to 48 hours, depending on the severity of the underlying condition. The optimal MAP is unknown and probably needs to be individualized according to age, hypertension status, and degree of peripheral artery and renovascular disease. Any potentially nephrotoxic agents should be avoided, including intravascular iodinated contrast. Gadoliniumbased contrast agents are associated with the risk of developing nephrogenic systemic fibrosis (NSF) in patients with eGFR lower than 30 mL/min. The risk of NSF is higher with group I (linear) agents and lower with newer group II (cyclic) agents, such as gadobenate dimeglumine, gadobutrol, gadoteridol, and gadoterate meglumine. The risk with group III agents remains unknown. If gadolinium-based contrast agents need to be used in AKI, patients should be informed about the risk for nephrogenic systemic fibrosis, and group II agents should be preferred. The lowest dosage possible should be administered and repeated exposures avoided. Antimicrobial agents such as aminoglycosides, amphotericin, acyclovir, and pentamidine should be avoided whenever possible, or their dose should be adjusted to prevent further insult. Any medications associated with AKI also should be avoided if possible.

Fluid and Electrolyte Management

Although early and vigorous resuscitation with crystalloid solutions and aggressive infection control can reduce the incidence of AKI (see earlier discussion), the role of fluid resuscitation in established AKI not attributed to dehydration is less clear. Volume status is one of the most difficult parameters to assess, and fluid resuscitation should target a predefined preload, SV, or cardiac output rather than a set MAP. Nevertheless, many clinical studies have emphasized the limitations of static measures such as central venous pressure, right atrial pressure, and pulmonary artery occlusion pressure in predicting volume expansion efficacy. Other bedside indicators of preload, such as the right ventricular end-diastolic volume (evaluated by thermodilution) and the left ventricular end-diastolic area (measured by echocardiography), are ineffective in differentiating volume responder from nonresponder patients. As previously discussed, two techniques have an acceptable degree of clinical accuracy to determine fluid responsiveness: the passive leg raising maneuver and the fluid bolus test both coupled with real-time SV monitoring. In ICU patients receiving mechanical ventilation, respiratory changes in left ventricular SV also can predict fluid responsiveness. In hypovolemic patients, positive-pressure ventilation may induce a fall in the venous return and consequently in cardiac output. Based on the positive relationship between ventricular enddiastolic volume and SV, the expected hemodynamic response to volume expansion is an increase in right ventricular end-diastolic volume, left ventricular end-diastolic volume, SV, and cardiac output.

Volume expansion in ICU patients can frequently result in a relative increase in body weight of 10% to 15% or more, sometimes doubling the total body water in a short time. As previously highlighted, studies have demonstrated an association between fluid accumulation and mortality in AKI. A prospective multicenter observational study found that fluid overload at AKI diagnosis (defined as an increase in body weight of ≥10% relative to baseline) was independently associated with increased mortality.7 The risk for death was proportional to the magnitude and duration of fluid accumulation. However, the effect of fluid overload on kidney recovery was inconsistent. A second analysis from the Fluids and Catheters Treatment Trial (FACTT) in AKI patients confirmed that in early AKI, positive fluid balance is strongly associated with mortality. The study showed a protective effect of furosemide on mortality, which disappeared after adjustment for fluid balance. Other studies have shown a deleterious effect of fluid overload on kidney function. In summary, results from observational studies suggest that a conservative fluid approach may be beneficial in terms of mortality and kidney recovery in patients with severe AKI. Fluid resuscitation should be performed rapidly if there is hypoperfusion and then ideally should be guided based on the aforementioned dynamic measures. After the initial resuscitation period, treatment should focus

on preventing further fluid overload, monitoring signs of fluid overload, and ensuring early removal of excess volume. However, RCTs are required to confirm these findings before any formal recommendation can be made. Of note, in the STARRT-AKI RCT comparing standard versus accelerated strategies for KRT initiation, even in the subgroup where fluid overload was more common in the standard compared with the accelerated group (6.7% of body weight vs. 3.1%), 90-day mortality was similar between groups.

Drugs to Promote Recovery From Acute Kidney Injury

See Table 74.2 for a summary of drugs used in treatment of AKI.

Loop Diuretics

Although loop diuretics are often prescribed in established AKI, a meta-analysis confirmed that they are not associated with reduced mortality or improved kidney recovery.40 Other meta-analyses have shown that loop diuretics do not affect mortality, need for dialysis, or the number of dialysis sessions. Concomitant prescription of aminoglycosides and diuretics should be avoided because of an increased risk of ototoxicity. We suggest using diuretics to manage fluid overload as needed but not in attempts to speed recovery from AKI per se.

Natriuretics

Atrial natriuretic peptide (ANP) has been studied as a treatment for AKI in four RCTs. ANP was initially shown to reduce need for dialysis but not mortality. In the largest study published, ANP improved dialysis-free survival in the subgroup of oliguric patients only. Unfortunately, a subsequent trial including 222 oliguric patients did not confirm that ANP reduces mortality or dialysis-free survival.41 A smaller, more recent study showed that ANP decreased the probability of dialysis and improved dialysis-free survival. Therefore, larger studies are required to confirm the benefits of ANP in AKI. Nesiritide, a β-type natriuretic peptide, has been studied to treat heart failure. Nesiritide induces vasodilation and an indirect increase in cardiac output but has no inotropic effects and neutral effect on heart rate. In addition, it inhibits adverse neurohormonal activation and can result in natriuresis and diuresis in some individuals. However, in a large RCT in patients with acute heart failure, this drug did not decrease mortality or rehospitalization rates and had a nonsignificant effect on dyspnea.42 Nesiritide did not adversely affect kidney function, but it increased hypotension. Nesiritide also has been assessed in high-risk cardiovascular surgery, in which it reduced AKI rates in the immediate postoperative period but did not improve long-term survival. The KDIGO guideline does not support the use of ANP or nesiritide to treat AKI.

Vasoactive Agents: Vasopressors, Inotropes, and Vasodilators

Dopamine use to treat AKI is not recommended (see earlier discussion). Vasopressors often have been considered detrimental for organ perfusion. In septic shock, a small prospective study showed that norepinephrine improved serum creatinine and creatinine clearance when MAP was raised above 70 mm Hg. However, in another small RCT, increasing MAP from 65 to 85 mm Hg with norepinephrine did not

TABLE 74.2

Drugs Used in Treatment of Acute Kidney Injury

Drug	Level of Evidence

Results

Dopamine
Fenoldopam

RCTs
Small RCTs
One meta-analysis

Norepinephrine

Prospective observational studies

Angiotensin II

Post hoc analysis from one RCT
including patients with vasodilatory
shock on dialysis
RCTs and meta-analyses
RCTs

No effect on mortality or kidney function
No effect on mortality or kidney function
Beneficial effect on mortality and
need for dialysis
Possible beneficial effect on kidney
function
Decreased dialysis-dependence at
7 days

Loop diuretics
Atrial natriuretic peptide
B-type natriuretic peptide
Levosimendan

No effect on kidney function
Possible beneficial effect on survival
and kidney function
No effect on kidney function
Decreased need for dialysis

Mesenchymal stem cells

RCT in acute heart failure
Meta-analysis in critically ill patients
at risk or with AKI
Animal models and human studies

Alkaline phosphatase

Small phase II RCT

No effect on kidney function in sepsis

CD28 receptor antagonist (AB 103 –
Reltecimod)

Phase III RCT in necrotizing soft tissue
infections

Improved organ dysfunction

Hepatocyte growth factor (HGF)-like

peptide (ANG-3777)
AKI, Acute kidney injury; RCT, randomized controlled trial.

Beneficial effect on kidney function in
animal models but no effect in one
human RCT

Comments
Further studies required

Further studies required
Further studies required; one
RCT in hepatorenal syndrome
(NCT04048707)
Further studies required

Ongoing phase 4 trial in cardiac
surgery (LEVOAKI, NCT02531724)
Ongoing phase II studies
(NCT04194671, NCT03015623).
Study NCT03015623 showed that
mesenchymal stem cells can trigger
a phenotypic switch from tissue
injury to repair, but the study was
not powered for clinical efficacy.
Further studies required; ongoing
phase III trial (NCT04411472)
Further studies required; ongoing phase
II trial in peritonitis or necrotizing soft
tissue infections (NCT03403751)
Phase III trial in kidney transplants
with delayed graft function
(NCT02474667)

improve kidney function. No studies have compared the effect of different target MAPs to treat AKI.

A posthoc analysis of the ATHOS-3 data found that septic patients with AKI requiring dialysis who received angiotensin II were more likely to be dialysis-free at 7 days compared with placebo.43 Confirmation of these results in large prospective studies is needed.

In a meta-analysis, fenoldopam decreased the need for dialysis (7% vs. 10%) and in-hospital mortality (15% vs. 19%) in postoperative or ICU patients.28 Several limitations were present in this meta-analysis, such as absence of an independent measure of GFR and standardized criteria for initiation of dialysis, heterogeneity of populations, AKI definitions, dosage, and duration of treatments. In addition, fenoldopam has hypotensive properties and may be more dangerous in realworld patients than in selected trial participants. No individual trial has shown that fenoldopam can reduce the need for dialysis. The results of the meta-analysis should be confirmed with an adequately powered trial, and like the KDIGO guideline, we do not suggest using fenoldopam to treat AKI.

One small RCT is currently assessing the effect of levosimendan on kidney outcomes after cardiac surgery in patients with AKI (LEVOAKI, NCT02531724).

Specific therapy for patients with the hepatorenal syndrome includes the use of terlipressin in combination with octreotide (see Chapter 76). In countries such as the United States, where terlipressin is not available, a combination of midodrine, octreotide, and albumin infusions is often used. Norepinephrine also has been used in these settings with good response equivalent to that of terlipressin. One trial will test the efficacy of angiotensin II in hepatorenal syndrome (ANTHEM Trial, NCT04048707).

Tubular Repair Agents

Other agents have been studied for treatment of established AKI. ANG-3777, a hepatocyte growth factor (HGF)-like peptide, is evaluated in a phase III trial in kidney transplants having delayed graft function aiming to activate HGF-related repair pathways. One promising therapy is MSCs. MSCs are multipotent cells with antiinflammatory and immunomodulatory properties proven to be beneficial in animal models of myocardial ischemia, sepsis, and AKI. In animal models, infusion of MSCs improved recovery of kidney function in cisplatin-induced ischemia/reperfusion injury and glycerolinduced AKI. A dose-escalating phase I clinical trial was conducted to test the safety and preliminary efficacy of MSCs in patients at high risk for AKI.39 An experimental study using a model of progressive mesangioproliferative nephritis evaluated the long-term effects of intrakidney, syngeneic MSC transplantation. Although rats in the MSC-treated group had lower proteinuria and better kidney function on day 60, 20% of the glomeruli of MSC-treated rats contained single or clusters of large adipocytes with pronounced surrounding fibrosis. Therefore, the MSC benefit of maintaining kidney function in the short term needs to be balanced with a possible long-term effect of partial maldifferentiation of intraglomerular MSC into adipocytes and subsequent glomerular sclerosis. There are ongoing studies on the use of MSC to improve AKI outcomes (NCT04194671, NCT03015623). However, in a phase II trial of patients with cardiac surgery, no benefit from MSCs, administered into the aorta at the time of surgery, could be demonstrated.43a

Antiinflammatory Agents

In severe sepsis and septic shock, a small study has shown that the infusion of alkaline phosphatase, an enzyme expressed along the brush border of the proximal tubule, improves kidney function,

possibly through reduced kidney inflammation. A phase II study assessing the effect of recombinant alkaline phosphatase in septic patients with AKI failed to show an improvement in 7-day kidney function.44 However, there were dose-dependent signals of beneficial effects on kidney function and mortality, prompting a phase III RCT (NCT04411472).

In a phase III RCT including critically ill patients with necrotizing soft tissue infections, reltecimod, a CD28 receptor antagonist, improved resolution of organ dysfunction/failure by day 14.45 This agent was designed to help control the cytokine storm, by modulating rather than inhibiting acute inflammation. A phase II including patients with peritonitis or necrotizing soft tissue infections is currently underway to determine whether this drug can improve kidney recovery (NCT03403751).

Summary

Dehydration, hypotension, and infections should be rapidly treated. Any potentially nephrotoxic agents should be avoided, including intravascular iodinated contrast. Gadolinium-based contrast agents should also be avoided. Fluid overload should be minimized and eventually corrected once the patient’s clinical condition permits. No agent has been clearly shown to facilitate kidney recovery. Several studies are ongoing to test the efficacy of new drugs to treat AKI in specific conditions.

TREATMENT OF ACUTE KIDNEY INJURY COMPLICATIONS

Fluid Overload

When fluid overload occurs in AKI, all intakes should be minimized and medical treatment should be attempted before dialysis initiation.

In patients with positive fluid balance with large fluid intake and inadequate urine output and in those presenting with symptomatic volume overload, a loop diuretic can be initiated with measures to optimize systemic and kidney perfusion. IV bolus doses of diuretics may be necessary to optimize the response, especially in patients with heart failure and nephrotic syndrome. If there is a response to an IV bolus, continuous infusion can be considered because it is less ototoxic. When starting or increasing the dose of a continuous infusion, a bolus should be administered before. Natriuretic peptides inhibit sodium reabsorption in the nephron, resulting in net sodium excretion. There is currently no evidence to support the use of natriuretic peptides as an adjunctive treatment in AKI.

Morphine and nitrates can be used to alleviate the respiratory symptoms of pulmonary edema in urgent situations. Morphine can be administered intravenously at an initial dose of 2 to 4 mg over a 3-minute period and repeated at 5- to 15-minute intervals as needed. Nitrates are also commonly used. Nitroglycerin reduces left ventricular filling pressure through venodilation; an initial dose of 5 µg of IV nitroglycerin per minute can be used. When fluid overload cannot be rapidly treated with medical management, positive-pressure ventilation may be initiated with or without endotracheal intubation and dialysis, depending on the clinical situation.

Potassium Disorders

Hyperkalemia, covered in detail in Chapter 10, is a frequent complication of AKI that may affect cardiac conduction and lead to bradycardia or even asystole. If electrocardiographic changes are present, IV administration of calcium is urgently needed. Sources of potassium should be removed, including drugs with effect on potassium handling, such as β-adrenergic antagonists, potassium-sparing diuretics, ACE inhibitors, and ARBs.

The next step is to enhance the shift of potassium to the intracellular space by parenteral glucose and insulin infusions. Sodium bicarbonate also promotes shift of potassium and is most efficient when there is concomitant metabolic acidosis. It can be started if there is no concern regarding fluid overload. β-Adrenergic agonists given as aerosols are effective at very high doses but more likely to produce side effects and therefore are rarely prescribed to treat hyperkalemia.

Potassium excretion should be increased by the administration of saline, loop diuretics, and cation exchange resins such as sodium polystyrene sulfonate or calcium resins. The resins can be administered orally or rectally as a retention enema and are usually not effective after a single dose only. There is concern that coadministration of sorbitol with sodium polystyrene sulfonate may promote intestinal necrosis. Sodium polystyrene sulfonate should be avoided postoperatively until normal bowel function resumes and in patients with bowel obstruction or ileus. Newer agents, such as sodium zirconium cyclosilicate (SZC) and patiromer, have shown reductions in potassium levels within hours of administration. SZC has been effective in normalizing average potassium levels of 5.5 mmol/L (range, 5.1–7.3) in 82% of subjects within 24 hours, and in 96% within 48 hours.46 If hyperkalemia is unresponsive to conservative measures, emergency HD is the treatment of choice. If HD is unavailable, continuous KRT can be used with higher volumes of replacement solution and/or dialysate and low or no potassium content. Because KRT initiation usually takes a few hours, medical management always should be used pending initiation of dialysis. Monitoring of potassium levels should continue after conservative or dialytic management to prevent and treat rebound hyperkalemia.

Sodium Disorders

Hyponatremia can occur as a result of relative impairment in free water excretion and is more common in AKI associated with heart failure, liver failure, or diuretics. In these settings, water restriction to below the level of output is mandatory. Sodium restriction is usually necessary to treat fluid overload and edema. In patients with true volume depletion and prerenal AKI, isotonic saline needs to be administered to correct both disorders.

In patients with AKI and hypernatremia, treatment of the cause is necessary and water deficit should be estimated. Water should be administered orally or intravenously as dextrose in water to correct serum sodium concentration at a maximum rate of 12 mmol/L/day. Dialysis and continuous KRT may be required to optimally correct sodium disorders in AKI.

Calcium, Phosphorus, and Magnesium Disorders

Hyperphosphatemia and hypocalcemia are common in AKI. Hyperphosphatemia is usually caused by reduced excretion by the kidneys, and continuous release from rhabdomyolysis or TLS also can be contributive (see Chapters 11 and 70). As phosphorus levels increase, calcium levels decrease, resulting in hypocalcemia. Total calcium levels usually drop to 7 to 8 mg/dL (1.75–2.0 mmol/L). Other causes of hypocalcemia in AKI are skeletal resistance to parathyroid hormone (PTH) and low calcitriol production. Hypocalcemia is aggravated when bicarbonate is administered to correct acidosis. A high-calcium, high-phosphorus product could theoretically trigger tissue calcium deposition, which can cause cardiac arrhythmia. No RCT has evaluated the benefits of treating these disorders. However, because hyperphosphatemia caused by oral phosphorus-containing medications and TLS can cause AKI, severe hyperphosphatemia should be avoided to prevent further damage. Calcium-based phosphate binders and other phosphate binders can be used in this setting. If there is symptomatic hypocalcemia or hemodynamic instability, calcium gluconate infusion should be administered.

Hypercalcemia is rare in AKI and is usually seen in the recovery phase of rhabdomyolysis when calcium is released from calciumcontaining complexes in muscle (see Chapters 11 and 70). In addition, when production of calcitriol is reestablished by the recovering kidney, an enhanced responsiveness to PTH can be seen. Hypercalcemia in this setting is rarely problematic and can be easily treated with medical management. Mild hypermagnesemia is frequent in AKI and usually does not have clinical consequences.

Acid-Base Disorders

In AKI, normal anion gap metabolic acidosis is the most common acidbase abnormality (see Chapter 13) because of reduced regeneration of bicarbonate and failure to excrete ammonium ions. Accumulation of phosphate and unexcreted unmeasured anions, such as sulfate, urate, hippurate, hydroxypropionate, furanpropionate, and oxalate, is contributory. Hypoalbuminemia can attenuate this acidification process, and it is exacerbated by lactic acidosis. Despite retention of unmeasured anions, the anion gap remains within normal in 50% of patients.

Although metabolic acidosis is frequent, triple acid-base disturbances also can occur. The approach to acid-base disturbances in AKI needs to be adjusted according to the underlying causes.

When metabolic acidosis is a complication of AKI, sodium bicarbonate can be administered if the serum bicarbonate concentrations fall below 15 to 18 mmol/L. In stable patients, oral sodium bicarbonate may be given because volume overload can occur after the administration of IV bicarbonate. The administration of bicarbonate in shock with lactic acidosis is controversial, given the possibility of an increase in carbon dioxide generation, worsening of the intracellular acidosis, and volume overload. In addition, bicarbonate therapy may reduce calcium and potassium levels. However, the recent BICAR-ICU trial has shown that in critically ill patients with AKI stage 2 or higher and lactic acidosis with pH less than 7.2, bicarbonate administration may prevent the need for dialysis and improve survival.47 Alternative forms of base treatment such as tris(hydroxymethyl)aminomethane (THAM) are not recommended in patients with AKI because THAM can cause hyperkalemia. Restriction of protein intake also has been suggested as a method of acidosis control because protein breakdown has been associated with worsening acidosis, as in CKD. However, protein restriction is not recommended in AKI.

Nutrition

Patients with AKI have an increased risk for protein-energy malnutrition because of poor nutrient intake and high catabolic rate.

Nutritional assessment is difficult, especially in AKI patients with high metabolic demands. Subjective global assessment evaluates nutritional status, requires no additional laboratory testing, and is highly predictive of outcome.

Patients with AKI should receive a basic intake of 0.8 to 1.0 g of protein/kg/day if not catabolic and a total energy intake of 20 to 30 kcal/kg/day, as recommended in the KDIGO guidelines. In addition, in patients on KRT, 1.0 to 1.5 g of protein/kg/day should be administered up to 1.7 g/kg/day in continuous KRT and hypercatabolic patients. The enteral route should be favored if the gastrointestinal tract is functioning; parenteral nutrition should be prescribed only when the gastrointestinal tract cannot be used or when the enteral route is inadequate to reach nutrient intake goals.

SELF-ASSESSMENT QUESTIONS

1. In a general population of critically ill patients, administering starches has proven to be:

A. beneficial for kidney function (decrease in need for KRT).
B. beneficial for hypotension.
C. detrimental for kidney function (increase in need for KRT).
D. detrimental for hypotension.

2. Which of the following drugs should be stopped, if feasible, 48 hours before iodinated contrast administration in patients with chronic kidney disease and a glomerular filtration rate below 45 mL/min/1.73 m^2?

A. Furosemide
B. Metformin
C. NSAIDs
D. Thiazide diuretics
E. All the above

3. The measures to prevent AKI in patients with traumatic rhabdomyolysis include all of these statements except:

A. Urine output should be maintained around 300 mL/h until CK levels are lower than 1000 U/L.
B. Urine output should be maintained around 300 mL/h until myoglobinuria disappears.
C. Mannitol may be beneficial because of diuretic, antioxidant, and vasodilatory properties.
D. Mannitol can prevent kidney tubular cast deposition, expand extracellular volume, and reduce intracompartmental pressure, muscle edema, and pain.
E. Monitoring of ionized calcium is important to avoid $NaHCO_3$ induced hypocalcemia (as a result of metabolic alkalosis).

4. Regarding fluid administration for critically ill patients at risk for AKI, all the following statements are true except:

A. Chloride-restrictive fluids (lactated solution, Plasma-Lyte 148, or chloride-poor 20% albumin) seem preferable to chloriderich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution), although further studies are needed and ongoing.
B. Volume expansion should be maintained after major vascular surgeries unless patients develop evidence of pulmonary congestion.
C. Guidelines on sepsis management mention that septic patients should receive initial fluid resuscitation with crystalloids at a minimum of 30 mL/kg.
D. Intravenous administration of albumin can be considered in patients with sepsis who require substantial amounts of crystalloid to maintain adequate mean arterial pressure.
E. Fluid expansion should be stopped when patients are no longer fluid responsive.

REFERENCES

1. Coca SG, Yusuf B, Shlipak MG, et al. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;53:961–973.
2. Thakar CV, Christianson A, Freyberg R, et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med. 2009;37:2552–2558.
3. Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. Kidney Int. 2016;89:555–564.
4. Ansari BM, Zochios V, Falter F, et al. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systematic review. Anaesthesia. 2016;71:94–105.
5. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid!. Crit Care. 2015;19:18.
6. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113:740–747.
7. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76:422–427.
8. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564–2575.
9. Chen CY, Zhou Y, Wang P, et al. Elevated central venous pressure is associated with increased mortality and acute kidney injury in critically ill patients: a meta-analysis. Crit Care. 2020;24:80.
10. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
11. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367: 1901–1911.
12. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus ringer’s acetate in severe sepsis. N Engl J Med. 2012;367:124–134.
13. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–2256.
14. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378:829–839.
15. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018;378:819–828.
16. Hammond DA, Lam SW, Rech MA, et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. Ann Pharmacother. 2020;54:5–13.
17. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
18. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA. 2016;316: 509–518.
19. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370:1583–1593.
20. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378:603–614.
21. Bell S, Davey P, Nathwani D, et al. Risk of AKI with gentamicin as surgical prophylaxis. J Am Soc Nephrol. 2014;25:2625–2632.
22. Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol. 2010;149:578–586.
23. Sever MS, Vanholder R. Management of crush victims in mass disasters: highlights from recently published recommendations. Clin J Am Soc Nephrol. 2013;8:328–335.

24. Menting TP, Wever KE, Ozdemir-van Brunschot DM, et al. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. Cochrane Database Syst Rev. 2017;3:CD010777.

25. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ. 2006;333:420.
26. Sezai A, Hata M, Niino T, et al. Results of low-dose human atrial natriuretic peptide infusion in nondialysis patients with chronic kidney disease undergoing coronary artery bypass grafting: the NU-HIT (Nihon University working group study of low-dose HANP Infusion Therapy during cardiac surgery) trial for CKD. J Am Coll Cardiol. 2011;58:897–903.
27. Friedrich JO, Adhikari N, Herridge MS, et al. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med. 2005;142:510–524.
28. Landoni G, Biondi-Zoccai GG, Tumlin JA, et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Am J Kidney Dis. 2007;49:56–68.
29. Gillies MA, Kakar V, Parker RJ, et al. Fenoldopam to prevent acute kidney injury after major surgery-a systematic review and meta-analysis. Crit Care. 2015;19:449.
30. Mehta RH, Leimberger JD, van Diepen S, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med. 2017;376:2032–2042.
31. Su X, Xie X, Liu L, et al. Comparative effectiveness of 12 treatment strategies for preventing contrast-induced acute kidney injury: a systematic review and bayesian network meta-analysis. Am J Kidney Dis. 2017;69:69–77.
32. Cho A, Lee YK, Sohn SY. Beneficial effect of statin on preventing contrast-induced acute kidney injury in patients with renal insufficiency: a meta-analysis. Medicine (Baltim). 2020;99:e19473.
33. Park JH, Shin HJ, Choi JY, et al. Is there association between statin usage and contrast-associated acute kidney injury after intravenous administration of iodine-based contrast media in enhanced computed tomography? Eur Radiol. 2020;30:5261–5271.
34. FTt B, Hendricks PA, Schildcrout JS, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016;315:877–888.
35. Liu Y, Sheng B, Wang S, et al. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2018;18:7.
36. Soh S, Shim JK, Song JW, et al. Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. Br J Anaesth. 2020.
37. Hsing CH, Chou W, Wang JJ, et al. Propofol increases bone morphogenetic protein-7 and decreases oxidative stress in sepsis-induced acute kidney injury. Nephrol Dial Transplant. 2011;26:1162–1172.
38. Himmelfarb J, Chertow GM, McCullough PA, et al. Perioperative THR-184 and AKI after cardiac surgery. J Am Soc Nephrol. 2018;29: 670–679.
39. Togel FE, Westenfelder C. Mesenchymal stem cells: a new therapeutic tool for AKI. Nat Rev Nephrol. 2010;6:179–183.
40. Bagshaw SM, Delaney A, Haase M, et al. Loop diuretics in the management of acute renal failure: a systematic review and metaanalysis. Crit Care Resusc. 2007;9:60–68.
41. Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis. 2000;36:767–774.
42. O’Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365:32–43.
43. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with

intravenous angiotensin II. Crit Care Med. 2018;46:949–957.
43a. Swaminathan M, Stafford-Smith M, Chertow GM, et al. ACT-AKI investigators. Allogeneic mesenchymal stem cells for treatment of AKI after cardiac surgery. J Am Soc Nephrol. 2018;29(1):260–267.
44. Pickkers P, Mehta RL, Murray PT, et al. Effect of human recombinant alkaline phosphatase on 7-day creatinine clearance in patients with sepsis-associated acute kidney injury: a randomized clinical trial. JAMA. 2018;320:1998–2009.

45. Bulger EM, May AK, Robinson BRH, et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, phase 3 randomized controlled trial of reltecimod (AB 103). Ann Surg. 2020.
46. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. Clin J Am Soc Nephrol. 2019;14:798–809.

47. Jaber S, Paugam C, Futier E, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 2018;392:31–40.

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Extracorporeal Therapies for Acute Kidney Injury and Heart Failure

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Acute kidney injury (AKI) is a common complication of critically ill patients and is most commonly caused by sepsis, hypoperfusion, congestive heart failure, liver failure, or nephrotoxins. AKI is associated with increased morbidity, length of stay, health care costs, and adverse clinical outcomes, including death, development/progression of chronic kidney disease (CKD), and end-stage kidney disease (ESKD). Furthermore, AKI affects distant organs (e.g., heart, lungs, brain, and liver), contributing to their dysfunction during critical illness. Therefore, much effort is aimed at preventing its development and progression. Despite this, approximately 5% to 10% of patients will ultimately require kidney replacement therapy (KRT).1 This chapter reviews best practices for providing KRT in critically ill patients and those with advanced heart failure (Box 75.1).

ESSENTIALS OF ACUTE KIDNEY REPLACEMENT THERAPY

Mechanisms of Water and Solute Transport

There are four mechanisms by which water and solute are removed with extracorporeal blood purification techniques. Fluid transport across semipermeable membranes is driven by ultrafiltration (UF), whereas solute transport occurs via convection, diffusion, and adsorption (Fig. 75.1A). These mechanisms are used by the blood purification techniques described in this chapter (Fig. 75.2). The necessary formulas for calculating essential functions are presented in Table 75.1

Ultrafiltration and Convection

UF is the process by which plasma water is pushed through a semipermeable membrane, driven by a hydrostatic pressure gradient. Its rate, QUF, is determined by the transmembrane pressure (TMP) and the filter’s UF coefficient (DKUF, the product of the membrane’s KUF and its surface area).2 In KRT, the TMP is the pressure gradient between the blood and effluent compartments; it is generated by the blood pump (causing a positive blood compartment pressure) and the effluent pump, which maintains the desired QUF. The TMP necessary to maintain a determined QUF increases over time because the membrane gets coated with macromolecules (creating a secondary membrane), decreasing its permeability. When UF is prescribed as a stand-alone procedure, it is called isolated UF or slow continuous UF (SCUF),3 depending on the technique. An additional mechanism generating UF is by osmotic gradients, which is a key mechanism of volume removal during peritoneal dialysis (PD), but it is of limited significance in KRT. UF also results in solute clearance via solvent drag (convection). Because convection drags any solute that fits through the pores across the membrane, it allows for small- and medium-solute transport. The convective flux of a solute depends on the QUF, the membrane surface area, the solute concentration in plasma, and its sieving coefficient.2 Solute clearance is limited in isolated UF because progressive volume depletion limits the amount of attainable UF. This complication is avoided by administering replacement fluids at sufficient quantities to allow for the desired QUF, and consequently solute clearance, a process referred to as hemofiltration. The quantity of replacement fluid to be infused equals the total UF volume (UFTotal) minus the volume needed to achieve the desired negative balance in the patient, resulting in a net UF (UFNET, or net volume removed from the patient). From a clearance perspective, the fluid is ideally replaced postfilter (postdilution). However, higher QUF rates lead to hemoconcentration in the filter, which increases the blood viscosity and facilitates premature clotting of the filter. Thus, the filtration fraction should not exceed 30%.4 This problem is ameliorated by increasing blood flow rate (Qb) or administering some or all of the replacement fluid prefilter, thus diluting the blood before it reaches the filter (predilution). The disadvantage of predilution is that it lowers the concentration of the uremic solutes in the blood reaching the hemofilter, thus decreasing net clearance.5 6 The magnitude of the decreased clearance varies depending on the Qb and replacement fluid rate (Qr).

Diffusion

Diffusion is the net movement of solutes from a region of higher concentration to one of lower concentration. In KRT, the concentration gradient across the filter membrane is created by running dialysate in the effluent compartment. The diffusive flux follows Fick’s law of diffusion7; it is proportional to the diffusion coefficient of the solute (as approximated using Stokes-Einstein equation) and inversely proportional to the distance between the compartments (membrane thickness and permeability also add resistance). Because the diffusivity coefficient is inversely proportional to a molecule’s radius,2 this mechanism results in very efficient transport of the fast-moving small solutes, but inefficient transport of the slower-moving larger solutes, even those small enough to fit through the filter pore. Other factors that influence solute clearance include its protein binding and electrical charge. The differences in solute clearance between diffusion and convection are depicted in Fig. 75.1B

Adsorption

Adsorption is the process that refers to the binding of blood components to the membrane, and is determined by the specific characteristics of each molecule (i.e., dimension, charge, and structure) and each membrane (i.e., porosity, composition, hydrophobicity, surface potential).2 It was originally thought that adsorption may contribute substantially to overall clearance of certain substances during KRT. However, the rapid saturation of the membrane binding sites limits its effectiveness. Consequently, specialized adsorption cartridges with higher affinity and capacity for targeted substance have been developed. Their clinical effectiveness remains unproven.

BOX 75.1

Key Clinical Practice Guidelines

General

Clinical Practice Guidelines, 5th edition: UK Renal Association (2011)
Kidney Disease: Improving Global Outcomes (KDIGO): Clinical practice guideline for acute kidney injury (2012)
Acute Kidney Injury: Prevention, detection and management: National Institute for Health and Care Excellence (2013)
Kidney replacement therapy in adult and pediatric intensive care: Recommendations by an expert panel (2015)
Acute Disease Quality Initiative (ADQI) 17; Precision CRRT (2016)
Acute Disease Quality Initiative (ADQI) 22; AKI Quality Improvement (2019)
Acute Disease Quality Initiative (ADQI) 25; AKI in COVID-19 (2020)
International Organization for Standardization documents ISO 11663 (Quality of Dialysis Fluid for Haemodialysis and Related Therapies), ISO 13958 (Concentrates for Haemodialysis and Related Therapies), ISO 13959 (Water for Haemodialysis and Related Therapies), and ISO 26722 (Water Treatment Equipment for Haemodialysis Applications and Related Therapies) (www.iso.org)

Vascular Access and Infections

Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Work Group: Clinical practice guidelines for vascular access (2006)
Locking solutions for hemodialysis catheters; heparin and citrate—a position paper by the American Society of Diagnostic and Interventional Nephrology (2008)
European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section V: Chronic Intermittent Haemodialysis and Prevention of Clotting in the Extracorporeal System (2002)
Parenteral anticoagulants: American College of Chest Physicians EvidenceBased Clinical Practice Guidelines, 8th edition (2008)
National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England (2007)
Institute for Healthcare Improvement: How-to Guide: Prevent Central Line–Associated Bloodstream Infections (2012)
Centers for Disease Control and Prevention 2016 Update to the 2001 Recommendations for Preventing Transmission of Infections in Chronic Hemodialysis Patients

Who, When, and How of Acute Kidney Replacement Therapy

Initiating Kidney Replacement Therapy

Classic indications for starting KRT include volume overload, metabolic acidosis, or hyperkalemia refractory to medical management, and overt uremia. However, specific thresholds for these indications are empiric and subject to individual preference. Many have argued for early initiation to prevent, rather than treat these complications. Indeed, KRT is commonly initiated to prior to the development of life-threatening complications. This approach has been supported by early observational studies that found a strong association between the severity of volume overload and mortality.8-10 However, a causal relationship is not proven, and it remains unknown whether removal of excessive fluid improves outcomes. Any potential benefits of early initiation must be balanced with the potential harmful complications of KRT, including catheter-related infection, hypotension, electrolyte disturbances, suboptimal dosing of antibiotics, nutrition, and so forth. Recent randomized controlled trials (RCT) have addressed the question of early versus late initiation of KRT (Table 75.2).11-16 Five used

Kidney Diseases Improving Global Outcomes (KDIGO) criteria to determine the severity of AKI.11-15 Of these, one found that starting very early (within 8 hours of KDIGO stage 2 AKI) was associated with better survival.11 However, this was a single center study of mainly cardiac surgical patients and had a fragility index of 3 (a measure of the robustness or fragility of the results of a clinical trial), thus limiting its external validity. Three of the remaining five studies were multicenter RCTs and had a more representative mix of AKI12-14; they found no difference in outcomes between early and late start. Because of the lack of benefit in starting early, the AKIKI 2 (Artificial Kidney Initiation in Kidney Injury 2) study examined whether there was any benefit in implementing an even more delayed strategy; they compared a delayed versus very delayed initiation strategy.15 Although crude mortality was not different between groups, a prespecified multivariate analysis indicated a higher 60-day mortality in the very delayed group. It is important to note that 38% to 50% of patients randomized to the late start groups in the 3 multicenter RCTs never required KRT. This not only suggests that many patients in the early start group would not have required KRT, but also that our ability to predict who will ultimately require KRT is suboptimal. This highlights the need to identify markers that better predict who will require KRT and then establish its optimal timing.

The furosemide stress test* trial was a pilot study that examined this question; they only randomized patients nonresponsive to the furosemide stress test, thus enriching the study population with those patients most likely to require KRT.15 In this study, 75% of the late patients required KRT, but there was no difference in outcomes between early and late initiation of KRT. The overall evidence obtained from these trials suggests that routinely starting KRT early is not beneficial. However, waiting for absolute indications before considering KRT is also not appropriate and creates logistical challenges. Hence, KRT should be initiated if the burden of fluid and solute derangements is increasing and anticipated to result in complications, remembering that patients with certain illnesses, such as heart and lung disease, may have less tolerance to these homeostatic derangements. A systematic approach to initiating KRT, derived from existing guidelines, is presented in Fig. 75.2 17

Therapeutic Goals

When preparing the dialysis prescription in acutely ill patients, one should first clearly delineate the goals of therapy and then tailor the prescription to achieve these goals. That is, the prescription should be individualized to the patient. Therapeutic goals for KRT are divided into (1) physiologic targets, (2) dose of KRT delivered, and (3) volume status goals. These goals should be achieved without exacerbating hemodynamic instability, increasing end organ damage, or delaying kidney recovery.

Physiologic targets refer to the correction of the metabolic abnormalities. In general, ensuring delivery of an adequate dose (see later) is sufficient to normalize most metabolic derangements. However, there are circumstances that may require adjustments of doses and solutions to achieve the desired electrolyte homeostasis (e.g., severe rhabdomyolysis) or clearance of a specific toxin, as may occur during intoxications or severe hyperammonemia (e.g., in infants with inborn errors of urea metabolism, or occasionally postlung transplant patients).† Of note, continuous KRT (CKRT) is not an effective therapy for lactic acidosis (hepatic clearance is 10- to 100-fold greater).18 The only effective treatment is to address the cause of the lactic acidosis (e.g., improving tissue

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*The furosemide stress test consists of giving 1 mg/kg intravenous bolus (1.5 mg/kg in patients who are chronically on a loop diuretic). Urine output is then monitored for 2 hours. A urine output of less than 200 mL is considered nonresponsive and predicts progression to renal replacement therapy with an area under the curve of approximately

0.87.
†The use of kidney replacement therapy for this indication has not been established.

Molecular Mechanisms of Clearance Across a
Semipermeable Membrane
Convection

Ultrafiltration
Blood
Inlet

Blood
Inlet
Prefilter
Replacement Fluid

UF or
Effluent

High Pressure

Low Pressure

Low Pressure

High Pressure

UF or
Effluent

Postfilter
Replacement Fluid

Blood
Outlet

Middle Molecular Weight
Small Molecular Weight
Water Flux

Adsorption

Diffusion

Blood
Inlet

Blood
Inlet

Dialysate

UF or
Effluent

High Concentration

Low Concentration

UF or
Effluent

Blood

Outlet

Blood
Outlet

Blood
Outlet

A

Molecular Clearance According to Mechanism and Solute Size

80

40

n
tio
ec
nv
Co

60

ion
fus
Dif

Percent Clearance

100

K
id
ne
y

20
0
0

B

2500

10000 20000 30000 40000 50000 60000
Molecular Weight

Fig. 75.1 (A) Mechanisms of water and solute clearance in extracorporeal blood purification techniques. (B) A comparison of the size-selective clearance of convection, diffusion, and the native kidney. UF, Ultrafiltration.

Algorithm for Initiating KRT in Patients With AKI
AKI

Presence of medically refractory, life-threatening
complications of AKI

Yes

Start KRT
(unless not appropriate)

No
Optimize systemic hemodynamics
Optimize volume status
Avoid exacerbation of kidney injury

Consider baseline kidney
function and reserve
Monitor severity of
illness and trajectory

Monitor response to resuscitation/optimization
Assess for recovery of kidney function
Watch for development of complications of AKI

Presence of persistent or worsening AKI
and evidence of one or more of the following:

- Progressive fluid accumulation
- Complication of fluid overload
- Persistent/worsening hyperkalemia*
- Persistent/worsening acidosis*
- Persistent or worsening oliguria exacerbating fluid accumulation/overload*
- Persistent or worsening nonrenal organ dysfunction that may be modified by KRT
- Anticipated burden of fluid and/or solute complications (e.g., tumor lysis syndrome, rhabdomyolysis)

Yes

Consider KRT
(unless not appropriate)

Fig. 75.2 Algorithm for Initiation of Acute Kidney Replacement Therapy (KRT) in Critically ill Patients With Acute Kidney Injury (AKI). ∗Refractory to medical management. (From Bagshaw SM, Wald R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. Kidney Int. 2017;91[5]:1022–1032.)

oxygenation, removing dead gut). Finally, standard modalities are not effective at clearing inflammatory cytokines in a sustained manner and have not been shown to improve clinical outcomes.19 20 Thus, cytokine clearance should not be a therapeutic goal of KRT.

The dose of KRT delivered should at minimum meet the available evidence-based targets for each modality. In intermittent kidney replacement therapy (IKRT) and prolonged intermittent kidney replacement therapy (PIKRT), adequacy is measured as small solute clearance. The lower limit for intermittent hemodialysis (IHD) is a delivered single-pool Kt/V (spKt/V) of 1.0 per session, because doses below this were associated with decreased survival in patients with intermediate severity of illness.21 The VA/NIH ATN study (which permitted switching of KRT modality, depending on the Sequential Organ Failure Assessment [SOFA] cardiovascular score) showed that increasing the delivery of an spKt/V of 1.2 or more, from three to six times weekly, did not provide additional benefit.22 Subsequently, the minimum delivered spKt/V when using IKRT in patients with AKI was recommended to be 1.3 or more per session thrice weekly.23 However, because solute clearance is commonly decreased in the acutely ill patient, the spKt/V target is frequently not achieved with standard dialysis prescriptions. Indeed, the ATN study found that delivered spKt/V was approximately 1.1 after the first treatment and the prescribed dialysis time had to be increased to approximately 4 hours. Thus, to avoid underdelivery of IKRT, measurements of the delivered dose should be undertaken and the IKRT prescription adjusted accordingly (Box 75.2). Another way of expressing urea clearance is as continuous small-solute clearance (corrected equivalent renal urea clearance [EKRc]), which kinetically quantifies the “time-averaged KT.” It is particularly useful for PIKRT because EKRc is independent of treatment type and schedule. The Hannover Dialysis Outcome Study of PIKRT found that patients treated with PIKRT to achieve an EKRc of 20 mL/min (plasma urea level = 11.3 ± 4 mmol/L) had outcomes indistinguishable from those in which the EKRc was 13 mL/min (plasma urea levels = 19 ± 6 mmol/L).24 Note that the lower EKRc dose (13 mL/min) in this study was equivalent to a spKt/V of 1.2 to 1.4 per treatment three times weekly. Thus, the recommended EKRc target is a value of 13 mL/min or higher.25 26 The nomogram in Fig. 75.327 expresses the EKRc at distinct combinations of HD dose and frequency, thus providing a comparison between IKRT and PIKRT dosing.

TABLE 75.1

Essential Formulas Used in Kidney Replacement Therapies

Parameter
Transmembrane pressure (TMP)

Membrane ultrafiltration coefficient (KUF)

Definitions

Formula
TMP =

KUF =

(PF + Pr)

2

QUF

×

TMP

Ultrafiltration rate (QUF)

QUF = DKUF ×浼TMP

Filtration fraction (FF)
Convective flux (Jc)
Solute diffusive flux (Jd)

Diffusivity coefficient (D)

CUF = Solute concentration in UF
Cpi = Plasma solute concentrations at the inlet
Cpo = Plasma solute concentrations at the outlet

CUF
(Cpi + Cpo)/2

Qp = Plasma flow rate

QUF

FF =

Qp
QUFo

Jc =

A

Jd =

D=

QUF = Ultrafiltration flow rate
A = Membrane surface area

1

$DKUF = KUF \times$ 浼A

$SC =$

PF = Prefilter pressure
Pr = Return pressure
Pe = Effluent pressure

Pe

A

Filter ultrafiltration coefficient (DKUF)
Sieving coefficient (SC)

867

$\times C_{pi} \times SC$

D

D = Diffusivity coefficientdc = Concentration gradient
($dc = C1 - C2$)
dx = Distance between compartments

dc
dx

kB = Boltzmann constant
T = Absolute temperature
μ = Viscosity of the medium
R = Effective radius of the molecules

k_BT
$6\pi\mu R$

Rejection coefficient

$RC = 1 - SC$

CVVH postdilution

$K = QUF\ SC \times 60/\text{body weight}$

CVVH predilution

$K = QUF \times SC \times / [QBW\ (QBW + Q)] \times 60/\text{body weight}$

QBW = Blood water flow rate
QR = Replacement fluid rate

CVVHD

$K = Qd + Sd$

Qd = Dialysate rate
Sd = Saturation coefficient

CVVHDF

$K = (QUF + Qd) \times$ ✓ Sd

CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration.

In CKRT the clearance of urea and other small solutes is proportional to the total effluent flow (the sum of the dialysate and QUF; Fig. 75.4).28 CKRT dose is thus expressed as effluent volume flow rate per unit of premorbid or pre–intensive care unit (ICU) weight (mL/kg/h). Several early small studies suggested that increasing the CKRT dose from 20 mL/kg/h to more than 35 mL/kg/h may increase survival.29 30 However, these findings were not replicated in 2 large RCTs. The first, the VA/NIH ATN trial,22 utilized IKRT and CKRT as mentioned before, whereas the second, the Randomised Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy,31 only used CKRT. Based on these studies, there appears to be a dose of CKRT (20–25 mL/kg/h) above which survival becomes dose independent, and thus routine use of higher doses is not warranted. Although a lower dosing limit has not been established, 20 to 25 mL/kg/h is accepted because this was the lowest dose tested in the trials. In clinical practice, interruptions to CKRT due to diagnostic or therapeutic procedures often compromise the dose delivered, thus it is recommended to prescribe 25 to 30 mL/kg/h to ensure adequate dose delivery.

Fluid management is the other essential therapeutic target. Some patients present with fluid overload and simply need its removal. However, fluid management is usually more complex in critically ill patients. Initially, they often require volume resuscitation due to leaky capillaries and hemodynamic compromise. However, care should be given to avoid overzealous fluid administration because it leads to volume overload, increasing the risk for intraabdominal hypertension, poor wound healing, and impairment of oxygenation; indeed, it is associated with increased mortality.8-10 The resuscitation phase is followed by optimization and de-escalation phases where smaller adjustments are made and fluid may need to be removed. Thus, fluid management is a dynamic process that requires frequent assessment of volume status and targets.

The assessment of volume status is difficult because physical signs are generally not informative and surrogates of cardiac filling (e.g., by central venous filling pressures, cardiac or vena cava dimensions) may be inaccurate in critically ill patients. An alternative approach is to test the effect of therapeutic maneuvers, such as fluid challenge on measures of cardiac filling, stroke volume, and blood pressure. Even after fluid status has been assessed, determining the correct therapeutic goal is difficult and optimal strategies to achieve that goal are uncertain. KRT removes fluid from the intravascular compartment, and thus depends on adequate refilling from the interstitial compartment to maintain adequate hemodynamics. Consequently, close monitoring of hemodynamics is needed and UF targets individualized so that adequate cardiopulmonary and extracellular volume status is achieved while avoiding hypotension. Observational studies have shown that fluid accumulation of greater than 10% of body weight ([(Total input − Total output)/Patient body weight] × 100%) is associated with poor outcomes; thus maintaining it below this threshold should be considered.32 However, this approach needs to be tested in prospective clinical trials.

TABLE 75.2 Randomized Control Trials Comparing Early Versus Late Kidney Replacement Therapy Initiation

	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI	AKIKI-2	FST Trial
Location	Germany Single center n = 231	France Multicenter n = 620	France Multicenter n = 488	Multinational Multicenter n = 2927	France Multicenter n = 278	Thailand Multicenter n = 297
Inclusion criteria	KDIGO Stage 2 + NGAL >150 ng/mL	Stage 3 AKI + ventilator (85%) Pressors (85%) Sepsis (56%)	RIFLE Stage F Septic shock + Pressors (100%)	Stage 2 and 3	Stage 3 AKI Oliguria >72 h or BUN 40–50 mmol/L	AKI (any stage) + clinical ATN; FST

= NR

Timing of KRT

Early
<8 h post-AKI

Early
<6 h post-AKI

Early
<12 h post-AKI

Early
<12 h post-AKI

Delayed
<12 h post-AKI

Early
<6 h post-AKI

Late
<12 h or no
initiation

Late
BUN >40 mmol/L
Oliguria >72 h
life-threatening

Late
48 h
postrandomization
if no kidney
recovery

Late
AKI ≥72 h
Life threatening

More delayed
KRT postponed 1
day, or BUN >50
mmol/L or lifethreatening

Standard

% of KRT early
vs. late

100% vs. 91%

98% vs. 51%

97% vs. 62%

97% vs. 62%

Delayed (98%)
More delayed (79%)

98% vs. 75%

Type of KRT

100% CVVHDF

IHD (55%) CKRT
(45%)

IHD (43%)
PIKRT/CKRT (57%)

IHD, PIKRT, or
CKRT (68%)

Delayed:
IHD (60%)
CKRT (39%)
Both (1%)
More delayed:
IHD (58%)
CKRT 40%
Both (3%)

Mortality early
vs. late

60 days: 38.4%
vs. 50.4%
90 days: 39.3%
vs. 54.75%*

60 days: 48.5%
vs. 49.7%

90 days: 58% vs.
54%

90 days: 44% vs.
44%

28 days: 38% vs.
45%
60 days: 44% vs.
55%

28 days: 62.1% vs.
58.3%

Duration of stay
in ICU

Not significant:
19 vs. 22 days

Not significant:
13 vs. 13 days

Not significant: 12 vs.
12 days

Lower in Early
group

No difference: 18 vs.
16 days

No difference: 12 vs. 13.5 days

Mechanical ventilation days

125 vs. 181 hours

No difference: 7 vs. 6 days

No difference: 2 vs. 3 days

No difference

No difference

No difference: 4 vs. 0.5 days

*Statistically significant.
AKI, Acute kidney injury; BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; FST, furosemide stress test; ICU, intensive care unit; IHD, intermittent hemodialysis; NGAL, neutrophil gelatinase–associated lipocalin; PIRRT, prolonged intermittent kidney replacement therapy; KRT, kidney replacement therapy.

ACUTE KIDNEY REPLACEMENT THERAPY MODALITIES

The main modalities of KRT are IKRT, PIKRT, CKRT and PD. Within each one of these modalities there are variations according to the mechanism of clearance, access, and duration (Table 75.3). The choice of modality is largely based on institutional (preference, expertise, and available resources) and patient factors (hemodynamic stability, comorbidities), as several RCTs did not suggest an overall superiority of one modality over another.33-34 It has also been proposed that patients who are hemodynamically unstable have better organ recovery if they are treated with PIKRT or CKRT.35 36 However, appropriately powered RCTs have not been designed to test this directly, thus it remains speculative.

However, this does not mean that the modalities are clinically equivalent. For instance, patients on IKRT often require prolonging their therapy time or switching to CKRT because of progressive hemodynamic instability, poor metabolic control, or inability to meet their UF targets.22 33 34 We consider the different modalities to be complementary therapies with distinct strengths and weaknesses; thus, the choice of modality should be based on clinical context. Indeed, most will transition between modalities as their clinical status changes. For most, the modality choice still depends primarily on the desired rate of solute and fluid removal23 and on hemodynamic parameters.37 In addition, there are specific scenarios in which a particular modality may be preferred. For instance, IKRT is the preferred treatment when rapid clearance is desired (e.g., intoxications), whereas PIKRT and CKRT are more desirable when solute disequilibrium should be minimized to avoid water influx into tissues (e.g., patients at risk for dialysis disequilibrium, including those with increased intracranial pressure or abdominal compartment syndrome).38 PD is provided in a similar manner to ESKD patients. The spectrum of dialytic modalities used in acutely ill patients and their general characteristics are listed in Fig. 75.5

Economic factors may also play a role, as CKRT can be more expensive. However, economic considerations vary widely between different programs because of differences in nursing structures, quality of CKRT delivery, and other associated factors.39 Thus, economic evaluations comparing modalities needs to be conducted locally, with careful consideration of underlying assumptions about costs and outcomes.

Measures to Increase Intermittent Hemodialysis Dose

BOX 75.2

- Maximize hemodialyzer surface area (up to 2–2.2 m2)
- Maximize hemodialyzer porosity (high flux)
- Maximize blood flow rate
- Maximize internal lumen diameters of hemodialysis catheter
- Optimize blood flow
- Ensure positioning of the hemodialysis catheter tip at the caval atrial junction and IVC as appropriate
- Use right internal jugular vein approach, particularly in patients with a BMI of ≥27 kg/m²
- Minimize access recirculation
- Ensure positioning of the hemodialysis catheter tip at the caval atrial junction or IVC as appropriate
- Maximize dialysate flow rate
- Add postdilution replacement fluid to increase convective clearance (hemodiafiltration)
- Optimize anticoagulation to reduce hemodialyzer fiber bundle clotting
- Increase treatment frequency (up to daily)
- Increased treatment duration and/or consider PIKRT or CKRT
- Optimize patient’s hemodynamics to reduce compartmental urea sequestration

BMI, Body mass index; CKRT, continuous kidney replacement therapy; IVC, inferior vena cava; PIKRT, prolonged intermittent kidney replacement therapy.

Intermittent Kidney Replacement Therapy

IKRT, most frequently performed as IHD, makes use of the equipment, methods, and nursing staff established for chronic hemodialysis (HD). It provides rapid solute clearance and UF during relatively brief (3–5 hour) treatments. To achieve this, the Qb and Qd are set at relatively rapid rates (Qb is commonly 300–500 mL/min and Qd 300–800 mL/h). The dialysate can be delivered by either a batch or single-pass system. Water purity is important to avoid back-filtration of bacterial contaminants and other impurities, which can be detrimental to the patient (see Chapter 99). Reference standards for water purity in the ICU setting are the same as those for the ESKD setting. IKRT is the modality that removes solutes the fastest, thus decreasing the time a patient is exposed to the extracorporeal circuit. In IHD, small solutes are removed very quickly, making it an ideal therapy for conditions such as life-threatening hyperkalemia and intoxications. A theoretical disadvantage of IHD is that middle and larger molecules are not removed efficiently because the main mechanism of clearance is via diffusion. However, this can be improved by adding a component of convection, where QUF is tailored to the desired clearance and replacement fluid delivered to achieve the desired fluid balance (hemodiafiltration [HDF]). The replacement fluid should be sterile and can be the same as those used during CKRT, or generated online as ultrapure dialysate (sterilized via ultrafilters) and infused directly into the extracorporeal blood circuit.

Some suggest sterile dialysate for all acute IHD; however, data are insufficient to support a strong recommendation. Finally, highflux membranes have also been used to provide greater convective removal of middle molecules. Despite the rationale for increasing middle molecule clearance, there is no evidence suggesting improved outcomes.

Continuous renal urea clearance (mL/min)

Relationship Between Renal Urea Clearance and Single-Pool Kt/V
7 IHD/week

38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0

6 IHD/week

5 IHD/week
4 IHD/week
Alternate-day iHD
3 IHD/week

0.4 0.5 0.6 0.7 0.8 0.9

1

869

1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9

2

Single-pool Kt/V (per iHD treatment)

Fig. 75.3 Relationship between corrected continuous kidney urea clearance and single-pool Kt/V (weekly urea clearance/volume of distribution of urea) per treatment for a frequency of three to seven treatments per week. IHD, Intermittent hemodialysis. (From Casino F, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis. Nephrol Dial Transplant. 1996;11:1574–1581.)

Strategies to Reduce Intradialytic Hemodynamic Instability During Intermittent Kidney Replacement Therapy

The consequences of dialysis-related hypotension are not well studied in the critically ill AKI population but may be detrimental to kidney recovery and end organ function. Indeed, the injured kidney is prone to hypoperfusion due to its impaired autoregulatory responses. Moreover, IKRT can precipitate myocardial stunning, a phenomenon reported in patients with AKI (even treated with CKRT), which in turn may further impair kidney perfusion and impair kidney recovery.40 Axiomatically, the most effective measure to improve hemodynamically stability is increasing the frequency and treatment time, thereby decreasing rates of fluid and solute removal (optimized IKRT). This was one of the main reasons that slower modalities were developed. Studies show better preservation of blood pressure and lower vasopressor requirements in those treated with CKRT and PIKRT compared with IKRT.41-43 Thus, they have become the preferred option for hemodynamically unstable patients.23 However, switching modalities is not always possible or desired. Consequently, several strategies, borrowed from the ESKD literature, have been employed to avoid hypotension during IKRT in AKI patients. Although bicarbonate-based dialysate is the now the norm, most online dialysate still contains 4 to 8 mmol of acetate, which reportedly may increase blood acetate levels, hypotension, and arrhythmia in certain critically ill patients.44 Lowering the dialysate temperature to the lower limits of normal dialysate temperatures

Urea Clearance During
Continuous Hemodialysis

Urea clearance (mL/min)

150

Qd = 250 mL/min
100
Qd = 200 mL/min
Qd = 150 mL/min
Qd = 100 mL/min
50

Qd = 50 mL/min

0
0

50
100
150
Qb (mL/min)

Fig. 75.4 Determinants of Urea Clearance During Continuous Hemodialysis. Relationship among urea clearance, Qb (blood flow), and Qd (dialysate flow) during continuous hemodialysis. The flattening of the urea clearance curves describes the conditions in which increases in Qb do not enhance clearance. (From Kudoh Y, Iimura O. Slow continuous hemodialysis—new therapy for acute renal failure in critically ill patients. Part 1. Theoretical considerations and new technique. Jpn Circ J. 1988;52:1171–1182.)

TABLE 75.3

(35–36°C) lowers body temperature, which in turn increases vascular resistances and preserves blood pressure during dialysis without apparent deleterious effect.45 46 Blood temperature monitoring takes this a step further by controlling thermal transfer to and from dialysate in order to maintain blood temperature at a target value, thus avoiding vasodilation. However, the efficacy of modulating dialysate or blood temperature in the ICU setting has not been firmly established. High dialysate sodium concentrations (145–150 mEq/L) can prevent the fall in effective circulating volume that accompanies the rapid reduction in serum osmolality instigated by IKRT. Sodium profiling further ameliorates this process by inducing water flux into the vascular compartment. A clinical trial showed that intermittent HD with sodium profiling (from 160 to 140 mmol/L) combined with UF profiling improved hemodynamic stability.47 Similar data exist for PIKRT. Blood volume monitoring involves biofeedback systems that automatically adjust QUF and dialysate [Na+] in response to a fall in circulating blood volume. Although helpful in the ESKD setting, it has not been shown to prevent intradialytic hypotension in the ICU setting.48 49 HDF has been suggested to induce less intradialytic hypotension than IHD in the ESKD setting.38 Finally, if the main therapeutic goal is to remove fluid, isolated UF can be performed.3

Prolonged Intermittent Kidney Replacement Therapy

PIKRT was developed as a hybrid between IKRT and CKRT; indeed, urea clearance rates are lower than in IKRT but higher than CKRT. It is usually performed using standard IKRT equipment (CKRT equipment can also be used, as was necessary during the COVID-19 pandemic) but with lower solute clearances and QUF over longer durations. The intent was to provide the advantages of CKRT (slow, gentle solute clearance and QUF) while using available IKRT equipment, thus

Kidney Replacement Modalities and Their Subtypes

IKRT

PIKRT

CKRT

UF
Isolated ultrafiltration (also called sequential ultrafiltration)

EUF
Extended ultrafiltration (sometimes called SCUF)

SCUF
Slow continuous ultrafiltration

IHD
Intermittent hemodialysis

SLED
Slow low efficiency dialysis

CVVHD
Continuous venovenous hemodialysis

IHF
Intermittent hemofiltration

EHF or AVVH
Extended hemofiltration or accelerated venovenous Hemofiltration

CVVH
Continuous venovenous hemofiltration

IHDF
Intermittent hemodiafiltration

EHDF
Extended hemodiafiltration

CVVHDF
Continuous venovenous hemodiafiltration

CKRT, Continuous kidney replacement therapy; IKRT, intermittent kidney replacement therapy; PIKRT, prolonged intermittent kidney replacement therapy.

Spectrum of Acute Kidney Replacement Therapy
Severity of illness

Conventional
IKRD/IHD

Optimized
IKRT

PIKRT

CKRT

Peritoneal dialysis

Conventional
IKRT/IHD

Optimized
IKRT

PIKRT

CKRT

Clearance mechanisms

Diffusion

Diffusion

Diffusion or
convection

Diffusion +/−
convection

Type of machine

Standard

Standard or
CKRT

Standard or CKRT

CKRT

Blood flow (mL/min)

400–500

200–350

150–350

100–300

Effluent flow (mL/min)

600–800

400–600

100–200

25–65

Duration

3–4 h

4–6 h

8–12 h

Continuous

Frequency

3x/wk

4–5x/wk

4–7x/wk

Daily

Fluid removal rate

2–5 L/session
(0.75–1.5 L/h)

2–5 L/session
(0.5–1 L/h)

1–5 L/session
(250–500 mL/h)

0–300 mL/h

Access

AVF, AVG,
catheter

AVF, AVG,
catheter

Catheter
(? AVF/AVG)

Catheter

Weekly cost

$

$–$$

$$
(lower with auto)

$$$

Mobilization

Easy

Easy

+/− (easier if
performed overnight)

More challenging

Drug dosing

Straightforward

Straightforward

Limited data

More data

Staffing

HD RN

HD RN

HD or ICU RN

HD or ICU RN

Fig. 75.5 The Spectrum of Kidney Replacement Therapies in Acute Kidney Injury and Their General Characteristics. Although any modality may be used, each has advantages and disadvantages. Thus, the therapy may be tailored to the needs of the individual patient (e.g., patients with increased severity of illness and hypotension may benefit from slower therapies). Optimized IKRT represents IHD prescriptions that are a hybrid between PIKRT and IKRT, which is used to better reach patient therapy goals. AVF, Arteriovenous fistula; AVG, arteriovenous graft; CKRT, continuous kidney replacement therapy; HD, hemodialysis; ICU, intensive care unit; IHD, intermittent hemodialysis; IKRT, intermittent kidney replacement therapy; PIKRT, prolonged intermittent kidney replacement therapy; RN, registered nurse.

minimizing the additional equipment and complexities of implementing a CKRT program.28 PIKRT has the benefit of providing scheduled downtime, which allows the patient to get diagnostic studies, physical therapy, and so forth without compromising dialysis dose. Prescribed correctly, PIKRT provides a high dose of dialysis with minimal urea disequilibrium, excellent control of electrolytes, and good tolerance to UF (Fig. 75.3). PIKRT is usually delivered as a diffusive therapy, although there is increasing experience with combined diffusive and convective clearance. Treatment duration can vary from 6 to 18 hours using a Qb of 150 to 300 mL/min and Qd of 50 to 300 mL/min. This wide variation in operating parameters makes it difficult to interpret the literature on PIKRT and hence precisely define its role. In the older descriptions of PIKRT, the duration (12–18 hours) and other operating characteristics (Qb ≤250 mL/min, Qd ≤100 mL/min) were closer to those of CKRT, and treatment tolerance was excellent. The typical duration now is closer to 6 to 8 hours with faster Qb and Qd, and thus it may not be as well tolerated in high-risk populations, such as those with septic shock.[50] For this reason, we prefer lower efficiency prescriptions (i.e., lower QUF and slower solute removal) in the less stable patients (an algorithm to assist in prescribing PIKRT is presented in Fig. 75.6). Regardless, as with all forms of KRT, quality metrics for the parameters of interest (e.g., QUF, electrolyte and acid-base

Decision Process for Prescribing Prolonged Intermittent Kidney Replacement Therapy

Consider and set ultrafiltration goal, to be achieved in:

Session length
<8 hours

Session length
>8 hours

Dialysate flow
≥300 mL/min

Dialysate flow
~100–300 mL/min

Dialysate [K+]
3.0–4.0 mmol/L

Dialysate [K+]
4.0–5.0 mmol/L

Dialysate [HCO32–]
28–32 mmol/L

Dialysate [HCO32–]
24–28 mmol/L

Fig. 75.6 Overview of the decision processes for prescribing prolonged intermittent kidney replacement therapy.

management, anticoagulation, nutrition, medication dosing) should be identified, monitored, and promptly addressed (Table 75.4).

Continuous Kidney Replacement Therapies

CKRT involves the application of low solute clearance and QUF over 24 hours daily. The lower QUF provides the best hemodynamic stability of any KRT modality, and the longer treatment duration results in better and more consistent control of uremic solutes, especially for severely catabolic patients. It was first performed in an arteriovenous (AV) configuration in which blood flowed via an arterial catheter, through a simple extracorporeal circuit and filter, and then back to the patient via a venous catheter. This is largely an obsolete practice because of low effectiveness and high complication rate. The technique that is now routinely used is via the venovenous (VV) configuration, where blood is drawn from and returned to the central venous circulation via a mechanical blood pump. CKRT modalities are classified based on their mechanism of molecular clearance (Table 75.3). If the primary mechanism is via convection, it is called continuous venovenous hemofiltration (CVVH); as previously mentioned, the replacement fluid can be returned either prefilter or postfilter. If diffusion is the primary mechanism of clearance, it is called continuous venovenous hemodialysis (CVVHD). A combination of these 2 preceding techniques is called continuous venovenous hemodiafiltration (CVVHDF). The formulas used to calculate small solute clearance were shown in Table 75.1

The choice of technique depends on whether the primary need is for fluid and/or solute removal, and clinician expertise and preference. For isolated fluid removal (e.g., cardiorenal syndrome), SCUF is used. When solute removal is needed, the physician can choose either the convective or diffusive modalities, as there is clinical equipoise between them.51 Modern machines are able to provide reliable and rapid Qb (50–450 mL/min) and dialysate or replacement fluid rates that usually are in the 2 to 4 L/h range, but are capable of running at up to 12 L/h. The major limitations to implementing/sustaining CKRT programs have been cost and complexity. Some contributors to the costs of CKRT include nursing time, filters, and solutions. These are exacerbated by frequent circuit failure (mean operating time for CKRT is reported to be 17–22 h/day), which increases the work load and wastes.52 However, implementing simple standardized protocols

can result in the maintenance of a 2:1 patient:nurse ratio and circuit life spans of more than 60 hours, thus significantly decreasing the cost difference between modalities. For this, careful attention must be paid to the technical considerations of CKRT and a continuous quality program implemented.53

Extracorporeal Blood Purification

Critical illness is associated with increased production of cytokines, which are medium and large molecules that modulate the immune response. These trigger an inflammatory state, which is exacerbated in AKI, because cytokine clearance is decreased. Consequently, there has been an ongoing interest developing techniques that reduce cytokines during acute illness, especially sepsis. This interest was accentuated during the COVID-19 pandemic because of the profound inflammation milieu associated with SARS-CoV-2 infection. Cytokines can be removed with high levels of convective clearance, high cutoff hemofilters (membranes with a molecular weight cutoff of 60–150 kDa), bioadsorption devices, and coupled plasma filtration–adsorption (Table 75.5). Note that most of these techniques are not selective: they will remove any circulating substance that meets their clearance characteristics, including proinflammatory and antiinflammatory cytokines, as well as beneficial substances such as medications, including antibiotics. All of these techniques are experimental, supported only by observational studies and pilot trials. Larger multicenter trials are scarce and have not yet provided evidence of benefit. Better techniques are required to identify patients who might benefit from cytokine removal, as well as when and how cytokine removal should be applied.

OPERATIONAL ASPECTS OF ACUTE KIDNEY REPLACEMENT THERAPY

Advances in technology have facilitated the implementation of kidney replacement programs throughout the world. However, ensuring optimal quality and safety remains a challenge. Even now, many institutions lack quality monitoring programs such as monitoring clearance, be it IKRT, PIKRT, or CKRT. The need for defining and standardizing quality metrics in the care of AKI patients was addressed by an Acute Disease Quality Initiative (ADQI) series.53 They emphasize the need for all institutions to implement a quality initiative comprising integrating, monitoring, and reporting of quality metrics for all their KRT therapies. Table 75.4 provides an example of a quality dashboard that can be adapted to fit an institution’s needs. It is important to not only meet the individual benchmarks but to also determine the effect they have on overall efficacy and safety of the KRT program. For instance, the reason to monitor catheter function is to prevent premature circuit failure, which not only results in decreased delivery of the KRT dose but also causes blood loss and waste of disposables, alters delivery of medications and nutrition, and increases nurse workload, all of which increase health care costs.

Vascular Access

A prerequisite for IKRT, PIKRT, and CKRT is reliable vascular access through which blood is delivered to the membrane at an adequate flow rate for waste(s) removal but without clotting and circuit dysfunction. If the patient has an AV fistula or graft, this should be used for IKRT. Uncuffed, short-term HD catheters inserted into a central vein are the most commonly used access for CKRT. Although tunneled dialysis catheters may have better delivery metrics and fewer complications, they are usually reserved for patients who either already have one present or those expected to be on KRT for more than 3 weeks. Short-term HD catheters vary in material, size, lumens (number and lumen shape), catheter shape, and tip characteristics.53 However, the

TABLE 75.4

Example of a Quality Metric Dashboard for Kidney Replacement Therapy

Quality Indicator

Operational Definition

Proposed Benchmark

Access site

Right IJ vs. left IJ vs. femoral vein

For monitoring purposes

Tip placement

Tip within 3 cm of caval-atrial junction (for chest lines only)

1.0

Catheter dysfunction and failure

Number of catheters with dysfunction/total number of catheters

0.8

CLABSIs

CLABSIs/Number of catheter-line days

0 events per catheter

Vascular Access Related

Efficacy: Outcomes
Kt/V in IKRT and PIKRT

Kt/V after first session (weekly Kt/V to be calculated)

3.9 weekly

Filters used per session

Filters used/Number of sessions

1 per session

Filter life in CKRT

Number of filters lasting 60 h/Total number of filters used

>60% filters

Delivered dose

Actual delivered dose/24 h/Prescribed dose/24 h

>80% of dose

Fluid management

UF removed/24 h/Prescribed UF/24 h

>80% of UF

Small solute clearance

[sCr(d1) − sCr(d2)]/sCr(d2)

0

Unplanned time off CKRT

CKRT/24 h

<10% downtime

Downtime

Calculated from machine (e.g., delays in addressing alarms)

<10% downtime

Medication dosing

Appropriate dose adjustments per CKRT

Daily monitoring

Nutrition and supplements

Appropriate nutrition, vitamin, and trace element supplements

Daily monitoring

Number of adverse events/Number of patients on CKRT

0 events

Hypophosphatemia

Days with phosphate <2.5/Days of CKRT

0 days

Hypokalemia

Days with potassium <2.5/Days of CKRT

0 days

Hypomagnesemia

Days with magnesium <1.8/Days of CKRT

0 days

Safety Indicators
Adverse events
Electrolyte

Citrate-Related Errors

Calcium (high or low)

Days with phosphate <2.5/Days of CKRT

0 days

Alkalosis

Days with potassium <2.5/Days of CKRT

0 days

Hypomagnesemia

Days with magnesium <1.8/Days of CKRT

0 days

Structure indicators would be part of the framework of a CKRT quality program and may include a CKRT committee, defined training program, standardized order sets, infrastructure to support and measure these ongoing quality indicators and a process to ensure the proper functioning/ maintenance of KRT devices.
CLABSI, Catheter line–associated bloodstream infections; CKRT, continuous kidney replacement therapy; IJ, internal jugular; IKRT, intermittent kidney replacement therapy; PIKRT, prolonged intermittent kidney replacement therapy; UF, ultrafiltration.

TABLE 75.5

Techniques for Extracorporeal Blood Purification of Cytokines and Related Factors

Mechanism of Clearance

Therapy

Remarks

Filtration-based clearance

HVHF

Convective clearance

High cutoff membranes

Clearance by filtration via larger pore size

Plasmapheresis

Clearance by plasma exchange

Adsorption-based techniques

Combination techniques

AN69ST

Cytokine adsorption

Cytosorb

Cytokine adsorption

Depura D2000

Cytokine adsorption

HA 330

Cytokine adsorption

oXiris

Endotoxin and cytokine adsorption

Seraph100

Pathogen adsorption

Polymyxin B–based adsorption membranes

Adsorption of endotoxin

CPFA

Combined filtration and adsorption

CPFA, Coupled plasma filtration with adsorption; HA, hemadsorption; HVHF, high-volume hemofiltration.

TABLE 75.6 Determining the Length of Hemodialysis Catheters

Site	Formula	Accuracy
Right internal jugular	Height/10 cm	90%
Left internal jugular	Height/10 + 4 cm	94%
Right subclavian	Height/10 − 2 cm	96%
Left subclavian	Height/10 + 2 cm	97%

BOX 75.3

Insertion

- Hand hygiene and aseptic technique (including early replacement of catheters inserted in uncontrolled settings if adherence to these measures cannot be ensured)
- Maximum barrier precautions (hat, mask, sterile gloves, sterile gown, and full patient drape)
- Appropriate skin preparation using an alcohol-based chlorhexidine (>0.05%) solution; povidone-iodine (preferably with alcohol) or 70% alcohol can be used in patients with chlorhexidine intolerance
- Avoidance of the femoral site for catheter placement, especially in overweight patients (BMI ≥ 27 kg/m^2)
- Avoidance of catheter placement near open wounds

most important factors to ensure low resistance/high Qb are catheter diameter and location of the tip. Thus, the widest catheter with the shortest length that allows for proper tip placement should be used. The catheter length should be chosen based on the insertion site and height using the Peres formulas (Table 75.6).[54-56] The right internal jugular has usually been considered to be the first-choice insertion site, followed by the left internal jugular and femoral veins.[57] The use of the subclavian vein is not recommended, as cannulation can lead to increased risk of venous stenosis. Several studies have challenged the superiority of the internal jugular approach, suggesting that the femoral vein performs as well as the right internal jugular vein (except in the heaviest tertile) and better than the left internal jugular vein.[58,59]

Consequently, the latest guidelines have placed the femoral before the left internal jugular vein. However, it should be noted that the treating center was an independent predictor of short-term HD catheter dysfunction, and it is thus recommended that each center identify their own best practices by monitoring their internal data.[53]

The demands placed on a short-term HD catheter by and PIKRT are somewhat different than during IKRT (see also Chapter 96). On the one hand, the Qb demands are less than in IKRT: Qb usually are 300 mL/min or less. But on the other hand, they are being used from prolonged periods during which it is manipulated or mobilized, thereby increasing the risk of complications and so forth. From a functional standpoint, poorly functioning catheters involve either catheter dysfunction or catheter failure. Catheter dysfunction in CKRT is when suboptimal catheter function is causing premature circuit failure or inadequate clearance in the absence of frequent alarms or obvious drops in Qb, and thus may not be readily detected.[54] Catheter failure is when the Qb obtainable through the catheter is insufficient to maintain a functioning CKRT; it is characterized by frequent alarms and stopping of the Qb pump. Causes of early dysfunction or failure include kinking and suboptimal tip placement. Late dysfunction/failure is more often due to intrinsic or extrinsic obstruction caused by thrombosis.

Another complication of dialysis catheters is infection. Although largely preventable, they remain problematic, especially in the ICU setting where patients frequently have other intravenous catheters and lines. Hence, catheter-associated bloodstream infections are still too common. There is ongoing controversy around the risk for infection with different insertion sites, but on balance the internal jugular site is preferred, especially in those with a larger body mass index. However, it is likely that the way the catheter is handled is more important at preventing infection than the site in which it is inserted. Low rates of infection require the adherence to specific clinical guidelines and implementing a formal quality improvement program. There is strong evidence that implementing best practice catheter insertion techniques and maintenance results in a close to zero catheter-related infection rate (the core elements are listed in Box 75.3).[60] The relevant interventional bundles are contained in position statements of the Institute for Healthcare Improvement and the Centers for Disease Control and Prevention Healthcare Infection Control Practices Advisory Committee.[61] [62]

Best Practices to Minimize Catheter-Associated Bloodstream Infection

Maintenance

- Daily review of the need for the line, with prompt removal of unnecessary lines
- Appropriate dressing with sterile gauze or a sterile, transparent, semipermeable dressing
- Appropriate schedule for dressing changes according to condition and type of dressing
- Daily review of the catheter exit site with minimal disturbance to the dressing unless clinically indicated
- Appropriate skin preparation before ports are accessed
- Scrub-the-hub protocol for accessing the catheter
- Daily cleansing of patients with a 2% chlorhexidine wash
- Use of a sutureless securing device for catheter stabilization

BMI, Body mass index.

Circuit and Hemofilters

To ensure optimal KRT delivery, a thorough understanding of the circuit and hemofilter is needed. An ideal circuit is characterized by easy priming (low volumes), low resistance to Qb, biocompatible materials, minimal blood-air interfaces, and easily exchangeable hemofilters (see also Chapter 98). The KRT circuit begins and finishes at the patient’s vascular access (Fig. 75.7).54 It comprises a series of pumps connected by tubing segments containing sensors that enable the monitoring and regulation of blood and other solutions flowing through the circuit. It has 4 major segments: (1) an inflow (prefilter) segment carrying the blood from the patient’s vascular access to the hemofilter, (2) the hemofilter/dialysis membrane, (3) an outflow (postfilter or return segment) carrying “cleansed” blood back to the patient, and (4) the circuits carrying the nonblood solutions. The pressure sensors are strategically located to monitor for specific changes in the circuit dynamics. Any change in pressure detected by a sensor, in the absence of prescription change, reflects a change in the resistance along that segment, thereby facilitating early detection of an abnormality to the circuit dynamics. Modern hemofilters are made of synthetic biocompatible materials with surface areas that vary from as low as 0.1 m2 to over 2 m2. Although molecular size cutoffs vary between membranes, the primary determinant of size selectivity in standard KRT is the mechanism of clearance (convection vs. diffusion). Although studies have examined the potential benefits of using high cutoff hemofilters to clear more middle molecules (e.g., cytokines), they have not been shown to improve outcomes.

Replacement Fluids and Dialysate

CKRT requires sterile replacement fluid or dialysate for blood purification, with composition that is determined by the clinical requirements

Kidney Replacement Circuit Including Blood Conduit and Nonblood Segments
Outflow
pressure
pod

Effluent
pressure
pod

Prefilter
pressure
pod

Inflow
pressure
pod

Heparin

Postfilter
replacement
fluid

Effluent

Dialysate

Prefilter
replacement
fluid

Pre–blood
pump fluid

Fig. 75.7 Typical continuous kidney replacement therapy circuit including the blood conduit and nonblood segments. (From Juncos LA, Chandrashekar K, Karakala N, Baldwin I. Vascular access, membranes and circuit for CRRT. Semin Dial. 2021;34[6]:406–415.)

for acid-base control and electrolyte management (see also Chapter 98). Commercially available fluids are the norm, but appropriate fluids can also be prepared derived from peritoneal dialysate and standard intravenous fluids if commercial products are unavailable. Moreover, bagged dialysate solutions for CKRT machines have been generated using single-pass dialysis machines during periods of severe shortages, such as during the COVID-19 pandemic.63 In general, the generation of fluid via pharmacy compounding is avoided because of the increased costs and potential for human error. Bicarbonate buffered solutions are now preferred because they provide superior acid-base control, hemodynamic stability, urea generation, cerebral dysfunction, and may improve survival in select patient groups.64 Bicarbonate concentrations in fluid are typically 32 to 35 mmol/L, but 22 to 25 mmol/L concentrations are available for when using citrate anticoagulation. Potassium concentrations vary from 0 to 4 mEq/L. The vast majority of the time a 4 mEq/L solution is sufficient to maintain normokalemia in CKRT, unless the delivered dose is insufficient. The lower potassium concentrations are used when initiating hyperkalemic patients or in those with elevated redistribution of potassium from the intracellular compartment due to tissue breakdown (e.g., rhabdomyolysis). Despite its commercial availability, we do not believe the use of a 0 mEq/L solution is ever warranted in IKRT or PIKRT and is only beneficial in very select/rare circumstances during CKRT. Calcium comes in 2.5, 3, 3.5, or 0 mEq/L configurations. Intravenous calcium replacement is necessary when using the lower calcium concentrations and citrate anticoagulation. Magnesium comes in 1.0 to 1.5 mEq/L configurations, and therefore periodic repletion of the patient’s magnesium levels may be necessary. While phosphate-containing solutions are becoming increasingly available, most continue to lack phosphate; thus supplementation is almost always required after the first few days of CKRT to avoid hypophosphatemia. Phosphate replacement should begin as soon as plasma levels approach low-normal levels and can be accomplished by (1) initiating a continuous infusion (e.g., starting at approximately 1 to 1.5 mmol/h and titrating to maintain normal plasma levels), (2) provding phosphate via the gastrointestinal tract 2 to 3 times daily, or (3) adding appropriate quantities of phosphate into the dialysate.65 Because hypophosphatemia has been associated with muscle weakness, including respiratory muscle weakness accompanied by longer duration of mechanical ventilation and mortality, its prevention is an important quality metric to monitor. Finally, dextrose-free solutions may induce euglycemic ketoacidosis; therefore, patients being treated with these solutions should be monitored for this complication.65

Anticoagulation in Acute Kidney Replacement Therapy

Most ICU patients can avoid any anticoagulation during intermittent HD because of short treatment duration, but most on PIKRT or CKRT benefit from anticoagulation. Although numerous protocols with anticoagulants have been developed, the most commonly used are based on unfractionated heparin and citrate (see also Chapter 98).66 Unfractionated heparin can be used by infusing heparin either via the syringe in the KRT device, along the inflow segment of the circuit, or systemically. A common protocol starts with an initial bolus dose of 25 to 30 U/kg followed by an infusion of 5 to 20 U/kg/hr titrated to keep the activated partial thromboplastin time (APTT) in the venous blood line 1.5 to 2 times the control value. Advantages of unfractionated heparin include low cost, relative safety, and ease of monitoring. Risks include bleeding in up to 25% to 30% of patients, hyperkalemia, elevated hepatic transaminases, and heparin-induced thrombocytopenia (HIT) in 3% to 5% of patients. To decrease the bleeding risk, a regional heparin/protamine sulfate anticoagulation protocol was proposed in which 1 mg of protamine for every 100 U heparin is infused into the venous line, thus reversing heparin’s effect.67 However, rebound bleeding can occur when the neutralization with protamine wears off faster than the anticoagulation from heparin. Furthermore, protamine may cause sudden hypotension, bradycardia, or anaphylactoid reactions.

Regional citrate anticoagulation is suggested as the first line strategy by KDIGO guidelines.68 It provides the greatest prolongation of filter life and lowest rates of hemorrhage. Regional citrate anticoagulation comprises calcium chelation in the extracorporeal blood circuit and with a calcium infusion either into the return segment or intravenously to restore systemic calcium levels. For intermittent HD and PIKRT, this involves an infusion of 4% trisodium citrate into the arterial blood line, a zero/low-calcium dialysate. For CKRT, either 4% trisodium citrate or anticoagulant citrate dextrose A (ACD-A) is infused into the inflow segment. The rate of citrate is calculated so that blood citrate levels are between 3 and 4 mmol/L or postfilter ionized calcium is less than 0.35 mmol/L. Because the 4% trisodium citrate solution is hypertonic, its use will require an additional infusion of hypotonic fluid or the use of dialysate that is hyponatremic to avoid hypernatremia. Although the ACD-A solution is also hypernatremic, it is not sufficient to induce significant hypernatremia when using appropriate infusion and clearance rates. Both solutions require the use of the lower bicarbonate solutions (22–25 mEq/L) to prevent the alkalosis caused by the subsequent metabolism of the infused citrate into bicarbonate in the liver (in a 1:3 ratio). Frequent monitoring and titration of citrate dose have been advocated to keep the ionized calcium within a therapeutic range. However, many centers now use a simplified fixed-dose anticoagulant citrate dextrose, which minimizes the need to measure postfilter calcium or adjust the citrate infusions. Major complications of regional citrate anticoagulation include systemic hypocalcemia and metabolic alkalosis from citrate toxicity. There is increasing experience with commercial replacement solutions containing citrate as buffer; this chelates calcium in the blood without the need for a separate citrate infusion. Some CKRT devices allow for direct coupling of citrate and calcium infusions, such that a change in Qb leads to an automatic change in the infusion rates of citrate and calcium. This does not obviate monitoring for systemic hypocalcemia and metabolic alkalosis but is expected to be safer and will likely become the standard approach in the future.

Protocols with other anticoagulants have also been described, but are used less frequently. Low-molecular-weight heparin is theoretically advantageous because of increased antithrombotic activity. However, disadvantages include a prolonged half-life (approximately doubled in Acute Kidney Injury Network [AKIN] stage 3, with no significant clearance during KRT), incomplete reversal with protamine, and limited availability of appropriate monitoring by serial anti–factor Xa determinations (recommended level 0.25–0.35 U/mL). Most experience is with dalteparin administered as a single bolus of approximately 20 to 30 U/kg for intermittent HD, followed by an infusion of approximately 10 U/kg/h for PIKRT or CKRT. Overall, the evidence does not support its use over unfractionated heparin in the critically ill AKI setting. Argatroban does not cross-react with heparin antibodies and is the preferred approach for HIT because of its hepatic clearance (halflife ~35 minutes, no significant clearance during KRT[69]) and ease of monitoring with APTT. It is administered as a 0.1 to 0.25 mg/kg bolus before intermittent HD or an infusion of 0.1 to 0.2 mg/kg/h during PIKRT or CKRT, titrated according to APPT. Bivalirudin may be used as an alternative to argatroban in patients with combined kidney and liver failure. Prostacyclin is another effective anticoagulant, but causes variable but occasionally marked falls in BP. Moreover, there is a risk for worsening ventilation-perfusion mismatch and lactic acidosis in patients with multiorgan dysfunction and a risk for increasing intracranial pressure in patients with combined liver and kidney failure. Other less frequently used approaches include antithrombin-dependent factor Xa inhibitors (e.g., fondaparinux) and serine protease inhibitors (nafamostat mesilate).

Drug Dosage in Acute Kidney Replacement Therapy

The effect of AKI and KRT modalities on pharmacokinetics and pharmacodynamic responses remains inadequately studied. Medication dosing data is largely derived from patients with ESKD undergoing IHD and are extrapolated to patients with AKI using the same pharmacologic principals (e.g., size, degree of protein binding, volume of distribution, lipophilicity vs. hydrophilicity). Calculating KRT dosing can be helpful in determining appropriate dosing regimens. For instance, a 70-kg male on CKRT at 25 mL/kg/h (which is 1750 mL/h) corresponds to a glomerular filtration rate (GFR) of approximately 30 mL/min, and the dose of drugs should be calculated accordingly. Drugs with wide therapeutic indices should be used when possible, and drug levels, particularly of those with low therapeutic indices, should be periodically monitored (when possible).

EXTRACORPOREAL KIDNEY THERAPY IN HEART FAILURE AND MECHANICAL CIRCULATORY AND VENTILATORY SUPPORT

Nephrologists are frequently involved in management of patients with heart failure (HF) complicated by diuretic resistance (i.e., failure to reach the therapeutically desired reduction in edema despite adequate and escalating diuretics) and/or kidney dysfunction. The rationale for this is not only because of our expertise in removing fluid (be it by optimizing diuretics or providing KRT) but also because the pathophysiology of HF with diuretic resistance is intimately related to progressive kidney dysfunction (Fig. 75.8). Activation of neurohumoral pathways and venous congestion are of particular importance. The neurohormonal pathways most implicated are the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Activation of these systems induces vasoconstriction of the renal arterioles, alters the autoregulatory curve (shifting it downward and to the right), and promotes sodium retention. Venous congestion exacerbates these maladaptive changes by inducing preglomerular myogenic responses, narrowing the arterial-to-venous pressure gradient, and increasing kidney interstitial pressure, all of which lower kidney perfusion and GFR. Indeed, kidney function in decompensated HF correlates better with central venous pressures than ejection fraction or cardiac index and is associated with increased mortality.[70] The interplay between the neurohumoral systems and venous congestion is also important when considering mechanisms of decompensation and responses to therapy. That is, because the venous system contains approximately 70% of the circulatory volume, venous vasoconstriction (causing decreased capacitance) can increase preload and decompensate HF without there being an actual increase in body weight.[71]

Conversely, increasing venous capacitance can ameliorate HF symptoms despite the absence of fluid removal. This variation in the venous reservoir volume complicates the interpretation of efficacy of fluid removal strategies in HF.

Reciprocal Pathophysiologic Pathways Linking Heart Failure, Kidney Dysfunction, and Congestion in Cardiorenal Syndrome

Cardiac
output

Decompensated
heart failure

LVF

Vasodilators
Mechanical interventions
Coronary ischemia interventions
Correct severe anemia
Inotropes
IABP
LVAD
Neurohormonal
activity

Inflammatory
cytokines
Endothelial
activation

Serelaxin

Effective
volume

Venous
circumferential
stretch

LVEDP

Inotropes

Inflammatory
cytokines
(IL-6, TNF-α, MCP-1)

Right atrial
pressure

Diuretic
resistance

Tissue
perfusion

ERA

Renal
perfusion

Oxidative
stress

Congestion
Diuretics
Ultrafiltration

Systemic
vasoconstriction

LVF

Arterial
underfilling

ACE-I
ARB
BB

ARNI
AA1RA
Dopamine
Denervation
Renal dysfunction

Intraabdominal
pressure

Renal venous
pressure

MRA
Secondary
hyperaldosteronism

Paracentesis
Distal sodium
delivery

Sodium
retention
Water
retention

Diuretics
Ultrafiltration
VRA

Dietary restriction
Diuretics
Ultrafiltration
ARNI
NPs

Fig. 75.8 Reciprocal Pathophysiologic Pathways Linking Heart Failure, Kidney Dysfunction, and Congestion in Cardiorenal Syndrome. Decompensation of heart failure can lead to deterioration in kidney function via exacerbated neurohormonal activity and/or kidney venous congestion. The impact of various pharmacologic and nonpharmacologic therapeutic options on the underlying pathophysiologic mechanisms is illustrated. AA1RA, Adenosine A1 receptor antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, β-blocker; ERA, endothelin receptor antagonist; IABP, intraaortic balloon pump; IL-6, interleukin-6; LVAD, left ventricular assist device;

LVEDP, left ventricular end-diastolic pressure, LVF, left ventricular function; MCP-1, monocyte chemoattractant protein-1; MRA, mineralocorticoid receptor antagonist; NP, natriuretic peptide; TNF-α, tumor necrosis factor-α; VRA, vasopressin receptor antagonist.

Therapeutic Options for Venous Congestion

Diuretics

Treatment of HF requires addressing treatable causes, instituting diet and lifestyle changes, titrating pharmacologic therapies, and considering mechanical options. The cornerstone of HF therapy for nephrologists revolves around volume management. Indeed, more than 90% of patients admitted with HF are fluid overloaded; the prerenal picture is due to venous congestion, not intravascular volume depletion. Hence, intensifying the diuretic regimen by increasing the dose is the first step. Increasing the frequency or starting a continuous drip are alternative strategies in those with suboptimal responses. RCTs have demonstrated clinical equipoise between approaches, thus one can

tailor it to individual patient responsiveness. A reasonable approach is that used in the DOSE study,72 in which the outpatient diuretic dose was increased 2.5-fold and then titrated per clinical responsiveness. Because the dose-response curve to loop diuretics is logarithmic, doubling the dose is warranted until a diuretic response is achieved or the maximal dose reached. In the absence of an adequate response, the reason for resistance should be identified and strategies to improve diuretic responsiveness implemented. Blocking adjacent nephron segments using other diuretics, most commonly thiazide-like agents, may increase natriuresis. Urine sodium monitoring may assist in guiding diuretic regimens. Despite optimization of diuretic regimens, many patients ultimately require other forms of volume removal.

Extracorporeal Ultrafiltration

Intermittent isolated UF and SCUF are characterized by isolated fluid removal; solute clearance is minimal. This was initially reserved for patients with advanced HF and diuretic resistance. Enthusiasm for its use increased greatly following development of commercially available devices that facilitated the procedure and results of early studies.[73-74] Consequently, more definitive studies were attempted. The UNLOAD trial[75] compared early UF versus intravenous diuretics. Despite the UF group having greater weight loss and fewer rehospitalizations (it was not sufficiently powered to establish this endpoint though), there were no differences in secondary endpoints (dyspnea scores, kidney function, 6-minute walking tests, or mortality). The CARRESS-HF study[76] did not show superiority of UF to diuretics (using a stepped-based algorithm); it did not improve weight loss, dyspnea, well-being scale scores, or diuretic dose, but had a higher rate of adverse events (kidney failure, bleeding, and catheter-related complications). There were no differences in mortality, emergency visits, or rehospitalizations between groups at 60 days.[76] These studies led to decreased interest. Indeed, the AVOID-HF trial[77] was stopped after just 224 (of a planned 810) hospitalized patients were enrolled. Early flexible UF therapy was found to have a greater net fluid loss compared with diuretics without obvious evidence signs of kidney dysfunction. However, the study was underpowered to draw any definitive conclusions regarding hard outcomes. Although several metanalysis have been performed, the differences between study protocols limit their interpretation. Consequently, isolated UF techniques should now be reserved for patients in whom diuretics are insufficient to achieve/maintain adequate volume status.

Peritoneal Dialysis

PD to treat patients with HF has been used for more than 70 years. When used primarily for UF, PD regimens are simpler than in ESKD; fewer daily exchanges or therapy days per week are needed and thus easily implemented and sustained.[78] PD catheters can be placed under local anesthesia and used immediately (using low dwell volumes), but laparoscopic insertion, using general anesthesia, is often performed without problems.[79] Use of PD is associated with improvement in various parameters including electrolytes, fluid status (reduced body weight and diuretic responsiveness), New York Heart Association class, 6-minute walk capacity, hospitalization days, quality of life, cardiac hemodynamics, and HF biomarker levels (BNP, aldosterone); and it does so without activating the SNS or RAAS.[80] However, this evidence is limited to observational studies and cohorts. Thus, it is possible that the purported benefits of PD may simply reflect patient selection or the extra care provided by the PD/research teams. Available evidence suggests that PD is well tolerated and has a low rate of complications, and thus may be offered as a selective therapy to improve fluid status and symptoms in HF patients with advanced CKD.

Kidney Replacement Therapy in Mechanical Cardiopulmonary Support

The two forms of mechanical circulatory support that are most commonly encountered by nephrologists are extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). In ECMO, deoxygenated blood is taken from a central vein and pumped through an oxygenator back into either a central vein (VV) or the arterial system (venoarterial), thereby providing respiratory or cardiorespiratory support, respectively. VADs assist the left (LVAD) and right ventricles (RVAD) in patients with refractory heart failure or cardiogenic shock. They are used as a bridge to recovery or transplantation or as destination therapy for patients ineligible for transplantation. Continuous flow devices have almost completely supplanted the earlier pulsatile flow pumps. Another modality of respiratory support available in some countries is extracorporeal carbon dioxide removal (ECCO2R). It removes carbon dioxide via a minimally invasive approach that requires lower blood flow and smaller cannulas than ECMO. ECCO2R can also be achieved, albeit with varying success, via a modified CKRT system linked to a gas exchange membrane.[81]

AKI is common in patients with circulatory and/or respiratory failure. If hypoperfusion is causing AKI, initiating mechanical cardiopulmonary support (MCS) may improve kidney function.[82] However, the incidence of intrinsic AKI (and the need for acute KRT) is high because patients requiring MCS are sicker, and MCS can be complicated by periprocedural hypotension, inflammation, thromboembolism, and hemolysis. Although scant data are available regarding the use of KRT during MCS, the general principles are similar to those for other ICU patients. However, prolonged or continuous acute KRT modalities may be especially advantageous during MCS because they allow for more effective management of patients receiving large fluid volumes. Maintaining adequate volume balance facilitates weaning of MCS, whereas volume overload is associated with worse outcomes.

Technical Aspects of Kidney Replacement Therapy During Mechanical Cardiopulmonary Support

The available modalities for providing KRT during MCS are the same as in other situations: PD, IKRT, PIKRT, and CKRT. Preferences vary according to the type of MCS provided. In ECMO, the preferred modality is usually CKRT because it facilitates volume management with less hemodynamic compromise. This is now usually delivered via the standard CKRT devices via HD catheters, or by directly integrating into the ECMO circuit (Fig. 75.9).[83] An alternative method, which is simple but less precise, is to provide CKRT by creating a shunt that contains a hemofilter in the ECMO circuit. Blood flow through the shunt is driven by the pressure gradient between these two segments, while infusion pumps regulate dialysate, replacement fluid, and UF rates. PD, which was usually used in infants, is now less common.

The preferred KRT in critically ill patients with VADs, particularly in the postimplantation period, is usually CKRT. This is eventually transitioned to IHD or PD once the patient is hemodynamically stable. Either modality can be continued in the outpatient setting. The most commonly used modality is IHD. This is initially done via a dialysis catheter, but this carries a high risk of infection and should thus be changed over to an AV access as soon as possible. AV grafts are preferred because the fistulas may not mature adequately in the nonpulsatile environment. Another challenge in providing KRT to patients with LVADs is the monitoring and maintenance of adequate preload and afterload during IHD.[84] This is of vital importance because the function of LVADs depends greatly on these parameters, both of which can change quickly during an IHD session. Afterload is monitored by measuring blood pressure, which is difficult in patients with continuous-flow VADs due to their minimal pulses, thus rendering standard plethysmography unsuitable. Instead, it is measured using Doppler ultrasonography or specialized cuffs with low pulsatility modes.[84] Stringent blood pressure control is desirable to avoid increased afterload-induced decreases in LVAD pump flow. Preload can be assessed by central venous pressure, echocardiogram, or the pulsatility index (in the Heartmate II). KRT-associated decreases in preload may lead to left ventricular collapse with subsequent fall in MCS flow, pump overdrive, hypotension, and ventricular arrhythmias. This is corrected by gentle volume administration, as other causes of preload reduction (e.g., bleeding, sepsis) are considered. Decreasing the pump speed and treating arrhythmias usually should be performed only after consultation with appropriate VAD personnel.

PD is an underutilized modality in patients with VADs, mainly because of the common misconception that it is contraindicated

In-Line Inclusion of a Hemofilter Into an ECMO Circuit

Blood return to patient
Heat exchanger

Oxygenator

Blood pump

Replacement fluids

UF

Replacement fluids

In-Line Inclusion of a Continuous KRT Device Into an ECMO Circuit

Blood return to patient
Heat exchanger
Alternative approach

Oxygenator

Preferred approach

Blood pump

Fig. 75.9 Extracorporeal Membrane Oxygenation (ECMO) Circuit With an In-line Hemofilter (Top Panel) or Continuous Kidney Replacement Therapy Device Integrated Into the ECMO Circuit. Two potential connections (preferred and alternative) are illustrated in the bottom panel. CKRT, Continuous kidney replacement therapy; UF, ultrafiltration. (From Karakala N, Juncos LA. Providing continuous renal replacement therapy in patients on extracorporeal membrane oxygenation. Clin J Amer Soc Nephrol. 2020;15[5]:704–706.)

because of increased risk of infection. This concept originated from older generations of VADs, which were implanted into the peritoneal cavity or abdominal wall, and thereby susceptible to infection. However, newer LVADs are extraperitoneal and thus devoid of this intravascular infection risk. Benefits of PD include gentle UF with no abrupt changes in preload, no abrupt electrolyte shifts,

and low risk of bacteremia from catheter infections. Moreover, it is performed at home, which precludes the problem of finding an outpatient dialysis center that will accept them, as most are not comfortable in accepting LVAD patients. More experience is needed to determine the optimal provision of KRT in these patients.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is true with regard to the different acute KRT modalities?
A. The routine use of CKRT rather than IKRT is associated with improved survival.
B. When opting for IKRT, one should routinely use a daily rather than thrice-weekly treatment schedule in order to improve survival.

C. The best available data suggest delivering a minimum dose of 20 mL/kg/h (for CRRT) or a single-pool Kt/V of ≥1.2 thrice weekly in critically ill patients receiving hemodialysis.

D. Using higher doses of continuous KRT has been shown to increase cytokine removal and improve outcomes in patients with septic shock and AKI.

2. Which of the following is true regarding initiating KRT in critically ill patients?
A. A positive test for TIMP2/IGFBP7 predicts the future development of severe AKI; thus the patient should be prepared for initiation of acute KRT.
B. The use of biomarkers of AKI (e.g., neutrophil gelatinase–associated lipocalin) improves diagnosis and facilitates deciding who should receive KRT.
C. Using the furosemide stress test to assist in the decision to initiate KRT was found to improve clinically meaningful patient outcomes and prevent the unnecessary initiation of KRT in patients who rapidly recovered renal function.
D. The available randomized trials have failed to identify markers that dictate the initiation of KRT in a manner that has a favorable effect on meaningful clinical outcomes.
3. Which of the following statements is true regarding central venous catheters for acute KRT in critically ill patients?
A. Temporary nontunneled dialysis catheters placed in the femoral vein have the same catheter dysfunction and infection rates as those placed in the internal jugular veins.
B. Tunneled dialysis catheters are associated with better function and fewer infections than temporary nontunneled dialysis catheters in critically ill patients. Thus, evidence-based guidelines recommend that they be used in patients expected to require KRT for more than 7 days.
C. Catheters should be placed and used in all critically ill patients requiring KRT, regardless of the presence of arteriovenous fistulas or grafts.
D. Internal jugular catheters are routinely preferred to femoral ones.
4. Which of the following interventions is not recommended to reduce central venous catheter–associated bloodstream infection during KRT for critically ill patients?
A. A formal quality improvement framework and program for catheter insertion and maintenance
B. Cleaning of catheter tips with a chlorhexidine-based solution
C. Routine use of antibiotic locks
D. Routine placement of catheters in the internal jugular site in obese patients
5. Which of the following statements is false regarding anticoagulation for acute KRT in critically ill patients?
A. Patients receiving anticoagulation with heparin have a lower incidence of circuit failure but a higher incidence of bleeding complications compared with to no anticoagulation.
B. Argatroban is a preferred approach in those with heparininduced thrombocytopenia.
C. A high calcium gap (citrate lock) is a common adverse event associated with citrate use.
D. Periodic flushing of the circuit with saline has been found to prolong circuit life in patients who are not on anticoagulation.

REFERENCES

1. Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17:1143–1150.
2. Neri M, Villa G, Garzotto F, et al. Nomenclature Standardization Initiative: a nomenclature for renal replacement therapy in acute kidney injury: basic principles. Crit Care. 2016;20:318.
3. Paganini EP, Nakamoto S. Continuous slow ultrafiltration in oliguric acute renal failure. Am Soc Artif Intern Organs J. 1980;26.
4. Joannidis M, Oudemans-van Straaten HM. Clinical review: patency of the circuit in continuous renal replacement therapy. Crit Care (London, England). 2007;11. 218–218.
5. Brunet S, Leblanc M, Geadah D, et al. Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. Am J Kidney Dis. 1999;34: 486–492.
6. Troyanov S, Cardinal J, Geadah D, et al. Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using Multiflow–100 and HF1000 filters. Nephrol Dial Transplant. 2003;18:961–966.
7. Ronco C, Ghezzi PM, Brendolan A, Crepaldi C, La Greca G. The haemodialysis system: basic mechanisms of water and solute transport in extracorporeal renal replacement therapies. Nephrol Dial Transplant. 1998;13(suppl 6):3–9.
8. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12:R74.
9. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76:422–427.
10. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. Ann Am Thorac Soc. 2015;12:1837–1844.
11. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315:2190–2199.
12. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal–replacement therapy in the intensive care unit. N Engl J Med. 2016;375:122–133.
13. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of renal–replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018;379:1431–1442.
14. Bagshaw SM, Wald R, Adhikari NKJ, et al. Timing of initiation of renal–replacement therapy in acute kidney injury. N Engl J Med. 2020;383:240–251.
15. Gaudry S, Hajage D, Martin–Lefevre L, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open–label, randomised, controlled trial. Lancet. 2021;397:1293–1300.
16. Lumlertgul N, Peerapornratana S, Trakarnvanich T, et al. Early versus standard initiation of renal replacement therapy in furosemide stress test non–responsive acute kidney injury patients (the FST trial). Crit Care. 2018;22:101.
17. Bagshaw SM, Wald R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. Kidney Int. 2017;91(5):1022–1032.
18. Cheungpasitporn W, Zand L, Dillon JJ, Qian Q, Leung N. Lactate clearance and metabolic aspects of continuous high–volume hemofiltration. Clin Kidney J. 2015;8:374–377.
19. Joannes–Boyau O, Honore PM, Perez P, et al. High–volume versus standard–volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med. 2013;39:1535–1546.

20. Mayeur N, Rostaing L, Nogier MB, et al. Kinetics of plasmatic cytokines and cystatin C during and after hemodialysis in septic shock–related acute renal failure. Crit Care. 2010;14(3):R115.

21. Paganini EP, Tapolyai MB, Goormastic M, et al. Establishing a dialysis therapy/patient outcome link in intensive care unit acute dialysis for patients with acute renal failure. Am J Kidney Dis. 1996;28.
22. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359:7–20.
23. Dialysis interventions for treatment of AKI. Section 5. Kidney Int Suppl (2011). 2012;2:89–115, 2012.
24. Faulhaber-Walter R, Hafer C, Jahr N, et al. The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. Nephrol Dial Transplant. 2009;24:2179–2186.
25. Casino FG, Marshall MR. Simple and accurate quantification of dialysis in acute renal failure patients during either urea non-steady state or treatment with irregular or continuous schedules. Nephrol Dial Transplant. 2004;19:1454–1466.
26. Claure-Del Granado R, Macedo E, Chertow GM, et al. Toward the optimal dose metric in continuous renal replacement therapy. Int J Artif Organs. 2012;35:413–424.
27. Casino F, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis. Nephrol Dial Transplant. 1996;11:1574–1581.
28. Kudoh Y, Iimura O. Slow continuous hemodialysis—new therapy for acute renal failure in critically ill patients. Part 1. Theoretical considerations and new technique. Jpn Circ J. 1988;52:1171–1182.
29. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356:26–30.
30. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int. 2006;70:1312–1317.
31. The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361:1627–1638.
32. Fülöp T, Pathak MB, Schmidt DW, et al. Volume-related weight gain and subsequent mortality in acute renal failure patients treated with continuous renal replacement therapy. ASAIO J. 2010;56(4):333–337.
33. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet. 2006;368:379–385.
34. Schefold JC, von Haehling S, Pschowski R, et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Crit Care. 2014;18:R11.
35. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med. 2008;36:610–617.
36. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M. Alberta Kidney Disease Network: renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299:793–805.
37. Cerda J, Ronco C. Modalities of continuous renal replacement therapy: technical and clinical considerations. Semin Dial. 2009;22:114–122.
38. Marshall MR. Measuring the patient response to dialysis therapy: hemodiafiltration and clinical trials. Kidney Int. 2017;91:1279–1282.
39. Srisawat N, Lawsin L, Uchino S, et al. Cost of acute renal replacement therapy in the intensive care unit: results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. Crit Care. 2010;14:R46.
40. Slessarev M, Salerno F, Ball IM, McIntyre CW. Continuous renal replacement therapy is associated with acute cardiac stunning in critically

ill patients. Hemodial Int. 2019;23:325–332.
41. Marshall MR, Golper TA. Low-efficiency acute renal replacement therapy: role in acute kidney injury. Semin Dial. 2011;24:142–148.
42. Kielstein JT, Kretschmer U, Ernst T, et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. Am J Kidney Dis. 2004;43:342–349.
43. Schwenger V, Weigand MA, Hoffmann O, et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury—a

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References

randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts. Crit Care. 2012;16:R140.
Unarokov ZM, Mukhoedova TV, Shuvaeva OV. Comparison of sustained low-efficiency dialysis with acetate-free and acetate-containing bicarbonate dialysate in unstable patients: reply to comments. Artif Organs. 2014;38:906–907.
Yu AW, Ing TS, Zabaneh RI, Daugirdas JT. Effect of dialysate temperature on central hemodynamics and urea kinetics. Kidney Int. 1995;48:237–243.
Jost CM, Agarwal R, Khair-el-Din T, Grayburn PA, Victor RG, Henrich WL. Effects of cooler temperature dialysate on hemodynamic stability in “problem” dialysis patients. Kidney Int. 1993;44:606–612.
Paganini EP, Sandy D, Moreno L, Kozlowski L, Sakai K. The effect of sodium and ultrafiltration modelling on plasma volume changes and haemodynamic stability in intensive care patients receiving haemodialysis for acute renal failure: a prospective, stratified, randomized, cross-over study. Nephrol Dial Transplant. 1996;11(suppl 8):32–37.
du Cheyron D, Terzi N, Seguin A, et al. Use of online blood volume and blood temperature monitoring during haemodialysis in critically ill patients with acute kidney injury: a single-centre randomized controlled trial. Nephrol Dial Transplant. 2013;28:430–437.
Tonelli M, Astephen P, Andreou P, et al. Blood volume monitoring in intermittent hemodialysis for acute renal failure. Kidney Int. 2002;62:1075–1080.
Sun Z, Ye H, Shen X, Chao H, Wu X, Yang J. Continuous venovenous hemofiltration versus extended daily hemofiltration in patients with septic acute kidney injury: a retrospective cohort study. Crit Care. 2014;18:R70.

Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta–analysis. Crit Care. 2012;16:R146.
Rewa O, Tolwani A, Ronco C, et al. Quality of care and safety measures of acute renal replacement therapy: workgroup statements from the 22nd Acute Disease Quality Initiative (ADQI) Consensus Conference. J Crit Care. 2019;54:52–57.
Kashani K, Rosner MH, Haase M, et al. Quality improvement goals for acute kidney injury. Clin J Am Soc Nephrol. 2019;14:941–953.
Juncos LA, Chandrashekar K, Karakala N, Baldwin I. Vascular access, membranes and circuit for CRRT. Semin Dial. 2021.
Peres PW. Positioning central venous catheters––a prospective survey. Anaesth Intensive Care. 1990;18:536–539.
Czepizak CA, O’Callaghan JM, Venus B. Evaluation of formulas for optimal positioning of central venous catheters. Chest. 1995;107:1662–1664.
Oliver MJ. Acute dialysis catheters. Semin Dial. 2001;14:432–435.
Baldwin I, Bellomo R, Koch B. Blood flow reductions during continuous renal replacement therapy and circuit life. Intensive Care Med. 2004;30(11):2074–2079.
Parienti JJ, Thirion M, Mégarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA. 2008;299(20):2413–2422.
McLaws ML, Burrell AR. Zero risk for central line–associated bloodstream infection: are we there yet? Crit Care Med. 2012;40:388–393.
Improvement IH. How–to Guide: Prevent central Line–Associated Bloodstream Infections. Cambridge, MA: Institute for Healthcare Improvement; 2012.
O’Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter–related infections. Clin Infect Dis. 2011;52:e162–e193.
Moses AA, Stevens JS, Fine D, et al. Protocol for local on–site dialysate production for continuous renal replacement therapy during the COVID–19 pandemic. Kidney360. 2021;2:1152–1155.

64. Kashani K, Thongprayoon C, Cheungpasitporn W, Iacovella GM, Akhoundi A, Albright Jr RC. Association between mortality and replacement solution bicarbonate concentration in continuous renal replacement therapy: a propensity–matched cohort study. PLoS One. 2017;12. e0185064–e0185064.
65. Ebah LM, Akhtar M, Wilde I, et al. Phosphate enrichment of dialysate for use in standard and extended haemodialysis. Blood Purif. 2012;34:28–33.
66. Tolwani AJ, Wille KM. Anticoagulation for continuous renal replacement therapy. Semin Dial. 2009;22:141–145.
67. Morabito S, Guzzo I, Solazzo A, Muzi L, Luciani R, Pierucci A. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. J Nephrol. 2003;16:566–571.
68. Group, KDIGOKAKIW. KDIGO Clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2011;2:1–138.
69. Bambrah RK, Pham DC, Rana F. Argatroban in heparin–induced thrombocytopenia: rationale for use and place in therapy. Ther Adv Chronic Dis. 2013;4:302–304.
70. Khan NA, Ma I, Thompson CR, et al. Kidney function and mortality among patients with left ventricular systolic dysfunction. J Am Soc Nephrol. 2006;17:244–253.
71. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011;4:669–675.
72. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805.
73. Costanzo MR, Saltzberg M, O’Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol. 2005;46:2047–2051.

74. Bartone C, Saghir S, Menon SG, et al. Comparison of ultrafiltration, nesiritide, and usual care in acute decompensated heart failure. Congest Heart Fail. 2008;14:298–301.
75. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49:675–683.
76. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367:2296–2304.
77. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. JACC Heart Fail. 2016;4:95–105.
78. Koch M, Haastert B, Kohnle M, et al. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. Eur J Heart Fail. 2012;14:530–539.
79. Bar–Zohar D, Sagie B, Lubezky N, Blum M, Klausner J, Abu–Abeid S. Laparoscopic implantation of the Tenckhoff catheter for the treatment of end–stage renal failure and congestive heart failure: experience with the pelvic fixation technique. Isr Med Assoc J. 2006;8:174–178.
80. Ryckelynck JP, Lobbedez T, Valette B, et al. Peritoneal ultrafiltration and treatment–resistant heart failure. Nephrol Dial Transplan. 1998;13(suppl 4):56–59.
81. Cove ME, MacLaren G, Federspiel WJ, Kellum JA. Bench to bedside review: extracorporeal carbon dioxide removal, past present and future. Crit Care. 2012;16:232.
82. Hasin T, Topilsky Y, Schirger JA, et al. Changes in renal function after implantation of continuous–flow left ventricular assist devices. J Am Coll Cardiol. 2012;59:26–36.
83. Karakala N, Juncos LA. How I treat: providing Continuous renal replacement therapy in patients on extracorporeal membrane oxygenation. Clin J Amer Soc Nephrol. 2020.
84. Patel AM, Eduardo Rame J, Rudnick MR. How does the nephrologist manage an LVAD patient on chronic maintenance dialysis? Semin Dial. 2014;27:284–288.

76

Hepatorenal Syndrome

Javier Fernández, Vicente Arroyo

DEFINITION

Hepatorenal syndrome (HRS) is a potentially reversible functional kidney failure that occurs in patients with acute or chronic liver disease, advanced hepatic failure, and portal hypertension. Although it may occur in patients with subacute liver failure or severe acute alcoholic hepatitis, HRS is mainly observed in patients with advanced cirrhosis. HRS is characterized by impaired kidney function and marked abnormalities in the arterial circulation and endogenous vasoactive systems. In the kidney, there is pronounced vasoconstriction resulting in low glomerular filtration rate (GFR). In the splanchnic circulation, there is marked arteriolar vasodilation resulting in reduction of systemic vascular resistance and arterial hypotension.1–3 Along with cardiocirculatory dysfunction secondary to portal hypertension, systemic inflammation also plays a major role in the pathogenesis of HRS.4 Two forms of HRS can be identified on the basis of the progression of the disease (Box 76.1). The acute form (type 1) is characterized by an acute and rapid deterioration in GFR that occurs in the setting of intense systemic inflammation and multiorgan failure (acute-on-chronic liver failure [ACLF]), whereas the chronic form (type 2) has an insidious onset and is characterized by less severe systemic inflammation and moderate kidney failure that follows a steady or slowly progressive course.1–4

PSEUDOHEPATORENAL SYNDROME

Pseudohepatorenal syndrome describes concurrent hepatic and kidney dysfunction secondary to a wide variety of infectious, systemic, circulatory, genetic, and other diseases or after exposure to a variety of drugs and toxins (Table 76.1).5 These entities must be excluded before the diagnosis of HRS can be established. In these conditions, the liver does not play a causal role in the pathogenesis of kidney failure. Pseudohepatorenal syndrome is usually easy to exclude because the causal agent is frequently known and both kidney and liver functional abnormalities are often found at the initial presentation, without evidence of advanced liver failure or portal hypertension. In contrast, HRS invariably occurs after liver failure and portal hypertension are fully established and frequently develops when the patient is undergoing treatment for these conditions or their complications.

PATHOPHYSIOLOGY AND PATHOGENESIS

Circulatory Dysfunction: Kidney and Systemic Hemodynamic Changes

In HRS, reduction in GFR occurs mainly because of kidney cortical hypoperfusion after intense cortical renal vasoconstriction, which can be demonstrated angiographically as marked beading and tortuosity of the interlobular and proximal arcuate arteries and the absence of a distinct cortical nephrogram and vascular filling of the cortical vessels (Fig. 76.1). Intense renal vasoconstriction is the final consequence of marked systemic circulatory dysfunction, characterized by progressive splanchnic arterial vasodilation, reduction of the effective arterial blood volume, hypotension, and homeostatic activation of the vasoconstrictor systems.3 This further compromises kidney perfusion because intense vasoconstriction results in blunting of the autoregulation of blood flow, so that kidney perfusion becomes more pressure dependent. In HRS, filtration fraction is also reduced, reflecting a dominant increase in afferent arteriolar tone and a decrease in the ultrafiltration coefficient. Serial systemic hemodynamic studies showed that HRS occurs in the setting of reduced mean arterial pressure (MAP), cardiac output, and wedge pulmonary pressure without change in systemic vascular resistance. These findings suggest that an inability to increase cardiac output to compensate for a decrease in preload (secondary to the accentuation of splanchnic arterial vasodilation) also contributes to the pathogenesis of HRS.6 Vasoconstriction is not confined to the renal vascular bed. In HRS it is also observed in other extrasplanchnic territories, including the liver, brain, muscle, and skin.2,3

Neurohumoral Abnormalities

The renal and systemic hemodynamic changes that characterize HRS are a direct consequence of neurohumoral disturbances.2,3 Activation of the vasoconstrictor systems (the renin-angiotensin-aldosterone system [RAAS], the sympathetic nervous system [SNS], and vasopressin) is the cause of kidney vasoconstriction; meanwhile, activation of the vasodilator systems occurs mainly in the splanchnic circulation and leads to splanchnic vasodilation. Increases in the serum and urinary levels of vasoconstrictors and in the plasma level of vasodilators are observed in patients with HRS. The vasoconstrictors include renin, norepinephrine, neuropeptide Y, arginine vasopressin, endothelin and F2 isoprostanes, and urinary cysteinyl leukotrienes; the vasodilators include plasma endotoxin, nitrite (end-product of nitric oxide [NO] metabolism), and glucagon. The sympathetic discharges through the renal nerves are also markedly increased.

In contrast to increased plasma and urinary levels of vasoconstrictors and plasma level of vasodilators, decreased urinary levels of vasodilators have been observed in HRS. These include prostaglandin E2, 6-keto-prostaglandin F1 (a stable metabolite of renal prostacyclin), and kallikrein. Because the urinary level of these vasodilators is normal in compensated cirrhosis and higher than normal in decompensated cirrhosis with ascites and normal kidney function, it is postulated that a reduction in the renal synthesis of vasodilators is the final event that leads to the development of HRS.3

Most of these neurohumoral abnormalities found in HRS are also detected, albeit to a lesser extent, in decompensated cirrhosis (with ascites) with normal kidney function and in compensated cirrhosis (without ascites). These findings support the hypothesis that HRS most likely represents one end of the spectrum of homeostatic abnormalities that occur in liver failure and portal hypertension.

Systemic Inflammation and Metabolic Derangement

Type 1 HRS is often precipitated by bacterial infections, particularly if these infections trigger a severe inflammatory response.3 Inflammation represents a major pathogenic factor for HRS. There is now evidence that type 1 HRS is part of a complex syndrome (ACLF) characterized by the development of organ failure(s) (kidneys, liver, brain, heart, peripheral circulation, gut, lungs, adrenal glands, defensive mechanisms against infections).4 7 The mechanism of ACLF has been related to intense systemic inflammation, activation of cytokines, NO and other mediators, oxidative stress, acute deterioration of systemic circulation, and organ failure. Systemic inflammation in cirrhosis mainly derives from the translocation of viable bacteria and/or pathogenassociated molecular patterns (PAMPs) from the intestinal lumen into the intestinal mucosa and the systemic circulation with or without

Main Clinical Characteristics of Type 1 and Type 2 HRS

BOX 76.1

Type 1 HRS
- Acute and rapid deterioration in glomerular filtration rate
- Occurs in parallel with the failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy)
- In cirrhosis, is a form of acute-on-chronic liver failure
- Frequently follows a precipitating event, mainly bacterial infection
- Rapidly fatal without treatment: mean survival 2 to 3 weeks

Type 2 HRS
- Moderate stable kidney impairment (average serum creatinine 2 mg/dL [176 µmol/L])
- Mainly causes refractory ascites
- Mean survival without treatment: 6 months

HRS, Hepatorenal syndrome.

TABLE 76.1

Infections
Drugs

Toxins

Systemic diseases
Circulatory failure
Malignancy
Congenital and genetic disorders

aAccidental

Summary of Pathogenesis

Fig. 76.2 shows the pathogenesis of HRS. Liver failure and portal hypertension through pathologic bacterial translocation and endotoxemia increase systemic inflammation and vascular production of vasodilators, including NO, carbon monoxide, and glucagon in the splanchnic circulation, leading to the initiating event of splanchnic arteriolar vasodilation (the peripheral arterial vasodilation hypothesis). Splanchnic vasodilation leads to a decrease in systemic vascular resistance, but MAP is initially maintained by an increase in cardiac output, resulting in a hyperdynamic circulation. Splanchnic vasodilation also decreases arterial filling and reduces the effective arterial blood volume. The subsequent stimulation of the central volume baroreceptors leads to compensatory activation of the vasoconstrictor systems, in particular the arginine vasopressin system, RAAS, and SNS (including its hormones norepinephrine and neuropeptide Y), which help restore effective arterial blood volume. This restoration is achieved in patients with compensated cirrhosis but not in patients with decompensated cirrhosis, in whom progressive splanchnic arteriolar vasodilation leads to increased splanchnic capillary pressure, resulting in an increase in lymph formation that exceeds reabsorption capacity. In parallel, further contraction of the effective arterial blood volume leads to reduction of systemic MAP and further stimulation of the vasoconstrictor systems, resulting in sodium and water retention. The net result of these combined effects is continuous ascites formation (the forward theory of ascites formation).2 3

Causes of Pseudohepatorenal Syndrome

Potential Causes

Miscellaneous

overt bacterial infection. “Sterile” inflammation can also be caused by the release of danger-associated molecular patterns (DAMPS) by dying hepatocytes in acute hepatic processes (i.e., alcoholic and viral hepatitis). The subsequent sustained activation of innate host immunity leads to the release of proinflammatory cytokines and oxidative stress that impair cardiovascular function and could also damage the kidney and other organs, impairing their function.4 Systemic inflammation is associated with blood metabolite accumulation in ACLF, indicating marked alterations in major metabolic pathways, in particular mitochondrial dysfunction, which is involved in the development of kidney and extrarenal organ failure.8

Predominantly Tubulointerstitial Involvement
Sepsis, leptospirosis, brucellosis, tuberculosis, Epstein-Barr virus, hepatitis A virus
Tetracycline, rifampin, sulfonamide, phenytoin, allopurinol, fluroxene, methotrexate (high dose), acetaminophen overdose
Carbon tetrachloride, trichloroethylene, chloroform, elemental phosphorus, arsenic, copper, chromium, barium, amatoxins,a raw carp bile toxinsb
Sarcoidosis, Sjögren syndrome
Hypovolemic or cardiogenic shock
Lymphoma, leukemia
Polycystic liver and kidney disease, nephronophthisis, congenital hepatic fibrosis
Fatty liver of pregnancy, Reye syndrome

Predominantly Glomerular Involvement
Hepatitis B and C viruses, HIV infection, Schistosoma mansoni, liver abscess

Systemic lupus erythematosus, vasculitis, cryoglobulinemia, amyloidosis

Eclampsia, HELLP syndrome, cirrhotic glomerulopathy

poisoning after ingestion of mushrooms of the Amanita genus.
poisoning after ingestion of the raw gallbladder or bile of the grass carp (a common practice in rural East Asia).
HELLP, Hemolysis, elevated liver enzymes, low platelet count; HIV, human

immunodeficiency virus.
Data from Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310–1318.

bAccidental

A

B

Fig. 76.1 Kidney arteriography of a patient with hepatorenal syndrome (HRS). (A) Kidney angiogram (arrow marks the edge of the kidney). (B) Angiogram performed in the same kidney at autopsy. Note complete filling of the kidney arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously (A) are no longer present. The vessels are also histologically normal; this indicates the functional nature of the vascular abnormality in HRS. (From Levenson D, Korecki KL. Acute renal failure associated with hepatobiliary disease. In: Brenner BM, Lazarus JM, eds. Acute Renal Failure. Churchill Livingstone; 1988:535–580.)

The splanchnic circulation is resistant to the effects of vasoconstrictors because of local release of vasodilators; progressive splanchnic vasodilation continues to occur as liver failure and portal hypertension progress. This leads to continued contraction of effective arterial blood volume, which, together with the progressive inability of the cirrhotic heart to respond to reduced preload, results in further reduction of MAP and more intense stimulation of the vasoconstrictor systems.

Normally, the effect of vasoconstrictors on the kidney circulation is counterbalanced by the reactive production of intrarenal vasodilators. It is postulated that HRS develops when the balance between vasoconstrictors and vasodilators finally breaks down. The likelihood that this will occur increases with progressive or acute deterioration in liver function or increasing severity of portal hypertension (e.g., after acute alcoholic hepatitis) and is precipitated by events that lead to further volume contraction and reduction of the effective arterial blood volume (e.g., spontaneous bacterial peritonitis [SBP]; see later discussion).

Recently the peripheral arterial vasodilation hypothesis has been revisited. This hypothesis did not take into account that patients with cirrhosis and HRS frequently develop other types of organ failure (e.g., liver, brain, coagulation). This syndrome, known as ACLF, is characterized by systemic inflammation and high shortterm mortality.[4 7] The sustained activation of the innate immune system caused by an abnormal translocation of bacteria and bacterial products from the intestinal lumen (PAMPs) or by DAMPs would lead to the persistent activation of the innate pattern recognition receptors and subsequent chronic inflammation. This inflammatory process would have two major consequences: first, splanchnic arterial vasodilation secondary to local release of endogenous vasodilators, a feature impairing systemic hemodynamics and organ perfusion, and second, the extension of splanchnic inflammation to the peripheral blood and organs, a feature that could damage these organs, contributing to multiple organ failure

(Fig. 76.3).[4] Therefore, severe systemic inflammation and vasodilation are considered key pathogenic events in the development of HRS in the revisited hypothesis.

EPIDEMIOLOGY

The incidence of HRS in the cirrhotic patient is estimated to be 18% at 1 year and 39% at 5 years.[9] Neither the cause nor the Child-Pugh score or the model for end-stage liver disease (MELD) score (www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/) predicts the incidence of HRS. Rather, independent predictors of HRS include dilutional hyponatremia, impaired systemic hemodynamics (high plasma renin activity, noradrenaline concentration, and low cardiac output),6 9 abnormal kidney duplex Doppler ultrasound study findings (resistive index > 0.7),10 and low GFR.3

CLINICAL MANIFESTATIONS

Type 1 and type 2 HRS are considered to be different syndromes rather than different expressions of a common underlying disorder.2 3 Type 1 HRS is characterized by a rapid decline in GFR (see Box 76.1) and is observed in patients with acute decompensation of advanced cirrhosis, severe acute alcoholic hepatitis, or subacute liver failure. In addition to developing rapidly progressive acute kidney injury (AKI), patients also develop multiorgan dysfunction, including severe hepatic failure (jaundice, coagulopathy), brain failure (hepatic encephalopathy), and frequently relative adrenal insufficiency. Oliguria is a universal finding, hyponatremia is almost always present, and arterial blood pressure is usually low. Type 1 HRS may be precipitated by bacterial infections (especially spontaneous bacterial peritonitis), severe gastrointestinal (GI) bleeding, or total paracentesis without albumin administration. Left untreated, type 1 HRS tends to rapidly progress, resulting in death of the patient within 2 to 3 weeks.9

The Pathogenesis of Hepatorenal Syndrome Type 1
Portal hypertension, splanchnic vasodilation,
and cardiocirculatory dysfunction
Bacterial translocation/pathogen-associated
molecular patterns release
Release of proinflammatory molecules and
reactive oxygen species
Excessive systemic
inflammatory response
Rapid deterioration of cardiovascular function
and organ blood perfusion/organ damage

Kidneys
Intrarenal
vasoconstrictorvasodilator
imbalance
Type 1
hepatorenal
syndrome

Other organs
Liver

Jaundice, coagulopathy

Brain

Encephalopathy

Adrenal glands

Adrenal insufficiency

Gut

Increased translocation of
bacteria and bacterial products

Fig. 76.2 Pathogenesis of Type 1 Hepatorenal Syndrome (HRS). Mechanisms leading to type 1 HRS and multiorgan failure. Patients with cirrhosis and ascites present with severe cardiocirculatory dysfunction that may be further aggravated by infection through the exacerbation of systemic inflammation. Although circulatory dysfunction predominantly affects the kidneys and leads to the development of type 1 HRS, it also decreases the perfusion of other organs and systems such as the liver, with marked impairment in hepatic function and aggravation of portal hypertension; the brain, with the development of hepatic encephalopathy; the adrenal glands, with the development of relative adrenal dysfunction; and the gut, decreasing intestinal motility and promoting intestinal bacterial overgrowth and bacterial translocation. Intense systemic inflammation could also contribute to direct organ damage (immunopathology). (Modified from Arroyo V, Fernandez J, Ginès P. Pathogenesis and treatment of hepatorenal syndrome. Semin Liver Dis. 2008;28:81–95; Arroyo V, Fernandez J. Management of hepatorenal syndrome in patients with cirrhosis. Nat Rev Nephrol. 2011;7:517–526; and Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis:

from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatology. 2015;63:1272–1284.)

Type 2 HRS is characterized by insidious onset and slowly progressive deterioration of GFR. This is most often observed in patients with cirrhosis and portal hypertension. These patients tend to be less severely jaundiced and mainly present with refractory ascites caused by poor response to diuretics. Low-normal arterial blood pressure, modest prolongation of prothrombin time, and moderate or marked hypoalbuminemia and hyponatremia are usually present. Type 2 HRS tends to progress over months, which most likely reflects the natural course of the disease because additional precipitating factors are not usually identified.2 3 9 Mean survival time after onset of type 2 HRS is 6 months.

PATHOLOGY

HRS is mainly a functional kidney disorder, and the presence of significant glomerular and/or tubular disease excludes the diagnosis. However, glomerular abnormalities, including mesangial expansion, capillary wall thickening, mesangial and capillary wall electron-dense deposits, and immune deposits of C3 and immunoglobulin A (IgA), IgM, and IgG, are frequently found in cirrhotic patients with normal kidney function and minimal urinary abnormalities. The presence of such glomerular abnormalities in a cirrhotic patient, therefore, does

not exclude the diagnosis of HRS. Protrusion of the proximal tubular epithelium into Bowman’s space (glomerulotubular reflux) is not specific for HRS and is found in other conditions associated with profound kidney ischemia and terminal hypotension. Although early autopsy studies demonstrated normal tubular morphology in patients who had died of HRS, detailed light and electron microscopic studies have documented proximal tubular lesions consistent with ischemic injury. However, these lesions do not explain the low GFR in HRS patients.3 Finally, bile salt-related tubular damage can be observed in patients with HRS and severe cholestasis.11

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

HRS is mainly a diagnosis of exclusion and should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension who develops progressive kidney impairment. In patients with preexisting liver failure, portal hypertension, and kidney failure, the use of nephrotoxic agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] and aminoglycosides) must be stopped, and other conditions leading to kidney failure must be excluded by careful history, physical examination, urine examination, and ultrasound study before the diagnosis of HRS can be considered.

Systemic Inflammation Hypothesis of Cirrhosis Decompensation in Hepatorenal Syndrome and Acute-on-Chronic Liver Failure

Early
decompensated
cirrhosis

Significant BT

Significant
SAV;
no further
increase
in cardiac output

Moderate
systemic
and
organ
inflammation

Effective
hypovolemia
Organ dysfunction
No organ failure

Decompensated
cirrhosis

Acute-on-chronic
liver failure

Severe BT

Bacterial infection
Acute sterile inflammation
Severe burst of BT

Severe
SAV;
decreased
cardiac output

Significant
systemic and
organ
inflammation

Marked effective
hypovolemia
Organ dysfunction
kidney failure

Extreme
cardiocirculatory
dysfunction;
organ
hypoperfusion

Severe organ
inflammation

and oxidative
stress;
organ damage

Organ failure
Acute-on-chronic
liver failure

Fig. 76.3 Systemic Inflammation Hypothesis of Cirrhosis Decompensation in Hepatorenal Syndrome and Acute-on-Chronic Liver Failure (ACLF). According to the systemic inflammation hypothesis, bacterial translocation (BT) progressively affects the natural course of cirrhosis, from the compensated stage to hepatorenal syndrome and ACLF. An abrupt increase in systemic inflammation represents the pathophysiologic background for ACLF. SAV, Splanchnic arterial vasodilation. (Modified from Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatology. 2015;63:1272–1284.)

The absence of shock or GI bleeding and excess loss of extracellular fluid from the GI tract or urine or from equestration of ascites in the peritoneal cavity must be documented. Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge with albumin 1 g/kg body weight per day up to the maximum of 100 g/day for 2 days. Proteinuria of less than 500 mg/day and absence of microhematuria help exclude significant coexisting glomerular or tubulointerstitial disease leading to kidney failure and supports the diagnosis of HRS.

The diagnostic criteria for HRS were established by the International Ascites Club in 1996[1] and were revised in 2007, 2015, and 2019.[11–13] The main revisions were the exclusion of creatinine clearance as a measure of kidney function (because of the difficulty in obtaining accurate urine collection data), the removal of ongoing bacterial infection as an exclusion criterion (so that treatment of HRS is not delayed), the substitution of saline by albumin as the preferred fluid for plasma volume expansion, the removal of the minor criteria and, more importantly, the removal of a fixed cut-off value of serum creatinine (>1.5 mg/dL [132 µmol/L], >2.5 mg/dL [220 µmol/L] in cases of type 1 HRS) to establish the diagnosis of HRS. This definition of HRS-1 still requires that the diagnosis be established at an advanced stage of AKI (at least stage 2). The most recent revision allows the diagnosis of HRS-AKI in the presence of small increases in serum creatinine (≥ 0.3 mg/dL within 48 hours), therefore promoting the early initiation of vasoconstrictors plus albumin (Box 76.2).[11]

Serum creatinine and blood urea nitrogen (BUN) are poor markers of GFR in cirrhosis.[3] Patients with cirrhosis may have significantly reduced GFR despite normal serum creatinine or BUN because they are frequently malnourished, with reduced lean body mass, and often have a low urea generation rate because of liver failure and low protein intake.

Severe hyperbilirubinemia, which is often present in patients with HRS, interferes with the Jaffe reaction (picric acid) for creatinine quantification and may cause falsely low results. Enzymatic creatinine assays are less susceptible to high bilirubin levels. In cases of uncertainty, GFR may be assessed with use of iodine-125–iothalamate or chromium-51–labeled ethylenediaminetetraacetic acid (^{51}Cr-labeled EDTA). Small studies suggest that serum cystatin C could be an accurate GFR marker in the cirrhotic population,[14] but this requires confirmation.

The most important differential diagnosis for kidney failure in cirrhosis is between type 1 HRS (HRS-AKI) and AKI with acute tubular necrosis (ATN-AKI) because they require rapid therapeutic decisions with different treatments. The parameters traditionally used to differentiate ATN from functional kidney failure (urinary sodium excretion and urinary-plasma osmolality ratio) are classically considered of no value in patients with cirrhosis and ascites.3 However, a fractional excretion fraction of sodium less than 0.2% may help distinguish HRS from ATN.11 Granular casts may be found in the urinary sediment in both HRS and ATN. Recent data suggest that the determination of the urinary levels of neutrophil gelatinase–associated lipocalin (NGAL), a biomarker of tubular damage, could be helpful to differentiate these two entities. More specifically, a cut-off value of 220 μg/g of creatinine has been reported to have the best predictive accuracy for ATN diagnosis.11 15 Most patients with ATN-AKI have values greater than this threshold, whereas those with HRS-AKI usually have values less than it.11 However, further studies are needed to confirm this finding because this biomarker also can be increased in prerenal acute injury16 and HRS can progress to ATN. In patients with prolonged HRS-AKI, the kidney is damaged because of chronic ischemia and sustained inflammation. In these cases, granular casts can be observed.

New Diagnostic Criteria Hepatorenal Syndrome (HRS-AKI) According to the International Ascites Club

BOX 76.2

- Cirrhosis, acute liver failure, acute-on-chronic liver failure
- Increase in serum creatinine ≥ 0.3 mg/dL within 48 hours or ≥ 50% from baseline value according to ICA consensus document and/or urinary output ≤ 0.5 mL/kg body weight ≥ 6 hours[a]
- No full or partial response, according to the consensus document, after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day.
- Absence of shock
- No current or recent treatment with nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media)
- Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microhematuria (>50 red blood cells per high-power field), urinary injury biomarkers (if available), and/or abnormal kidney ultrasonography[b]
- Suggestion of renal vasoconstriction based on a fractional excretion of sodium of < 0.2% (with levels < 0.1% being highly predictive)

[a] Requires a urinary catheter.

[b] This criterion is not applicable in cases of known preexisting structural chronic kidney disease (e.g., diabetic or hypertensive nephropathy).

From Angeli P, Garcia-Tsao G, Nadim MK, et al. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites [ICA] consensus document. J Hepatology. 2019;71:811–822.

NATURAL HISTORY

Without treatment, the median survival rate for type 1 HRS is about 2 weeks; that of type 2 HRS is about 4 to 6 months.[3,9] Patients with type 1 HRS usually die in the setting of multiple organ failure and are now considered to have ACLF, a syndrome recently redefined and characterized by the presence not only of organ failure(s) and high mortality rate but also of systemic inflammation.[7] Severe hepatic encephalopathy, GI bleeding, and sepsis are common final events in these patients.

Patients with type 2 HRS are at higher risk for type 1 HRS after the development of a precipitating event.[3]

PREVENTION AND TREATMENT

General Principles in the Prevention of Acute Kidney Injury

In patients with cirrhosis and ascites, excessive diuretic therapy results in volume contraction and AKI. To avoid the latter, a stepwise approach to the treatment of ascites is recommended. All patients are advised to follow a low-sodium diet (60–90 mmol/day, equivalent to about 3.5–5 g of salt per day). After this, spironolactone is prescribed at increasing doses (100 mg/day as initial dose; if there is no response within 4 days, 200 mg/day). If required, furosemide is then added at increasing doses every 2 days of 40 to 80 mg/day. Maximum doses of spironolactone and furosemide are 400 and 160 mg/day, respectively.

In patients with diuretic resistance, therapeutic paracentesis is indicated but must be combined with plasma volume expansion with use of albumin (8 g/L of ascites removed) to decrease the incidence of circulatory dysfunction after treatment and to prevent development of HRS. The use of renin-angiotensin system blockers and potentially nephrotoxic agents, including NSAIDs, aminoglycosides, and radiocontrast media, should be avoided as much as possible.2 3 β-Blockers, used for primary or secondary prophylaxis of variceal bleeding, reduce MAP and GFR and must be used cautiously in patients with cirrhosis and ascites. Kidney function should be closely monitored, especially in patients with refractory ascites. β-Blockers may increase short-term mortality in this specific cirrhotic subpopulation and should therefore be replaced by band ligation of varices.17

Preventive Measures

Accepting the hypothesis that HRS represents one end of the spectrum of the homeostatic abnormalities in liver failure and portal hypertension and that it is precipitated by clinical events as volume contraction or bacterial infection, it follows that a major focus of treatment must be to prevent such events and to treat them promptly when they occur. There should be a low threshold for antibiotic therapy for suspected infection in cirrhosis. Spontaneous bacterial peritonitis must be excluded by regular examination of ascites whenever a patient is admitted to the hospital or clinically deteriorates. This infection must be treated not only with broadspectrum antibiotics but also with albumin infusion (1.5 g/kg at diagnosis and 1 g/kg at day 3) because the latter prevents the subsequent development of HRS and improves short-term survival.18 A recent randomized controlled trial (RCT) also shows that long-term albumin administration prevents kidney dysfunction and HRSAKI in patients with cirrhosis and ascites.19 In contrast, albumin administration is not effective in the prevention of HRS in patients with non-SBP infections nor in hospitalized subjects with acute decompensation and hypoalbuminemia.20 21 Primary prophylaxis with norfloxacin has been shown to prevent SBP, delay the development of HRS, and improve survival in cirrhotic patients at high risk for complications (low ascitic protein level <15 g/L; advanced liver failure with Child-Pugh score ≥9 and serum bilirubin ≥3 mg/dL or impaired kidney function with serum creatinine ≥1.2 mg/dL or serum sodium ≤130 mmol/L).22 Norfloxacin is thought to exert its renoprotective effect by reducing the subclinical translocation of viable bacteria and bacterial products from the intestine, systemic inflammation, and NO generation, which, in turn, leads to improved hemodynamics. Prophylactic use of pentoxifylline 400 mg orally three times per day also prevents the development of HRS in patients with acute alcoholic hepatitis, probably by inhibiting the synthesis of tumor necrosis factor-α 23

General Approach to Treatment

In patients with preexisting liver failure, portal hypertension, and kidney failure, nephrotoxic agents must be stopped. The absence of shock or GI bleeding, as well as fluid loss, must be documented. Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge with albumin (1 g/kg per day to a maximum of 100g/day for up to 48 hours). Absence of microhematuria and proteinuria also should be confirmed.

Once HRS-AKI has been diagnosed, patients should be assessed for orthotopic liver transplantation (OLT). Suitable candidates should be placed on the waiting list for deceased donor or, if possible, living donor liver transplantation. Bridge treatments are also needed. Pharmacotherapy (see later), transjugular intrahepatic portosystemic shunt, extracorporeal liver support therapy, and (in patients with advanced uremia) kidney replacement therapy should be considered.

Pharmacotherapy

The most promising pharmacotherapy appears to be vasoconstrictors in combination with albumin, targeted at reversal of splanchnic arteriolar vasodilation and restoration of the effective arterial blood volume (Box 76.3). Vasodilators (aiming to reverse renal vasoconstriction) are

Pharmacologic Options in the Treatment of Hepatorenal Syndrome

BOX 76.3

Terlipressin + albumin[a]: Terlipressin in IV boluses (0.5–1 mg/4–6 h to start, increasing to a maximum of 2 mg/4 h) or as continuous infusion (starting from 2 mg/24 h to maximum dose of 12 mg/24 h). Treatment is maintained until serum creatinine has reached a final value within 0.3 mg/dL of the patient's baseline serum creatinine. Maximum duration of treatment: 14 days.

Norepinephrine + albumin[a]: Norepinephrine IV infusion at 0.5 mg/h to start, increasing the dose by 0.25 to 0.5 mg/h every 4 h up to a maximum of 3 mg/h to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 14 days.

Vasopressin + albumin[a]: Vasopressin IV infusion at 0.01 U/min to start, increasing the dose upward to a maximum of 0.8 U/min to achieve an increase in MAP of at least 10 mm Hg. Maximum duration of treatment: 11 days.

Midodrine + octreotide + albumin[a]: Oral midodrine—2.5 to 7.5 mg/8 h + subcutaneous octreotide 100 μg/8 h to start, increasing midodrine dose to a maximum of 12.5 mg/8 h and octreotide dose to a maximum of 200 μg/8 h to achieve an increase in MAP of at least 15 mm Hg. Maximum duration of treatment: 14 days.

[a] Albumin dose: 1 g/kg on day 1 (up to 100 g) followed by 20 to 40 g/day. Central venous pressure monitoring is advised (but not mandatory) to achieve a value of 10 to 15 mm Hg.

IV, Intravenous; MAP, mean arterial pressure.

contraindicated in HRS because they are ineffective and can induce marked hypotension.

Vasopressin analogs exhibit preferential vasoconstrictor action on the splanchnic versus the kidney vascular bed. Terlipressin (triglycyllysine vasopressin) is a synthetic analog of vasopressin that, in addition to having a greater effect on the vascular vasopressin receptors (V1) than the kidney vasopressin receptors (V2), as a prodrug requiring transformation to the active form (lysine vasopressin), has a prolonged half-life and can be given as an intravenous (IV) bolus or as continuous IV infusion. Continuous administration improves the tolerability of the treatment (lower incidence of systemic ischemic side effects) and improves its effectiveness (treatment is effective at lower doses).[3,24] Prospective studies[25–27] and a large retrospective study[28] in patients with type 1 and type 2 HRS have shown that terlipressin combined with daily albumin infusion improved kidney function in 60% of the treated patients, with 37% surviving beyond 1 month (60% of them without OLT). Reversal of HRS was associated with improved survival.[26,28] The efficacy of terlipressin in the treatment of HRS has been confirmed in five RCTs (Table 76.2).[29–33] Terlipressin was given at a starting dose of 2 to 6 mg/day, and in three studies the dose was titrated upward on the basis of response to a maximum dose of 12 mg/day. Both treated patients and controls were given daily albumin infusion of 20 to 40 g/day. Reversal of HRS was associated with improved survival in only one study.[31] The inclusion of patients with more severe kidney failure in the treated group[30] and the unexpected high response and survival rates in controls[32] may explain why some of these studies did not show a survival benefit of treatment despite success in reversing HRS. The latter is likely a result of the more aggressive use of albumin infusion in these studies because such an approach has been shown to reverse HRS in a high proportion of patients. A meta-analysis confirms that terlipressin plus albumin prolongs short-term survival in patients with type 1 HRS.[34] Response to therapy is characterized by a slow and sustained reduction in serum creatinine and improvement in systemic hemodynamics (marked suppression of the plasma levels of renin and norepinephrine, increase in MAP), urine volume, and serum sodium concentration. Median time to reversal of HRS is 7 days and depends on pretreatment serum creatinine.[3]

Recurrence of HRS after successful treatment tends to be more common in type 2 (around 50%) than in type 1 HRS (20%).[25–27,30,32] Retreatment with terlipressin is successful in most patients.[26,30] Younger age,[28,31] lower baseline serum creatinine level,[32] Child-Pugh score of 12 or lower,[28,31] administration of albumin,[26] serum bilirubin less than 10 mg/dL, and increase in MAP by more than 5 mm Hg after initiation of terlipressin[35] are independent predictors of a successful response to treatment. In patients with severe alcoholic hepatitis, the absence of underlying cirrhosis increases the probability of response to treatment. Child-Pugh score (<12)[26,28,30,31] and MELD score[32] are independent predictors for survival. Transient abdominal pain and diarrhea after the first dose of terlipressin treatment are common. Significant ischemic side effects attributed to terlipressin occurred in an average of 4% to 12% of patients.[25–32] A recent RCT reported a higher rate of severe adverse events, including respiratory failure, in patients receiving terlipressin as IV boluses (10% vs. 3%).[33] Close clinical monitoring of patients (including central venous pressure measurement or noninvasive echocardiographic evaluation of cardiac volume status and function if possible) and administration of terlipressin as continuous infusion are therefore recommended to prevent or rapidly detect the development of any serious adverse event during treatment.

IV vasopressin has been used as an alternative to terlipressin in the treatment of HRS in countries where the latter is not available and was successful in reversing type 1 and type 2 HRS in 42% of patients in a retrospective study.[36] Responders had significantly lower mortality and a higher liver transplantation rate than nonresponders. No adverse effect related to therapy was observed.

IV norepinephrine combined with IV albumin and furosemide reversed type 1 HRS in 10 of 12 patients; 3 survived with OLT, and 4 survived for a median of 332 days without OLT.[37] With use of a similar dosage regimen, two randomized comparative studies showed that norepinephrine is as effective as terlipressin in the treatment of type 1 and type 2 HRS (see Table 76.2).[38,39] All recurrences were successfully retreated with the original regimen. Significant treatment-related side effects were low, and the cost of treatment with norepinephrine was 3 and 15 times lower, respectively, than with terlipressin.

Administration of midodrine (an oral vasoconstrictor with α adrenergic effect), subcutaneous octreotide, and albumin infusion is less effective in improving kidney function in patients with HRS than the combination of terlipressin plus albumin. In a recent RCT, reversal of HRS was achieved in 56% of patients receiving terlipressin plus albumin compared with only 5% in those receiving octreotide plus midodrine and albumin.[40] If these results are confirmed, octreotide plus midodrine and albumin should be considered the last treatment alternative for patients with type 1 HRS, with terlipressin or norepinephrine combined with IV albumin being the preferred options.

In countries where terlipressin is not available, patients with type 1 HRS should be treated with α-adrenergic drugs (IV norepinephrine or oral midodrine plus subcutaneous octreotide) administered with albumin.

Transjugular Intrahepatic Portosystemic Shunt

Portal hypertension is central in the pathogenesis of the homeostatic abnormalities in HRS. The high operative mortality precludes side-to-side portacaval shunts in HRS patients. The transjugular intrahepatic portosystemic shunt (TIPS) creates a parenchymal tract between branches of the hepatic and portal vein (Fig. 76.4).

Randomized Controlled Trials of Terlipressin or Norepinephrine in Hepatorenal

TABLE 76.2

Syndrome
Study

Treatment

Terlipressin + albumin
Solanki et al.,
200327
Placebo
Sanyal et al., 200828 Terlipressin + albumin
Placebo
Terlipressin + albumin
Neri et al., 200829
Albumin
Martín-Llahí et al., Terlipressin + albumin
200830
Albumin
Alessandria et al., Terlipressin + albumin
Norepinephrine +
200736
albumin
Sharma et al.,
Terlipressin + albumin
200837
Norepinephrine +
albumin
Wong et al., 202131 Terlipressin + albumin
Albumin

Vasoconstrictor
Dose

Patientsa

Reversal of HRSb Survival at 3
(%)
Months (%)

Survival at 6
Months (%)

1 mg/12 h
—
1–2 mg/6 h
—
0.5–1 mg/8 h
—
1–2 mg/4 h
—
1–2 mg/4 h
0.1–0.7 μg/kg/min

12 (0)
12 (0)
56 (0)
56 (0)

26 (0)
26 (0)
23 (6)
23 (5)
12 (7)
10 (6)

42c
0
34b
13
80b
19
39b
4
83
70

NA
0
NA
NA
54b
19
26
17
67
70

NA
0
43
38
42
15
NA
NA
67
70

0.5–2 mg/6 h
0.5–3 mg/h

20 (0)
20 (0)

50
50

NA
NA

NA
NA

1–2 mg/6 h
—

199 (0)
101(0)

39
18

49
55

NA
NA

[a] Number of patients with type 2 hepatorenal syndrome in parentheses.

[b] Serum creatinine ≤ 1.5 mg/dL.

[c] $P < .05$ versus placebo or control.

HRS, Hepatorenal syndrome.

Transjugular Intrahepatic Portosystemic Stent Shunt

Hepatic
vein

Portal
vein
Metallic
stent

B

A

Fig. 76.4 Transjugular Intrahepatic Portosystemic Shunt. (A) An intrahepatic tract has been created between the hepatic vein and the right portal vein. (B) The tract is dilated (arrow) and stented, creating a shunt as demonstrated on shuntogram. (Courtesy Dr. W.K. Tso, Queen Mary Hospital, Hong Kong.)

In experienced hands, operative mortality rates are 1% to 2%, and the morbidity rate is 10%. Procedure-related complications include intra-abdominal bleeding, cardiac arrhythmia, shunt migration and thrombosis, hemolytic anemia, fever, infection, and reactions to radiocontrast media (including nephrotoxicity). The resultant

diversion of portal blood flow from the liver to the systemic circulation may result in transient deterioration of liver function. Shunt stenosis and hepatic encephalopathy are the main long-term complications of TIPS. Exceptionally, TIPS induces disabling encephalopathy. In these cases, closure of the shunt should be performed.[41] In an earlier study, TIPS improved kidney function in 6 of 7 HRS patients (all with Child-Pugh score <12) and achieved a mean survival of 4.7 (0.3–17) months.42 A long-term study of 31 cirrhotic patients with HRS (14 type 1 and 17 type 2) who were not transplant candidates and did not have severe liver failure confirmed that TIPS improved kidney function and survival compared with controls.43 Shunt stenosis and occlusion occurred in 7 patients (treated in 6 by balloon dilation or stent prolongation), and 11 developed hepatic encephalopathy during follow-up. TIPS therefore could be an alternative treatment of type 1 HRS in patients without response to terlipressin/norepinephrine plus albumin.

Combined TIPS and IV terlipressin therapy was performed in nine patients with type 2 HRS.27 All seven patients who responded to terlipressin and relapsed after treatment cessation responded to TIPS. In another study, TIPS was performed in five patients with type 1 HRS after successful treatment with midodrine, octreotide, and albumin.44 Complete normalization of kidney function was observed in all patients at 12 months after TIPS. In both studies, improvement or elimination of ascites was an added benefit.

Extracorporeal Liver Support Therapy

Extracorporeal liver support therapy, as a bridge to OLT, relies on biologic (hepatocytes from human or animal source in an ex vivo perfusion system) or nonbiologic methods, including plasma exchange and albumin dialysis systems. Albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) may have beneficial effects in patients with type 1 HRS. In a small RCT, a mean of five treatments with MARS effectively removed albumin-bound toxic metabolites (i.e., bilirubin and bile acids), improved kidney function, and prolonged survival in eight patients (mean survival, 25 ± 5 days) with type 1 HRS and severe liver failure compared with five control patients treated only with hemodiafiltration (mean survival, 5 ± 2 days).45 In another study of eight encephalopathic patients with acute alcoholic hepatitis (five with type 1 and two with type 2 HRS), MARS improved kidney function, bilirubin, prothrombin time, grade of encephalopathy, MAP, systemic vascular resistance, and cardiac output, with four patients still alive without OLT at 3 months.46 Three large RCTs have evaluated albumin dialysis in patients with ACLF.47–49 In the first study, albumin dialysis with MARS was found to be more effective than standard medical therapy in the management of patients with grade 3 or 4 hepatic encephalopathy. Most patients had HRS, and the treatment was found to be safe.47 The two other trials compared albumin dialysis with standard medical therapy in patients with type 1 HRS (MARS) or with type 1 and 2 HRS (FPSA). A significant beneficial effect on hepatic encephalopathy was observed in the MARS study but not on survival.48 In the FPSA trial, no effect on survival was observed in the whole group or in patients with type 1 HRS, but a significant improvement was observed in patients with high MELD score (>30 points). The administered dosage of dialysis was very low in both studies (six sessions of 6 hours in 21 days). In these studies, therapy was well tolerated.48,49 Further studies are needed to ascertain the potential role of albumin dialysis in type 1 HRS. Patients with type 2 HRS are usually treated by total paracentesis or TIPS.

Kidney Replacement Therapy

Hemodialysis and peritoneal dialysis are difficult in HRS patients with advancing uremia. Conventional hemodialysis is hampered by the invariable systemic hypotension, and the efficacy and safety of peritoneal dialysis have not been well evaluated in these patients.

Continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodiafiltration (CVVHDF) has been advocated for the treatment of advancing uremia in HRS,50 especially patients with fulminant hepatic failure in whom intermittent dialysis can increase intracranial pressure. Anticoagulation should be minimized or avoided (especially in patients with severe coagulopathy) by giving the replacement fluid in the predilutional mode. When anticoagulation is needed, conventional heparin is generally recommended.

Regional citrate anticoagulation is not recommended in advanced cirrhosis because the liver plays a significant role in citrate metabolism. If used, dose adaptation and close metabolic monitoring are required, especially after prolonged use. Close serum calcium monitoring is mandatory because hypocalcemia is common because of impaired citrate clearance. Bicarbonate should be used instead of lactate as the buffer for the replacement solution to minimize metabolic acidosis. MARS may be combined with either CVVH or hemodialysis for the treatment of HRS, especially in patients with severe hepatic encephalopathy.

Liver Transplantation

Liver transplantation is the treatment of choice in patients with advanced cirrhosis, including those with type 1 and type 2 HRS.2,3,51,52 The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after liver transplantation. For this reason, calcineurin inhibitors should be withheld in the first few days after OLT to give the ischemic kidneys a chance to recover. Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than transplantation patients without HRS. The long-term survival of patients with HRS who undergo liver transplantation, however, is good (3year survival 60%) compared with transplantation in patients without HRS (70%–80%).51 Although kidney function improves after transplantation in HRS patients, it never reaches that observed in non-HRS patients.53 The incidence of end-stage kidney disease in patients with HRS is slightly higher than that observed in transplantation recipients without HRS (7% vs. 2%). Thus, OLT is associated with comparable liver outcome but inferior kidney outcome in patients with HRS. This problem cannot be overcome by performing combined kidney and liver transplantation in HRS, which overall produces outcomes no better than with OLT alone.54 However, in the rare subgroup of patients with HRS who required prolonged pretransplant dialysis for more than 2 months, combined kidney and liver transplantation did confer an advantage in patient survival and use of hospital resources. These infrequent patients usually have normal kidney size and morphology on ultrasound but develop some additional indications of organic nephropathy during follow-up (mild proteinuria or microhematuria).55

The main problem with liver transplantation in type 1 HRS is that most patients die before transplantation. The introduction of the MELD score for listing has partially solved the problem because patients with HRS are prioritized for transplantation. As mentioned earlier, treatment of HRS with vasoconstrictors and albumin improves survival in the group of patients with response to treatment, increasing the number of patients reaching liver transplantation. In addition, reversal of HRS before transplantation may decrease early morbidity and mortality after transplantation and prolong survival.52

Therapeutic Algorithm

Fig. 76.5 shows the recommended algorithm for the management of HRS. Recent recommendations have been published by the

Management of Type 1 Hepatorenal Syndrome
Vasoconstrictors and volume expansion
- IV terlipressin (bolus or continuous infusion) + albumin as first pharmacologic option
- Norepinephrine (continuous infusion) + albumin if terlipressin is not available

Treatment failure
Moderate
liver failure

TIPS
In patients without severe
hepatic encephalopathy
and Child-Pugh score
<12 points
HRS reversal
Evaluation for liver
transplantation

Severity of liver failure?

Advanced
liver failure

Albumin dialysis
(MARS or Prometheus)
In patients with severe hepatic
encephalopathy or Child-Pugh score
≥12 points
No response
Renal replacement
therapy (CVVHDF)
In critically ill patients with
severe uremia and/or volume
overload

Fig. 76.5 Algorithm for the Management of Type 1 Hepatorenal Syndrome (HRS). Initial treatment is based on the use of vasoconstrictor therapies plus albumin. Intravenous (IV) terlipressin is the most established and is the preferred therapy. If terlipressin is not available, continuous IV norepinephrine should be used. Patients with history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine. If pharmacologic therapy fails, the severity of liver failure should be assessed. In patients with less severe liver dysfunction (bilirubin < 5 mg/dL or 85.5 µmol/L and Child-Pugh score < 12) without severe hepatic encephalopathy (grade ≤ 2) or history of recurrent encephalopathy, transjugular intrahepatic portosystemic shunt (TIPS) should be considered. In patients with more severe liver failure (Child-Pugh score ≥ 12) and/or severe hepatic encephalopathy (grade > 2), albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) should be considered. In critically ill cirrhotic patients with advancing kidney failure, continuous venovenous hemodiafiltration (CVVHDF) is the treatment of choice.

International Ascites Club.11 56 OLT is undoubtedly the treatment of choice for patients with HRS, but other treatments described earlier must be used as a bridge to OLT and may improve the kidney outcome after successful OLT. In patients who are not transplantation candidates, these treatments are their only chance for increased survival and in some cases may improve their condition to an extent that may allow them to be reconsidered for transplantation. The choice of therapeutic modalities depends on the availability of resources and expertise on the one hand and the severity of underlying kidney and liver failure and the general condition of the patient on the other. All patients should be considered for vasoconstrictor therapy combined with albumin infusion. Among the vasoconstrictor therapies, IV terlipressin, combined with daily albumin infusion, is most established and is the preferred therapy.2 3 56 In countries where terlipressin is not available, continuous IV norepinephrine or vasopressin may be used as an alternative. Patients with a history of significant atherosclerotic or cardiovascular disease should be treated with norepinephrine plus albumin. Oral midodrine combined with subcutaneous octreotide and albumin is another alternative in the treatment of HRS, especially in patients with type 2 HRS. In patients with relatively well-preserved liver function (serum bilirubin <5 mg/dL or 85.5 µmol/L and ChildPugh score <12) without severe hepatic encephalopathy (grade ≤2) or history of recurrent encephalopathy, concurrent severe bacterial infection, or serious cardiovascular or pulmonary disease, TIPS should be considered, especially in patients with recurrence after vasoconstrictor therapy, a situation more commonly observed in HRS type 2 patients.3 In these patients, TIPS may have the added benefit of relieving refractory ascites. TIPS also appears to achieve complete normalization of kidney function in selected patients after an initial successful response to vasoconstrictor therapy. In patients with severe liver failure (ChildPugh score ≥12) and severe hepatic encephalopathy (grade >2), MARS should be considered. In critically ill cirrhotic patients with advancing kidney failure, CVVH is the treatment of choice and may be combined with other therapeutic modalities, especially MARS or FPSA.

SELF-ASSESSMENT QUESTIONS

1. Which of the following pathogenic events is/are usually not observed in patients with HRS?
A. Splanchnic vasodilation
B. Cardiac dysfunction
C. Systemic inflammation and mitochondrial dysfunction
D. Tubular and glomerular lesions

2. Diagnosis of HRS is established by which one of the following?
A. Liver biopsy
B. Kidney biopsy
C. Measurement of plasma renin activity
D. It is a clinical diagnosis and is established by exclusion.

3. Which affirmation(s) is/are incorrect in patients with hepatorenal syndrome?
A. It occurs in patients with subacute or chronic liver failure and portal hypertension.
B. Patients are normally hypertensive.
C. Plasma renin activity is usually high.
D. It can be observed in patients with and without ascites.
E. Patients can be infected.

4. Which affirmation(s) is/are incorrect regarding the treatment of patients with HRS?
A. The combination of terlipressin and albumin is the preferred treatment.
B. TIPS is an alternative treatment.
C. Patients must undergo early dialysis.
D. Albumin dialysis can be used in patients in whom pharmacologic treatment has failed.
E. The combination of midodrine, octreotide, and albumin is a very effective pharmacologic option.

5. Which affirmation(s) is/are correct in the prophylaxis of hepatorenal syndrome?
A. Norfloxacin prevents the development of HRS in patients with advanced cirrhosis and low-protein ascites.
B. Albumin infusion (1.5 g/kg at diagnosis and 1 g/kg at day 3) prevents the development of HRS and improves short-term survival in patients with SBP.
C. Albumin infusion prevents HRS in patients with infections other than SBP.
D. Oral midodrine prevents HRS.

REFERENCES

1. Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology. 1996;23:164–176.
2. Arroyo V, Fernandez J, Ginès P. Pathogenesis and treatment of hepatorenal syndrome. Semin Liver Dis. 2008;28:81–95.
3. Arroyo V, Fernandez J. Management of hepatorenal syndrome in patients with cirrhosis. Nat Rev Nephrol. 2011;7:517–526.
4. Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatology. 2015;63:1272–1284.
5. Levenson D, Korecki KL. Acute renal failure associated with hepatobiliary disease. In: Brenner BM, Lazarus JM, eds. Acute Renal Failure. New York: Churchill Livingstone; 1988:535–580.
6. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology. 2005;42:439–447.
7. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–1437.
8. Moreau R, Claria J, Aguilar F, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatology. 2020;72:688–701.
9. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology. 1993;105:229–236.
10. Platt JF, Ellis JH, Rubin JM, et al. Renal duplex doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. Hepatology. 1994;20:362–369.
11. Angeli P, Garcia-Tsao G, Nadim MK, et al. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. J Hepatology. 2019;71:811–822.
12. Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310–1318.
13. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015;64:531–537.
14. Demirtaş S, Bozbaş A, Akbay A, et al. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. Clin Chim Acta. 2001;311:81–89.
15. Fagundes C, Pépin MN, Guevara M, et al. Urinary neutrophil gelatinase–associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. J Hepatol. 2012;57:267–273.
16. Nejat M, Pickering JW, Devarajan P, et al. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney Int. 2012;81:1254–1262.
17. Sersté T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010;52:1017–1022.
18. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403–409.
19. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomized trial. Lancet. 2018;391:2417–2429.
20. Fernández J, Angeli P, Trebicka J, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2020;18:963–973.
21. China L, Freemantle N, Forrest E, et al. A randomized trial of albumin Infusions in hospitalized patients with cirrhosis. N Engl J Med. 2021;384:808–817.
22. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 2007;133:818–824.

23. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebocontrolled trial. Gastroenterology. 2000;119:1637–1648.
24. Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology. 2016;63:983–992.
25. Uriz J, Ginès P, Cárdenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol. 2000;33:43–48.
26. Ortega R, Ginès P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology. 2002;36:941–948.
27. Alessandria C, Venon WD, Marzano A, et al. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. Eur J Gastroenterol Hepatol. 2002;14:1363–1368.
28. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. Gastroenterology. 2002;122:923–930.
29. Solanki P, Chawla A, Garg R, et al. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol. 2003;18:152–156.
30. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology. 2008;134:1360–1368.
31. Neri S, Pulvirenti D, Malaguarnera M, et al. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. Dig Dis Sci. 2008;53:830–835.
32. Martín-Llahí M, Pépin MN, Guevara M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology. 2008;134:1352–1359.
33. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 2021;384:818–828.
34. Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology. 2010;51:576–584.
35. Nazar A, Pereira GH, Guevara M, et al. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology. 2010;51:219–226.
36. Kiser TH, Fish DN, Obritsch MD, et al. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol Dial Transplant. 2005;20:1813–1820.
37. Duvoux C, Zanditenas D, Hezode C, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology. 2002;36:374–380.
38. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol. 2007;47:499–505.
39. Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol. 2008;103:1689–1697.
40. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology. 2015;62:567–574.
41. Pomier-Layrargues G. TIPS and hepatic encephalopathy. Semin Liver Dis. 1996;16:315–320.
42. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology. 1998;28:416–422.
43. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut. 2000;47:288–295.

44. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology. 2004;40:55–64.

References

45. Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl. 2000;6:277–286.
46. Jalan R, Sen S, Steiner C, et al. Extracorporeal liver support with molecular
adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol. 2003;38:24–31.
47. Hassanein TI, Tofteng F, Brown Jr RS, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46:1853–1862.
48. Bañares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013;57:1153–1162.
49. Kribben A, Gerken G, Haag S, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology. 2012;142:782–789.
50. Epstein M, Perez GO. Continuous arterio-venous ultrafiltration in the management of the renal complications of liver disease. Int J Artif Organs. 1986;9:217–218.

51. Gonwa TA, McBride MA, Anderson K, et al. Continued influence of preoperative renal function on outcome of orthotopic liver transplant in the US: where will MELD lead us? Am J Transplant. 2006;6:2651–2659.
52. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. J Hepatol. 2004;40:140–146.
53. Gonwa TA, Klintmalm GB, Levy M, et al. Impact of pretransplant renal function on survival after liver transplantation. Transplantation. 1995;59:361–365.
54. Jeyarajah DR, Gonwa TA, McBride M, et al. Hepatorenal syndrome: combined liver kidney transplants versus isolated liver transplant. Transplantation. 1997;64:1760–1765.
55. Ruiz R, Kunitake H, Wilkinson AH, et al. Long-term analysis of combined liver and kidney transplantation at a single center. Arch Surg. 2006;141:735–741.
56. Angeli P, Bernardi M, Villanueva C, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatology. 2018;69:406–460.

77

Principles of Drug Therapy, Dosing, and Prescribing in Chronic Kidney Disease and Kidney Replacement Therapy

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Reduced glomerular filtration rate (GFR) can alter drug pharmacokinetics and, consequently, patients with chronic kidney disease (CKD) are at greater risk of adverse effects. In addition, these patients take multiple drugs and are at higher risk for drug interactions and drugrelated problems.1 To prescribe safely and effectively, clinicians should be familiar with the pharmacokinetics of drugs in varying stages of CKD and kidney replacement therapy (KRT) and ideally rely on data from these populations. Unfortunately, such information is not always available, and exclusion of these patients from clinical studies can lead to restrictive recommendations. This chapter describes pharmacokinetic principles and highlights common prescribing issues in patients with CKD, dialysis, and transplantation. Specific dose recommendations and pharmacokinetic data are not included but can be obtained elsewhere.2–5

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics describes the behavior of a drug (or metabolite) in the body in terms of its absorption, distribution, metabolism, and elimination (Fig. 77.1 and Table 77.1).6 7

Absorption

Bioavailability

Bioavailability (F) is the portion of the drug dose that appears in the systemic circulation after administration. Drugs given intravenously have 100% bioavailability, whereas drugs given by alternative routes pass through a series of biologic membranes before entering the systemic circulation so that only a fraction may reach the circulation.

After oral administration, the liver can metabolize a drug during first pass as it is being absorbed or later as it is delivered via systemic blood flow. First-pass metabolism can significantly reduce absorption. The gastrointestinal (GI) mucosa can also influence absorption by the presence of drug-metabolizing enzymes and drug efflux pumps including P-glycoprotein.8

CKD can theoretically influence drug absorption, although these effects are difficult to quantify, and clinical examples are limited. GI edema can limit oral drug absorption (e.g., furosemide in nephrotic syndrome). Nausea and vomiting from uremia can impair absorption and contact time between a drug and GI mucosa. In advanced uremia, the alkalinizing effect of salivary urea may decrease absorption of drugs

optimally absorbed in an acid milieu. Commonly prescribed metallic divalent ion phosphate binders (e.g., aluminum, calcium, and magnesium salts) can decrease drug absorption by forming nonabsorbable complexes with drugs (Table 77.2).9 Changes in cardiac output can reduce the rate and extent of absorption for drugs with significant first-pass metabolism.

Increased absorption in patients with CKD from reduced first-pass metabolism is seen with some β-blockers, dextropropoxyphene, and dihydrocodeine. Comorbidities in CKD patients also can have an effect (e.g., erratic absorption because of diabetic GI neuropathy).

Distribution

Volume of Distribution

After absorption, drugs may distribute from plasma to an extravascular compartment. Each drug has a characteristic volume of distribution (VD), which does not correspond to an anatomic space but instead relates the amount of drug in the plasma to the amount in tissue. A high VD means a relatively smaller amount remains in plasma and more is in tissues. VD is used to calculate the loading dose to achieve a desired plasma concentration (VD = dose/[plasma]). Water-soluble drugs tend to be restricted to the extracellular fluid space and have a relatively small VD. Lipid-soluble drugs penetrate body tissues and have a large VD. Increases in VD can occur with edema, ascites, or infection, particularly for water-soluble drugs. If usual doses are given, low concentrations result. Conversely, muscle wasting or volume depletion can decrease the VD of water-soluble drugs, and usual doses produce high concentrations.

Plasma Protein Binding

Some drugs bind extensively to plasma proteins.10 It is only the free (unbound) fraction that exerts a pharmacologic effect. If protein binding is reduced, a greater free fraction is available for any given total drug concentration, which may increase drug activity. Organic acids usually have a single binding site on albumin, whereas organic bases have multiple binding sites on glycoproteins. Protein binding can be altered in CKD, especially when serum albumin is low (e.g., nephrotic syndrome) or when uremic toxins displace drugs from binding sites (Table 77.3). Predicting the effect of changes in protein binding is difficult and effects may be transient after acute displacement. For example, phenytoin has marked decreases in protein binding in patients

Passage of a Drug Dose Through the Body
Absorption
Oral Administration

Parenteral Administration

Hepatic
First-Pass
Effect

Distribution

Systemic Circulation

Extravascular
Compartment

Protein-Bound Drug

Metabolism

Free Drug

Active/Inactive Metabolites

Active/Inactive
Metabolites

Tissue Receptor Action

Parent Drug

Elimination

Active/Inactive
Metabolites

Fig. 77.1 Passage of a drug dose through the body.

TABLE 77.1

Pharmacokinetic Parameters

Parameter

Definition

Application

Bioavailability (F)

Percentage of a dose that appears in the systemic circulation after administration.
Proportionality constant relating the amount of drug in the body at a given time to a simultaneously occurring drug concentration in plasma or blood. A primary pharmacokinetic parameter.
Volume of blood cleared of the drug in a unit of time; a primary pharmacokinetic parameter.
Time taken for the drug concentration in plasma to fall to half

its current value. A derived parameter calculated from both clearance and VD.

Determines the amount of drug reaching the systemic circulation. Determines intravenous and oral dose sizes. Determines the size of loading doses. Explains the percentage of the total drug residing in plasma.

Volume of distribution (VD)

Clearance
Half-life (t1/2)

with CKD, and toxicity can occur despite normal or low total plasma concentrations because of an increase in the free fraction. With albuminuria, bound drug may also be lost, which partially explains the refractoriness of nephrotic patients to diuretics. In CKD, high plasma levels of α1-acid glycoprotein are induced in acute and chronic inflammation, which can increase drug binding.

Metabolism

Drug metabolism is primarily a hepatic function by which drugs are converted to more water-soluble entities, which promotes elimination by the kidneys and bile. Despite the assumption that extra renal clearance is unchanged, reduced GFR can alter and slow drug metabolism.[11] Importantly, some drugs have active or toxic metabolites that are cleared by the kidney and such metabolites can accumulate in patients with CKD. The kidneys also have a metabolic role with insulin and imipenem.

Determines the “daily” maintenance dose and frequency of dosing.
Determines the frequency of administration and time to steady state.

Elimination

The kidney is the most important organ for drug and metabolite elimination. Terms to describe drug clearance are shown in Box 77.1. Total drug clearance is expressed as the volume of blood or plasma from which the drug is cleared per unit of time and can be calculated by dividing dose by the area under the drug concentration curve (AUC). Half-life describes the time taken for plasma concentrations to halve and is affected by both VD and clearance. Quantitation of drug elimination by the kidney is expressed as kidney clearance, which depends on renal blood flow and the innate ability of the kidney to remove the drug. Renal drug clearance is the sum of its removal by GFR and tubular secretion, minus that reabsorbed via tubular reabsorption. Glomerular filtration depends on molecular size (<10 kDa), charge, and free fraction. Tubular secretion of drugs may change with kidney disease, but measurement of tubular function is difficult. As GFR decreases, drugs dependent on tubular secretion are also excreted more

TABLE 77.2 Effect of Food and Phosphate Binders on Oral Drug Absorption

TABLE 77.3

Drug

Effect of Food

Major Effects

Captopril
Bisphosphonates (oral)
Cinacalcet
Iron (oral)
Ketoconazole or itraconazole
Sirolimus
Tacrolimus
Bisphosphonates (oral)

Decreases serum drug levels
Significantly reduce drug absorption
Significantly increases drug absorption
Decreases absorption
Increase absorption with reduced pH
High-fat meals increase absorption
Reduces drug absorption
Calcium-containing binders significantly
reduce absorption
Reduction in absorption
Reduction in absorption
Reduction in absorption

Albumin: Binding Sites for Acidic Compounds
Barbiturates (↓)
Ascorbic acid (↑)
Benzodiazepine (↑)
Valproate (↓)
Carbamazepine (↑)
Fatty acids (↑)
Fibrates (↑)
Nafcillin (↑)
Furosemide (↓)
Phenylbutazone (↓)
Mycophenolate mofetil (↑)
Probenecid (↑)
Penicillins (↑)
Thiopental (↓)
Phenytoin (↓)
Warfarin (↓)
Sulfonamides (↓)
Thyroxine (↓)

Fluoroquinolones
Tetracycline
Thyroid hormones

BOX 77.1

Mathematics of Drug Elimination

Total body clearance = Drug dose/AUC
Renal clearance = Total amount of drug in urine/plasma drug concentration
Total amount of drug in urine = [Drug] × Volume of the sample collected in a fixed time

Renal Disease

Protein Binding of Drugs in
Minor Effects

Globulins: Binding Site for Basic Compounds
Digoxin (↓)
Adenosine (↑)
Methadone (↑)
Amitriptyline (↑)
Propranolol (↑)
Chloramphenicol (↑)
↓ Indicates reduced protein binding in chronic kidney disease (CKD) patients; ↑ indicates increased protein binding in CKD patients. However, the therapeutic effect is not easily predicted (see text).

Ideally, drug doses should be modified based on published data on drug kinetics in varying stages of CKD. However, lack of reliable data and individual patient factors limit this.12 Dose nomograms, tables, and computer recommendations can guide dose modifications, but they are only a guide and therapeutic drug monitoring and clinical acumen are important too.

formula can give different estimates of kidney function, especially if not corrected for body surface area because they are not individualized and are normalized for body surface area (mL/min/1.73 m2). These equations can lead to recommendations different from those obtained by the Cockcroft-Gault equation. An important limitation of all kidney function estimates is inaccuracy of single-point estimates when kidney function is rapidly changing (and creatinine concentration is not at steady state). This may lead to overestimation or underestimation of kidney function and underdosing or overdosing. In patients with rapid-onset severe acute kidney injury (AKI), the decline in GFR is so rapid that patients may require doses for GFR below 10 mL/min. The opposite is true in rapidly improving kidney function after AKI or early posttransplant where there is a risk of underdosing.
Whether estimated using creatinine clearance or GFR, the greater the degree of reduction in kidney function, the greater the potential need for dose modification. With exceptions, dose modification usually is not clinically necessary until GFR (or creatinine clearance) is less than 30 mL/min/1.73m2. Assessment of kidney function for drug dosing is not a precise science. What is important for clinical decision making is awareness that kidney function is impaired, and approximately to what extent, rather than knowledge of the precise GFR.13
Using the extent of reduction in GFR to classify CKD severity is discussed in Chapters 3 and 80

Initial Assessment and Laboratory Data

Activity and Toxicity of Metabolites

A targeted history is important in assessing dose in CKD patients. Previous drug efficacy or toxicity should be determined and the current prescribed medications reviewed for potential interactions or nephrotoxins. Physical and laboratory parameters indicate volume status, height, weight, and extrarenal disease (e.g., liver).

It is important to consider the activity and/or toxicity of drug metabolites in addition to that of the parent drug when determining drug selection and dosing in patients with CKD because metabolites that are normally cleared by the kidney can accumulate, leading to enhanced drug action or toxicity (Table 77.4).

Estimating Renal Function for Drug Dosage

Fraction of Active Drug (and Active or Toxic Metabolite) Excreted Unchanged in Urine

Drug half-life ($t_{1/2}$) = VD × 0 693/Clearance
AUC, Area under the concentration-time curve; VD, volume of distribution (dose/blood concentration).

slowly, although tubular secretion may be relatively spared and total kidney clearance may be much higher than would be predicted from estimating GFR alone (e.g., penicillins). For a given level of extra renal clearance, as GFR falls, clearance of drugs (and metabolites) eliminated by the kidney also falls and half-life is prolonged.

PRESCRIBING PRINCIPLES FOR CHRONIC KIDNEY DISEASE AND KIDNEY REPLACEMENT THERAPY

Estimating kidney function is essential to guide drug dosing in patients with CKD. The Cockcroft-Gault equation estimates creatinine clearance and is individualized for each patient (by body weight) and has been the most widely used and accepted method for drug dosage calculation. The Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI)

The greater the fraction of active drug or metabolite excreted unchanged by the kidneys (fe), the greater is the need for dose modification. It is usually only clinically necessary to modify doses if the fe is greater than 25% to 50%. When ascertaining fe, it is important to note that values are often obtained from studies that do not distinguish between parent

Drugs With Active or Toxic Metabolites That Accumulate in Patients With Reduced Glomerular Filtration Rate

TABLE 77.4

Allopurinol
Cefotaxime
Glyburide
Morphine
Tramadol
Venlafaxine
Dapsone
Meperidine (pethidine)
Nitroprusside
Procainamide
Propoxyphene

Active Metabolite

Consequence

Oxypurinol
Desacetyl cefotaxime
4-trans-Hydroxyglibenclamide
3-cis-Hydroxyglibenclamide
Morphine-6-glucuronide
O-Desmethyltramadol
O-Desmethylvenlafaxine
Toxic Metabolite
Monoacetylated metabolite
Normeperidine (norpethidine)
Thiocyanate
N-Acetylprocainamide (NAPA)
Norpropoxyphene

Nil
Hypoglycemia
CNS side effects
CNS side effects
CNS and cardiovascular side effects
Consequence
CNS (seizures)
Cyanide toxicity
Arrhythmia
Cardiac toxicity

CNS, Central nervous system.

Fractional Drug or Metabolite Excretion in Urine
10%

Fractional excretion unchanged = 10%

50%

Inactive Metabolite M1

100% renally excreted

30%

Inactive Metabolite M2

100% renally excreted
Biliary clearance

50%

Fig. 77.2 Fraction of Drug or Metabolite Excreted in Urine. In this hypothetical example, 10% of the dose is excreted unchanged in urine (fe = 10%); 50% of the dose is metabolized to inactive metabolite M1, which is then all renally excreted; 30% of the dose is metabolized to inactive metabolite M2, which is all renally excreted; and the remaining 10% is excreted unchanged in bile. For this drug, the total excretion of drug dose in urine is 90%. However, this 90% includes 10% as parent drug and 80% as inactive metabolites, and dose modification is probably not essential even in severe chronic kidney disease. Total kidney excretion of the dose is 90%; however, the clinically significant fraction of active drug excreted in urine is 10%.

drug and metabolites. The contribution of inactive/nontoxic metabolites to overall kidney drug elimination may exaggerate the potential for harm. Active or toxic metabolites should be assessed separately for their dependence on kidney elimination in the same way as the parent drug (Fig. 77.2).

Therapeutic Index of the Drug or Metabolites

The decision to modify dosage in CKD patients is influenced by the therapeutic window or index of the drug. The therapeutic window is the range of plasma drug concentrations between the minimum concentration for clinical efficacy and minimum concentration for toxicity. The therapeutic index is the ratio of these concentrations (Fig. 77.3). If the therapeutic window is wide (e.g., many penicillins), there may be no clinical need for dose modification despite much higher plasma concentrations found in CKD patients. If the therapeutic window is narrow (e.g., digoxin), dose modification is more important.
Clinicians should judge the clinical relevance of increased exposure to drug or metabolites.

Avoiding Nephrotoxic Drugs

A wide range of drugs can cause nephrotoxicity (Table 77.5). Idiosyncratic nephrotoxicity (e.g., interstitial nephritis; see Chapter 64) is unpredictable and independent of dose. Predictable hemodynamicrelated nephrotoxicity can occur with any drug that reduces blood

Therapeutic Index of a Drug
Concentration

Minimum Toxic
Concentration
Narrow
Therapeutic
Index
Minimum Effective
Concentration

Minimum Toxic
Concentration
Wide
Therapeutic

Index
Minimum Effective
Concentration

Time

Fig. 77.3 Therapeutic Index of a Drug. Example of a drug with a narrow therapeutic index (left), and a drug with a wide therapeutic index (right).

volume, systemic blood pressure, or glomerular pressure because these affect the amount of blood delivered to the kidneys. These include all antihypertensives but especially angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, and laxatives. Many of these compounds result in a decrease in estimated GFR (eGFR) without structural injury and the eGFR reverses on stopping the drug

TABLE 77.5

Examples of Nephrotoxic Drugs

Examples

Mechanism

Prevention and Management

ACE inhibitors, ARBs

Impair angiotensin II–mediated afferent arteriole dilation during
kidney hypoperfusion
In proximal tubules, aminoglycosides bind to anionic phospholipid,
are delivered to megalin, are taken up into the cell, accumulate,
and cause direct toxicity.

Withdraw in kidney hypoperfusion (e.g.,
extracellular volume depletion)
Alternative if possible
Monitor drug concentrations
Avoid multiple daily doses
Withdraw if SCr rises
Avoid use
Administer slowly with hydration
Use liposomal preparations

Aminoglycosides (amikacin,
gentamicin, tobramycin)

Antifungals (amphotericin)

Antivirals
Acyclovir

Cidofovir
Foscarnet

Indinavir
Calcineurin inhibitors
(cyclosporine, tacrolimus)

Chemotherapeutics
Cisplatin

Ifosfamide

Intravenous immunoglobulin
(sucrose-containing products)

Lithium

NSAIDs

Proton pump inhibitors
Radiocontrast media
Sulfonamides

Afferent vasoconstriction and direct action to reduce GFR

Distal tubular injury via creation of pores that increase membrane permeability leading to hypokalemia, hypomagnesemia, metabolic acidosis caused by tubular acidosis, polyuria from nephrogenic diabetes insipidus
High drug levels result in drug crystals causing intratubular obstruction and foci of interstitial inflammation
Induces apoptosis in proximal tubule leading to tubular dysfunction, diabetes insipidus, kidney failure
Direct tubular toxicity leading to acute tubular necrosis, nephrogenic diabetes insipidus
Crystals in glomerular capillary lumen and proximal tubular lumen
Crystal neuropathy, nephrolithiasis leading to obstructive AKI
↓ PG and ↑ 20-HETE acid production leading to vasoconstriction, generation of H2O2 resulting in depleted glutathione leading to decreased GFR, ischemic collapse or scarring of the glomeruli, vacuolization of the tubules, and focal areas of tubular atrophy and interstitial fibrosis
Cis chloride replaced by H2O leading to highly reactive OH radical leading to DNA injury, tubular cell death, nephrogenic diabetes insipidus, hypomagnesemia (may be persistent)
Direct tubular injury and mitochondrial damage leading to kidney tubular acidosis, Fanconi-like syndrome, nephrogenic diabetes insipidus, hypokalemia
Accumulation of sucrose in proximal convoluted tubules
Increased osmolarity leading to cell swelling, vacuolization, and tubular luminal occlusion
Impairment of collecting duct concentrating ability leading to diabetes insipidus
Chronic tubulointerstitial nephropathy (tubular atrophy and interstitial fibrosis)
Hemodynamically induced AKI caused by vasoconstriction via reduced prostaglandin production
Recruitment and activation of lymphocytes leading to acute and chronic tubulointerstitial nephritis, with or without nephrotic syndrome
Allergic acute interstitial nephritis
High osmolarity, medullary vasoconstriction, ↑ active transport in thick ascending loop of Henle leading to ↑ O2 demand
Intrarenal precipitation leading to kidney stone formation

Avoid bolus dose
Reduce dose in CKD
Hydrate during therapy
Oral probenecid and hydration
Hydration

Hydration
Measure plasma concentrations
Avoid interacting drugs
Withdraw drug (switch to mTOR inhibitor)

Forced diuresis and hydration

Infusion rate < 3 mg sucrose/kg/min
Avoid radiocontrast
Avoid sucrose-containing product
Hydration
Measure plasma concentrations
Prevent dehydration
Avoid thiazides
Avoid NSAIDs
Avoid use
Withdraw during hypoperfusion
Withdraw (add corticosteroids)

Withdraw (add corticosteroids)
Hydration preprocedure and postprocedure
acetylcysteine
Fluid intake > 3 L/day; monitor urine for crystals
Alkalinize urine to pH > 7.15 if crystals seen

ACE, Angiotensin-converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; GFR, glomerular filtration rate; 20-HETE acid, 20-hydroxyeicosatetraenoic acid; H2O2, hydrogen peroxide; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs; PG, prostaglandin; SCr, serum creatinine.

(especially sodium-glucose cotransporter-2 [SGLT2] inhibitors and ACE inhibitors), but if perfusion pressure is sufficiently reduced, ischemic injury might occur. Direct tubular nephrotoxins include aminoglycosides, vancomycin, amphotericin, cisplatin, calcineurin inhibitors (CNIs), and radiographic contrast media. Obstructive uropathy can occur with crystallization of acyclovir or creatinine phosphokinase from statin-induced rhabdomyolysis. In dialysis patients with no significant residual kidney function, use of nephrotoxic drugs may be acceptable. Drug nephrotoxicity is discussed further in Chapter 70

Drugs That Aggravate the Metabolic/Biochemical Effects of Reduced Glomerular Filtration Rate

Some drugs have no direct adverse effect on kidney function but when used in CKD patients can aggravate the metabolic/biochemical consequences of reduced GFR. Hyperkalemia is exacerbated by potassium supplements, potassium-sparing diuretics, aldosterone antagonists, and blockers of the renin-angiotensin system. The catabolic effects of tetracycline can exacerbate uremia. Sodium-containing drugs and those that promote sodium and water retention (e.g., corticosteroids) should be used cautiously because they may provoke fluid overload and hypertension.

Effect of Reduced Glomerular Filtration Rate on Pharmacodynamic or Physiologic Mechanisms

CKD may alter a pharmacodynamic response or physiologic process, which, in turn, affects clinical response. For example, the inability of impaired kidneys to activate vitamin D precursors means that vitamins D2 and D3 may be less effective. Also, CKD patients often have a coagulopathy from the effects of uremia on platelet function and may be more prone to the bleeding complications of anticoagulant and antiplatelet therapy.

Effect of Reduced Glomerular Filtration Rate on the Concentration of Drug at the Site of Action

Reduced GFR can alter drug concentration at the site of action. Some diuretics (furosemide) and antibiotics (nitrofurantoin) are less effective in CKD patients because they do not achieve adequate concentrations at their site of action within the lumen of the kidney tubules (furosemide) or bladder (nitrofurantoin).

Location of Drug Action

Drugs that have negligible bioavailability and those that are used for a local or topical effect may be given safely at normal dose despite toxicity with systemic doses. These include topical NSAIDs, nebulized gentamicin, and oral vancomycin.

Method of Administration

In fluid-restricted patients, administration of intravenous (IV) drug infusions with approved fluid volumes may be undesirable. When the volume needed to administer IV drugs impacts on daily fluid restrictions, consider alternative drugs or more concentrated solutions, provided that physiochemical parameters allow. Similarly, oral drug administration that requires large fluid volumes (e.g., bisphosphonates) may be problematic. In patients with severe nausea and vomiting, “essential” drugs (e.g., immunosuppressants) should be administered intravenously.

Drug Interactions

Pharmacokinetic drug interactions are frequently problematic, and awareness of clinically significant interactions is essential, especially in patients taking transplant immunosuppressants. The most important of these are cyclosporine, tacrolimus, everolimus, and sirolimus, which are substrates of both the cytochrome P450 (3A4) drug metabolizing enzyme system and P-glycoprotein drug efflux system that is expressed in GI mucosa, kidney, and liver (Fig. 77.4).14 Coprescription of drugs that inhibit these systems (e.g., some azole antifungals, calcium channel blockers, macrolides, and grapefruit juice) can increase absorption and reduce clearance of the immunosuppressant, causing toxicity. Conversely, drugs that induce these systems (e.g., barbiturates, phenytoin, carbamazepine, rifampicin, and St. John’s wort [Hypericum]) can reduce absorption and increase clearance and therefore increase the risk for rejection (see Fig. 77.4). All drug changes in patients receiving transplant immunosuppression should be considered for their potential to interact, and appropriate dose modifications or alternatives should be used. In addition, enzymes in the epithelial cells of the proximal tubules show an activity similar to the corresponding liver enzymes. Therefore, the kidneys can produce inactive, active, or nephrotoxic metabolites (e.g., metabolites of paracetamol).

Clinical Condition of the Patient

Patient welfare should override theoretical concerns. Higher-thanrecommended doses may be appropriate when there is a strong clinical indication. For example, excessive reduction in initial antibiotic doses based on kidney function may be inappropriate in patients with life-threatening infection when the consequences of failed therapy are greater than those of potential toxicity.

METHODS OF DOSE REDUCTION IN CHRONIC KIDNEY DISEASE PATIENTS

Loading Doses

In general, steady-state drug concentrations are achieved after five drug half-lives. Steady-state can be achieved “earlier” by administering loading doses. If an appropriate (i.e., adjusted for GFR) dose is administered from the outset, attainment of steady state will be further prolonged (because half-life is longer). When a drug equilibrates rapidly with the tissues it diffuses into, the loading dose (mg/kg) is equal to the product of the desired plasma concentration (mg/mL) and VD (mL/kg) and is independent of clearance. If a drug equilibrates slowly with the tissues it diffuses into, several smaller loading doses will be needed (e.g., vancomycin loading doses rarely achieve steady state concentrations after the first loading dose). Provided the desired concentration and VD are unchanged, loading doses do not require modification in CKD patients. If VD increases and it is important to achieve a desired plasma concentration quickly, then a larger loading dose might be needed even though the affected drug is renally cleared (and hence subsequent, maintenance doses are lower than normal).

Maintenance Doses

When specific pharmacokinetic information is not available, and assuming no change in nonrenal clearance, maintenance doses should be reduced in proportion to the extent of reduction in GFR. For example, if kidney function is 50% of normal and the drug is 100% renally excreted, a maintenance dose of 50% is required. If the drug is 50% cleared by the kidney and GFR is 20% of normal, the dose should be 60% of normal. The dose reduction factor is estimated from first principles or the following formula:

Fraction of normal kidney function dose to use in kidney impairment = 1 − fe (1 − Fraction of normal kidney function)

where fe is the fraction of active drug excreted unchanged in urine.

CYP3A4 and P-Glycoprotein in Drug Absorption and Metabolism
Drug

2

100%

15%

15%

CYP3A4
P-gp
30%

1

2
100%

100%
P-gp
1

CYP3A4
30%

Lumen

Fig. 77.4 CYP3A4 and P-Glycoprotein (P-gp) in Drug Absorption and Metabolism. Schema for absorption and metabolism of drugs that are substrates for CYP3A4 and P-gp. Overall, approximately 15% of ingested drug reaches the systemic circulation. (1) Enterocyte: P-gp on the apical surface of enterocytes prevents drug absorption, maintaining drug in the gastrointestinal lumen; CYP3A4 in enterocytes metabolizes drug. The net effect is that approximately 30% of ingested drug reaches the portal circulation. (2) Hepatocyte: P-gp on the cell surface prevents drug entry into hepatocytes; CYP3A4 in hepatocytes metabolizes the drug. The net effect is that drug entry to the systemic circulation is further reduced.

Once a daily dose reduction factor has been determined, the clinician must decide on a dose reduction method. Two methods are used, either alone or in combination (Fig. 77.5).

Interval Method

Using this method, the usual dose is administered at prolonged intervals where the extent of prolongation is similar to the extent to which GFR is reduced. This method is particularly useful when peak blood concentrations are important for efficacy (e.g., aminoglycosides) and when therapeutic concentrations need to be achieved early (oseltamivir). If this method is used, practical dose intervals should be recommended rather than inconvenient or complex intervals.15

Dose Method

Using this method, a smaller dose is given at the usual interval. This method is common, especially when peak concentrations are less critical for efficacy. If this method is used, clinicians should consider the availability of smaller dose formulations and the ability of the patient to accurately and safely divide available dosage forms.

Combination Method

Sometimes, especially for drugs with a narrow therapeutic index, for which tight control of concentrations is required (e.g., digoxin), a combination of the dose and interval methods is used.

Ongoing Assessment

Even with appropriate dose modification in CKD patients, clinicians should always remain vigilant and closely monitor the response to therapy to guide dose titration.

Therapeutic Drug Monitoring

Therapeutic drug monitoring can provide objective information to guide dosing and is valuable for drugs with a narrow therapeutic window such as aminoglycosides, glycopeptides, digoxin, lithium, antiepileptics, and immunosuppressants (see Table 77.6). Assays usually measure total blood concentrations and may significantly underestimate plasma concentrations of the active or free concentration of the drug.

Clinical Response

Ultimately, clinical response should influence the need to modify doses. Doses should be carefully titrated according to response and adverse effects. Measures of response include blood pressure for antihypertensives, blood glucose concentration and hemoglobin A1c (HbA1c) for oral hypoglycemics/insulin, and kidney function for toxicity from ACE inhibitors, and ARBs and urine output for loop diuretics.

Methods of Dose Reduction

TABLE 77.6

Therapeutic Drug Monitoring

Drug

Therapeutic Range and When to Draw
Sample

in CKD

Log
concentration

Aminoglycosides
(24-h Dosing)
Dose schedule in normal renal function
Dose schedule in reduced GFR
Time

A

Gentamicin
Tobramycin

Log
concentration

Amikacin

Dose schedule in normal renal function
Dose schedule in reduced GFR
Time

B

Antipsychotics
Lithium
Dose schedule in normal renal function
Dose schedule in reduced GFR

C

Time

Fig. 77.5 Methods of Dose Reduction. (A) Interval method. (B) Dose method. (C) Combination method. GFR, Glomerular filtration rate.

EXTRACORPOREAL DRUG LOSSES

Failure to consider dialysis drug clearance may significantly reduce drug efficacy.5 7 Alternatively, dialysis may be used in overdose to assist drug removal (see Chapter 103). For example, some β-blockers have high dialysability and so are efficiently removed by dialysis (e.g., atenolol, acebutolol, metoprolol).16 In contrast, β-blockers with low dialysability are bisoprolol and propranolol. Studies of drug clearance with KRT modalities have often used variations in dialysis technique that make it difficult to compare results. Many studies before the 1990s report data from standard hemodialysis (HD) with low-flux membranes, which are less efficient at drug removal than the highflux membranes now widely used. Many recommendations report the need for supplemental doses, although clinically, supplemental doses are rarely used, especially if less than 30% of the drug is cleared or the drug has a wide therapeutic window. Rather, drugs known to be significantly cleared by dialysis should be administered after dialysis (Table 77.7). When drugs are given in multiple daily doses, at least one of the daily doses should be administered soon after the completion of dialysis.

Peak (30 min after a 30-min infusion) to ensure adequate peak concentration
Trough to guide time of next dose (2–3 halflives post-dose), noting that half-life will be increased in approximate proportion to degree of reduction in GFR
Peak: >10 mg/L
Trough: Depends on time after dose 0.5–2 mg/L
Peak: >10 mg/L
Trough: Depends on time after dose 0.5–2 mg/L
Peak: >30 mg/L
Trough: depends on time after dose 1.5–6 mg/L

Immunosuppressants
Cyclosporine
C0 (trough): 150–250 µg/mL
C2 (2 h after dose): 1200–1500 µg/mL
AUC0–4 >4400 µg/mL/h
Tacrolimus
C0 (trough): 4–12 µg/mL
Sirolimus
C0 (trough): 5–15 µg/mL
Antiarrhythmics
Digoxin
Lidocaine

Log
concentration

0.8–2.0 µg/mL (trough at least 6 h after dose)
1–5 µg/mL 8 h after IV infusion starts or is changed
Acute: 0.8–1.2 mmol/L (trough)
Chronic: 0.6–0.8 mmol/L (trough)

Antiepileptics
Carbamazepine
Phenytoin
Free phenytoin
Phenobarbital
Valproic acid

4–12 µg/mL (trough before administration)
10–20 µg/mL (trough before administration)
1–2 µg/mL (trough before administration)
15–40 µg/mL (trough before administration)
40–100 µg/mL (trough before administration)

Vancomycin

Trough: 15–20 mg/L (12 or 24 h trough)

Target levels are dependent on assay methodology and clinical context.
CKD, Chronic kidney disease; GFR, Glomerular filtration rate; IV, Intravenous.

Hemodialysis

Hemodialysis drug clearance occurs mainly by passive diffusion from blood (high concentration) to dialysate fluid (low concentration) but can also occur by convectional movement of dissolved drug in ultrafiltrated plasma.7 17 The efficiency of drug removal depends on its physiochemical properties. As molecular size decreases (typically <500 kDa) and water solubility increases, drug removal increases. Conversely, as protein binding and VD increase, the percentage of drug contained in plasma falls and dialysis clearance decreases. HD factors influencing drug removal include membrane type and surface area, blood and dialysate flow rates, and dialysis frequency and duration. HD sometimes removes drug from plasma faster than it can redistribute from tissue, so drug concentrations determined from samples drawn soon after beginning or completion of HD may be artificially low. Samples should preferably be drawn before dialysis or about 1 to 2 hours after to allow drug redistribution from tissues into plasma.

TABLE 77.7

Dialysis Clearance of Drugs

Drugs Significantly Cleared by Hemodialysis That Require Administration After Dialysis or a Supplement After Dialysis
Analgesics
Morphine 6-glucuronide (in toxicity)
Aspirin, high dose (contraindicated)
Antibiotics
Aminoglycosides
Amikacin
Gentamicin
Tobramycin
Cephalosporins
Cefotaxime
Cefazolin
Ceftazidime
Carbapenems
Imipenem
Meropenem
Metronidazole
Penicillins
Amoxicillin
Ticarcillin
Piperacillin
Fluoroquinolones
Ciprofloxacin
Glycopeptides
Vancomycin (high-flux dialyzers)
Teicoplanin
Miscellaneous antibiotics
Ethambutol
Cotrimoxazole
Antifungal
Fluconazole
Antivirals
Acyclovir
Cidofovir
Famciclovir
Foscarnet
Ganciclovir
Ribavirin
Valganciclovir
Zidovudine
Antineoplastics
Cyclophosphamide
Methotrexate
Anticoagulant
Lepirudin
Dabigatran (in overdose)
Antiepileptics
Gabapentin
Pregabalin
Levetiracetam

Drugs Not Significantly Cleared by Hemodialysis and That Do Not Require Administration After Dialysis or a Supplement After Dialysis or That Must Be Administered at Specific Times Independent of Hemodialysis

Anemia
Erythropoietins
Iron
Analgesics
Paracetamol
Fentanyl
Oxycodone
NSAIDs
Antibiotics
Penicillins
Flucloxacillin
Fluoroquinolones
Moxifloxacin
Rifamycins
Rifampin
Rifabutin
Glycopeptides
Vancomycin (oral administration)
Tetracyclines
Tetracycline
Doxycycline
Minocycline
Antifungals
Amphotericin
Voriconazole
Ketoconazole
Itraconazole
Antiviral
Amphotericin
Antiepileptic
Carbamazepine
Cardiovascular Agents
Amiodarone
Perhexiline
Nitrates
Anticoagulants
Heparin
Warfarin
LMWH
Rivaroxaban
Apixaban
Antiplatelet Drugs
Low-dose aspirin
Clopidogrel
Dipyridamole
Immunosuppressants
Azathioprine
Cyclosporine and tacrolimus
Mycophenolate
Prednisolone

TABLE 77.7

Dialysis Clearance of Drugs—cont’d

Drugs Significantly Cleared by Hemodialysis That Require Administration After Dialysis or a Supplement After Dialysis

Cardiovascular Agent	Sotalol
Antidiabetic	Metformin (in overdose)
Vitamins	Water-soluble B, C, and folate
Psychotropic	Lithium

Drugs Not Significantly Cleared by Hemodialysis and That Do Not Require Administration After Dialysis or a Supplement After Dialysis or That Must Be Administered at Specific Times Independent of Hemodialysis

	Sirolimus and everolimus
	T cell–depleting antibodies
	Rituximab
	Anti-CD25 antibodies
Antidiabetics	Sulfonylureas
Musculoskeletal Agents	Bisphosphonates
Antiepileptics	Sodium valproate Carbamazepine
Antidepressants	SSRIs (administer in morning)
Vitamins	Fat-soluble vitamins A, D, E, K

LMWHs, Low molecular weight heparins; NSAIDs, nonsteroidal antiinflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Peritoneal Dialysis

Many drug properties that affect removal by HD also apply to peritoneal dialysis (PD), but PD is usually less efficient.18 For significant removal by PD, the drug must have a very low VD and low protein binding. For most drugs, there is little evidence of significant removal during chronic PD. A few studies have examined drug clearance from automated PD that uses large volumes of short dwells overnight, often accompanied by one or more longer daytime dwells. Clearance of some drugs via automated PD is increased because of the increased drug concentration gradient between blood and dialysate. Increased drug dialyzability may occur with increased peritoneal dialysate flow rates or during peritonitis, although overall efficiency of drug and metabolite clearance is often reduced by peritonitis because of scarring of the peritoneal membranes, thereby reducing effective surface area.

Continuous Kidney Replacement Therapy

Drug clearance by continuous KRT (CKRT) with hemofiltration, HD, or hemodiafiltration differs from that by intermittent HD.19 Relying on continuous ultrafiltration of plasma, CKRT can remove large quantities of ultrafilterable drug. CKRT generally uses membranes with larger pore sizes and involves convective transport of solute. Hence, CKRT allows the passage of larger molecules (up to 5000 Da). A large VD and protein binding still prevents removal by CKRT. Protein binding and the filtration rate determine the rate of removal. A series of sieving coefficients is available that allows calculation of the amount of drug actually lost if the ultrafiltration flow rate is known.5 The sieving coefficient is the ratio of drug concentration in the ultrafiltrate to the prefilter plasma drug concentration. The closer the sieving coefficient is to 1.0, the more it passes across the filter. There are few detailed studies of drug clearance with use of these methods, and clinicians must rely on estimates from HD, known physiochemical properties, and clinical response.

POLYPHARMACY AND DEPRESCRIBING

Patients receiving dialysis typically receive 10 to 12 medications. Polypharmacy increases the risk of medicine-related problems, including adverse drug reactions and nonadherence. Polypharmacy may be systematically addressed through “deprescribing,” an evidencebased,20 patient-centered21 process that enables identification and elimination of unnecessary or inappropriate medications. In elderly patients on dialysis, consideration for deprescribing should be given to quinine, diuretics, α1-blockers, proton pump inhibitors, and statins.22 In older adults with CKD, medication optimization and deprescribing should focus on proton pump inhibitors, oral hypoglycemic agents, and statins.23

Electronic Medical Record

The implementation of electronic medical record (EMR) should improve health outcomes of kidney patients through improved clinical decision making, medication safety, patient education, and quality improvement and research. EMR should incorporate the design and development of clinical care pathways for patients with kidney disease. Medication therapy assessment and monitoring tools should be a part of computerized provider order entry (CPOE) for medication safety to provide evidence-based advice about drug interactions and dose adjustments for patients with kidney disease or transplantation. Furthermore, interactive educational programs and tools to aid medication adherence should be integrated into the patient EMR to improve health literacy and patient outcomes in vulnerable populations. Moreover, EMR data could be used in pharmacoepidemiology research to provide the best available evidence for treatment outcomes in the patient population that is frequently excluded from the randomized controlled studies.24

SELF-ASSESSMENT QUESTIONS

1. What percentage of the dose used in patients with normal kidney function should be given for a hypothetical drug that is 80% renally cleared unchanged in urine to a person with 25% of normal kidney function?

A. 20%
B. 30%
C. 40%
D. 60%
E. 80%

2. Which of the following factors or drug characteristics does not increase the likelihood of drug removal by hemodialysis?

A. High-flux membranes
B. Low protein binding
C. Low volume of distribution
D. Large molecular weight

3. Which of the following drugs does not require clinically relevant dose modification in patients with reduced GFR?

A. Amoxycillin
B. Ribavirin
C. Digoxin
D. Sotalol
E. Enoxaparin

4. Which of the following drug combinations is least likely to cause clinically significant drug interactions?

A. Adding clarithromycin to the regimen of a patient on sirolimus
B. Adding phenytoin to the regimen of a patient on prednisolone
C. Adding fluconazole to the regimen of a patient on tacrolimus
D. Adding roxithromycin to the regimen of a patient on cyclosporin
E. Adding verapamil to the regimen of a patient on everolimus

REFERENCES

1. Manley HJ, McClaran ML, Overbay DK, et al. Factors associated with medication related problems in ambulatory hemodialysis patients. Am J Kidney Dis. 2003;41:386–393.
2. Cervelli MJ, ed. The Renal Drug Reference Guide. MJC Pharma; 2007.
3. Ashley C, Dunleavy A, eds. The Renal Drug Handbook. 5th ed. CRC Press; 2018.
4. Aronoff GR, Berns JS, Brier ME, eds. Drug Prescribing in Renal Failure (Dosing Guidelines for Adults and Children). 5th ed. Philadelphia: American College of Physicians; 2007.
5. Johnson CA. Dialysis of Drugs. Verona, WI: CKD Insights; 2009.
6. Meibohm B, Evans WE. Clinical pharmacokinetics and pharmacodynamics. In: Helms R, Quani D, Herfindal ET, eds. Textbook of Therapeutics: Drug and Disease Management. Philadelphia: Lippincott Williams & Wilkins; 2006:1–30.
7. Matzke GR, Comstock TJ, et al. Influence of renal function and dialysis on drug disposition. In: Burton ME, Shaw LM, Schentag JJ, eds. Principles of Therapeutic Drug Monitoring. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
8. Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet. 2001;40:159–168.
9. Frost RW, Lasseter KC, Noe AJ, et al. Effects of aluminum hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin. Antimicrob Agents Chemother. 1992;36:830–832.
10. Reidenberg MM, Drayer DE. Alteration of drug-protein binding in renal disease. Clin Pharmacokinet. 1984;9(suppl 1):18–26.
11. Dreisbach AW, Lertora JJL. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. Semin Dial. 2003;16:45–50.
12. Lam YW, Banerji S, Hatfield C, Talbert RL. Principles of drug administration in renal insufficiency. Clin Pharmacokinet. 1997;32:30–57.
13. Reidenberg M. Kidney function and drug action. N Engl J Med. 1985;313:816–817.

14. Elbarbry FA, Marfleet T, Shoker AS. Drug-drug interactions with immunosuppressive agents: review of the in vitro functional assays and role of cytochrome P450 enzymes. Transplantation. 2008;85:1222–1229.
15. Jones TE. Oseltamivir: current dosing recommendations reduce the therapeutic benefit in patients with mild to moderate renal function and/or large body mass: a review of the literature with recommendations to optimize dosing, including the use of therapeutic drug monitoring. Ther Drug Monit. 2021;43(1):103–107.
16. Weir MA, Dixon SN, Fleet JL, et al. beta-Blocker dialyzability and mortality in older patients receiving hemodialysis. J Am Soc Nephrol. 2015;26(4):987–996.
17. Lee CS, Marbury TC. Drug therapy in patients undergoing haemodialysis (clinical pharmacokinetic considerations). Clin Pharmacokinet. 1984;9:42–66.
18. Paton TW, Cornish WR, Manuel MA, Hardy BG. Drug therapy in patients undergoing peritoneal dialysis: clinical pharmacokinetic considerations. Clin Pharmacokinet. 1985;10:404–426.
19. Bohler J, Donauer J, Keller F. Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. Kidney Int. 1999;56(suppl 72):S24–S28.
20. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827–834.
21. Todd A, Jansen J, Colvin J, McLachlan AJ. The deprescribing rainbow: a conceptual framework highlighting the importance of patient context when stopping medication in older people. BMC Geriatr. 2018;18(1):295.
22. McIntyre C, McQuillan R, Bell C, Battistella M. Targeted deprescribing in an outpatient hemodialysis unit: a quality improvement study to decrease polypharmacy. Am J Kidney Dis. 2017;70(5):611–618.
23. Triantafylidis LK, Hawley CE, Perry LP, Paik JM. The role of

deprescribing in older adults with chronic kidney disease. Drugs Aging. 2018;35(11):973–984.
24. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. J Am Soc Nephrol. 2004;15:411–419.

78

Common Issues in Prescribing in Kidney Disease and Kidney Replacement Therapy

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Appropriate prescribing for people with kidney disease is underpinned by the principles discussed in Chapter 77. Even experienced physicians will frequently need to check reference sources to be sure of the correct prescribing approach to medications with which they are less familiar. Up-to-date reference databases should be used to inform prescribing in patients with chronic kidney disease (CKD), those on dialysis, and after kidney transplantation.1-4

ANALGESICS

Various analgesics are excreted by the kidney, and dose modification or avoidance is required in people with impaired kidney function.5 Fear of adverse effects often prevents use of sufficient doses.

Acetaminophen (Paracetamol)

Despite suggestions that acetaminophen is nephrotoxic and has modest analgesic potency, its lack of platelet inhibition and gastrointestinal toxicity make it a safer base analgesic in CKD and renal replacement therapy than nonsteroidal antiinflammatory drugs (NSAIDs) and opioids. Acetaminophen is hepatically metabolized and does not require dose adjustment in dialysis or transplant patients.

Opioid Analgesics

Several opioids have active/toxic metabolites that are removed by the kidney,6 and accumulation of these metabolites prolongs drug action and predisposes to central nervous system (CNS) toxicity (sedation, respiratory depression, confusion, hallucinations, and seizures). Regular opioid use in fluid-restricted kidney patients can exacerbate constipation. Opioids should be used cautiously in CKD, with adequate doses given to establish control and titrated to the smallest effective dose. Morphine is metabolized to two active metabolites (morphine 3-glucuronide and morphine 6-glucuronide) that can accumulate in CKD, causing CNS toxicity, respiratory depression, and sedation. Meperidine (pethidine) should be avoided in moderate to severe CKD because it is metabolized to a metabolite (normeperidine) that accumulates in CKD and can cause CNS toxicity (seizures, myoclonus, opisthotonus, mental state changes, respiratory depression, and psychosis).7 Dextropropoxyphene should be avoided because it is metabolized to the metabolite norpropoxyphene, which is removed by the kidney and can cause cardiac toxicity.
Hydromorphone is metabolized to hydromorphone 3-glucuronide, which has minor activity and does not accumulate substantially.
Buprenorphine is metabolized to relatively inactive metabolites which are excreted in bile, and it is therefore relatively safe. Weaker opioids (codeine, dihydrocodeine, and hydrocodone) can still cause CNS and respiratory depression. With appropriate titration, alfentanil, fentanyl, sufentanil, methadone, and oxycodone are relatively safer choices because their metabolites are largely inactive. For this reason, fentanyl (parenteral and topical) and oxycodone (oral) are usually preferred opioids in CKD. The partial opioid tramadol is metabolized to an active metabolite, O-desmethyltramadol, whose half-life doubles in CKD and predisposes to seizures, respiratory depression, and other CNS adverse effects. In opioid intoxication, naloxone may be used at normal dose for reversal.

Nonsteroidal Antiinflammatory Drugs

The most frequent nephrotoxic effect of NSAIDs is acute kidney injury (AKI) caused by prevention of prostaglandin-mediated, afferent arteriolar vasodilation (see Chapter 70). In healthy individuals, cyclooxygenase (COX) inhibition has little effect on kidney function, but in individuals with CKD, nephrotoxicity is more likely to occur due to the greater dependence on prostaglandins to maintain kidney perfusion. Combining NSAIDs with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, or other antihypertensives increases the potential for nephrotoxicity, and such combinations should be prescribed cautiously.8 If essential, in stable patients with CKD, NSAIDs should be used at the lowest effective dose for the shortest period with monitoring of kidney function. Increases in plasma potassium and sodium, as well as fluid retention, also may occur. NSAIDs (especially fenoprofen) can cause a rare idiosyncratic reaction that may present with acute interstitial nephritis or nephrotic syndrome with a glomerular lesion resembling minimal change disease. Because COX-2 is expressed in the kidney, COX-2–selective agents offer no advantage in kidney toxicity over nonselective inhibitors.9 The potential for cardiovascular (CV) complications of COX-2 inhibitors is also undesirable in kidney patients at high risk of CV disease.

Drugs for Neuropathic Pain

Low-dose tricyclic antidepressants are used at normal doses in patients with reduced glomerular filtration rate (GFR), although they may be more sensitive to anticholinergic side effects. Low-dose valproate and carbamazepine are used at normal doses. Extreme caution and dose reductions are required with gabapentin10 and pregabalin11 because they are extensively removed by the kidney and can cause significant CNS adverse effects (somnolence, lethargy, dizziness, myoclonus, and ataxia).

ANTIMICROBIAL AGENTS

The kidneys excrete many antiinfective agents, and dose reduction is often required in severe CKD or those undergoing extended therapy.12 Many other antiinfectives have a wide therapeutic window, and dose adjustment is often clinically unnecessary despite their reliance on kidney excretion. An important principle of antiinfective therapy is to initiate effective drugs at sufficient doses rather than using conservative dose reductions that fail to achieve effective drug concentrations.

Normal or larger than expected doses based on kidney function may be appropriate when treating less susceptible organisms or when drug distribution to the site of infection is reduced (e.g., meningitis and urinary tract infections [UTIs]). Severe infection, especially in severely immunocompromised patients, may require extended therapy. In patients with UTI and severe CKD (e.g., GFR <30 mL/min/1.73 m2), antiinfectives that are only filtered by the kidneys are unlikely to achieve adequate concentrations in the urinary tract and are therefore unlikely to result in clinical cure. Because plasma concentrations will also be elevated, systemic toxicity is more likely (e.g., trimethoprim and nitrofurantoin). Administering a reduced dose of such antiinfectives is illogical because concentrations in the urinary tract will be further decreased and efficacy further reduced. Antiinfectives that are secreted by the tubules in addition to being filtered (e.g., penicillins) are more likely to achieve adequate concentrations in the urinary tract in advanced CKD and preferred agents.

Antibacterials

Aminoglycosides

Aminoglycosides are excreted unchanged by the kidneys and can cause nephrotoxicity, vestibular toxicity, and ototoxicity that can be severe and irreversible.13 When use is required, the total daily dose should be reduced, treatment courses kept to a minimum, and serum concentrations and kidney function monitored. Because aminoglycosides achieve high urine concentrations even in advanced CKD, lower doses may be appropriate for uncomplicated UTIs.

Aminoglycoside dosage schedules. Despite short half-lives (2–3 hours in normal kidney function), aminoglycosides are usually given once daily rather than in divided daily doses. This is based on two properties, namely, concentration-dependent killing and postantibiotic effect. The former requires that a high peak concentration (ideally 4–5 times the pathogen minimum inhibitory concentration [MIC]) is achieved. The latter allows the plasma concentration to fall below the MIC for much of the dosing interval without compromising efficacy. This “larger dose given less frequently” approach has been shown to be more efficacious and less toxic. The required dose regimen depends on volume of distribution (VD) and kidney clearance. Determining the best dose regimen in CKD involves reducing the normal daily dose (5–7 mg/kg/day)14 for gentamicin/tobramycin or 15 mg/kg for amikacin in proportion to kidney function (e.g., with 25% remaining kidney function, corresponding to GFR of ~25 mL/min/1.73 m2 or creatinine clearance [CrCl] of 25 mL/min, reduce total daily dose to 25% of normal). Aminoglycosides should be administered at a minimum effective dose (≥3 mg/kg for gentamicin and tobramycin; ≥7.5 mg/kg for amikacin) to achieve effective peak serum concentrations (>10 μg/mL for gentamicin and tobramycin; >30 μg/mL for amikacin). It is often necessary to increase the interval between doses (to >24 hours) to allow for an adequate dose (that will achieve a good peak concentration) to be administered.

Aminoglycoside concentration monitoring. Because of toxicity and pharmacokinetic variability in patients with infection and CKD, monitoring is essential to guide aminoglycoside dosing, particularly when therapy is initiated or significant changes occur in kidney function or clinical condition. Routine monitoring is not required for short treatment (<48 hours). Graphic methods using a single-point concentration 6 to 14 hours after administration are valid only with relatively normal GFR. They do not provide information on attainment of peak concentrations (for efficacy) and are not recommended in patients with CKD. Trough concentrations can be measured but must be interpreted in the context of the time after the dose when the sample was drawn. Trough monitoring does not provide information on the attainment of peak concentrations. Some patients, especially

those with severe sepsis and CKD, may have altered (usually higher) VD, which results in lower peak concentrations. Measuring peak concentrations (30 minutes after dosing) is the only certain way to determine dose adequacy. Combining peak and trough monitoring (approximately two half-lives after dosing) provides information on both VD and clearance and can therefore be used to determine both the size of individual doses and the administration interval. Provided the relationship between the time of administration and blood sampling is known, simple dose modifications are made on first principle estimates (see Chapter 77). Peak and trough target levels for aminoglycosides are shown in Table 77.6.

Carbapenems. Doripenem, imipenem, and meropenem are significantly excreted in urine but with appropriate dose modification can be used safely. Imipenem can cause significant neurotoxicity (myoclonic activity, seizures, and confusion), especially in high doses in those with underlying CNS disorders or CKD. Imipenem is inactivated by dehydropeptidase 1 in the kidney and is combined with cilastatin to prevent this.

Cephalosporins. Although most cephalosporins are predominantly removed by the kidney, their relative safety means that normal doses are used for most short-course therapies even in dialysis patients (e.g., ceftriaxone, cefaclor, and cephalexin). High-dose parenteral therapy and prolonged courses of some agents require dose reduction in severe impairment (e.g., cefepime, cefotaxime, ceftazidime, cefoxitin, and cefazolin). Therapeutic concentrations of cefazolin are maintained after doses of 20 mg/kg after dialysis three times weekly.15 Some cephalosporins (e.g., cefoxitin) interact with colorimetric assays for creatinine, resulting in falsely elevated serum creatinine values.16

Fluoroquinolones. Kidney excretion is significant with ciprofloxacin, norfloxacin, and gatifloxacin, and doses should be reduced if GFR is less than 30 mL/min/1.73 m2.17 Moxifloxacin is less dependent on kidney excretion, and dose reduction is not required. Norfloxacin plasma concentrations are too low for treating bloodborne infections, but urinary concentrations are adequate for treating UTIs. Quinolones are generally well tolerated but can cause CNS effects (headache, dizziness, insomnia, depression, restlessness, and tremors), interstitial nephritis, musculoskeletal effects (tendonitis and arthralgias), aortic aneurysms, and crystalluria. If use is essential, quinolones should be administered at least 1 hour before or 2 hours after meals and metallic phosphate binders, which may reduce absorption.

Glycopeptides. Vancomycin is a glycopeptide that is extensively removed by the kidney. Because of nephrotoxicity and ototoxicity, dose modification is essential even in mild to moderate impairment. Nephrotoxicity is more likely in those with preexisting CKD, with prolonged therapy, high plasma concentrations, and when concomitant nephrotoxins are prescribed. Ototoxicity may involve sensorineural deafness and tinnitus and is more likely with previous auditory compromise or impaired GFR. Rapid infusion also can cause an erythematous anaphylactoid-like reaction involving the upper body (red man syndrome) that usually resolves with slowing of the infusion rate and antihistamines. If vancomycin use is essential, duration of therapy should be minimized with regular monitoring of serum concentrations and GFR. Vancomycin should be administered once plasma serum concentrations have fallen below target values that are related to the MIC. Vancomycin distributes into body tissues, and clearance from the bloodstream after initial doses can appear greater than expected from estimates of GFR or CrCl. Once these tissues are saturated, clearance is purely via kidney clearance and is relatively predictable. In dialysis patients, single doses (e.g., 1 g of vancomycin) can maintain therapeutic concentrations (>15 µg/mL) for 3 to 5 days.18 Vancomycin is removed more extensively with modern high-flux than with older low-flux dialysis membranes. For teicoplanin, dose reduction is necessary when CrCl is less than 50 to 60 mL/min.

Lincosamides. Clindamycin and lincomycin are relatively safe and are not significantly excreted by the kidneys.

Macrolides. Macrolides are mostly hepatically cleared, and dose modifications are usually not required even in patients with advanced kidney failure. Dose reduction is required with high-dose or intravenous erythromycin, which may prolong QT interval and cause ototoxicity. Various macrolides are potent inhibitors of cytochrome P450 CYP3A4, 1A2, and P-glycoprotein, so there may be major interactions with and increased exposure to coadministered drugs that rely on CYP3A4, 1A2, or P-glycoprotein–mediated absorption and metabolism (including cyclosporine, tacrolimus, sirolimus, everolimus, and statins). Erythromycin and clarithromycin are the most potent inhibitors. Roxithromycin and azithromycin are much weaker inhibitors, causing few or no significant interactions (see Table 78.2).

Penicillins. Most penicillins have a short half-life and are rapidly eliminated by glomerular filtration and tubular secretion. Most have a relatively wide therapeutic window and are used at normal doses for short courses of oral therapy (e.g., amoxicillin) regardless of kidney function. High-dose parenteral therapy or prolonged high-dose oral therapy may require dose reduction to prevent electrolyte disturbances and neurotoxicity in kidney failure. Because the bactericidal effect of penicillins is not dependent on antibiotic concentration and exerts little or no postantibiotic effect, the amount of time above the MIC is more important than the maximum concentration. This translates into the frequency of dosing being more important than the size of each dose. For patients with UTIs who also have CrCl less than 40 to 50 mL/min, penicillins are a good choice (if the pathogen is sensitive) because urinary concentrations are higher than with agents that are merely filtered (e.g., trimethoprim). Dose reduction of benzyl penicillin, ticarcillin-clavulanate, and piperacillintazobactam are advised in patients with CrCl less than 40 to 50 mL/min.

Rifamycins. Rifamycins are mainly hepatically metabolized and used at normal doses. Orange-red coloration of body fluids (e.g., urine and peritoneal dialysis [PD] fluid) is common. These agents cause hepatotoxicity and blood dyscrasias. Rifampin is a potent CYP450 enzyme inducer and significantly increases metabolism of drugs, including immunosuppressants and oral contraceptives. Rifabutin does not induce CYP450 enzymes to the same extent.

Tetracyclines. Tetracycline was the originator of this class but has largely been replaced by newer derivatives due to the need for frequent administration, adverse effects (including Fanconi-like syndrome from outdated tetracycline), and resistance among pathogens. In CKD, tetracycline should be avoided because it is catabolic, causing uremia, hyperphosphatemia, and metabolic acidosis; it also may aggravate preexisting kidney failure.19 Doxycycline, minocycline, and tigecycline are newer derivatives that are not significantly dependent on kidney clearance and may be used as usual.

Sulfonamides and trimethoprim. Many sulfonamides are eliminated by acetylation followed by kidney excretion. Acetylated metabolites may cause crystalluria and tubular damage. Sulfamethoxazole and trimethoprim display similar kidney excretion except at extremes of urine pH. Alkaline urine promotes sulfamethoxazole excretion, whereas acidic urine promotes trimethoprim excretion. Both accumulate in CKD, and dose reduction is advisable except perhaps in the treatment of UTIs when higher plasma concentrations might be required to facilitate adequate urinary concentrations. Trimethoprim inhibits tubular secretion of creatinine, resulting in an increase in serum creatinine20 that does not reflect a true change in GFR and can be misinterpreted as nephrotoxicity.

Other antibiotics. Linezolid is used at a normal dose. Metronidazole has a partially active metabolite, although only 15% of the parent drug is removed by the kidney. It is usually given in usual doses or reduced to twice-daily doses with dialysis.

Antimycobacterials

Ethambutol is extensively removed by the kidney, and dose reduction is required when CrCl is less than 30 mL/min to avoid visual toxicity.21 Isoniazid, pyrazinamide, and rifampin-rifabutin can be given in usual doses. Rifampin causes induction of hepatic enzymes and severe drug interactions with transplant immunosuppressants. Amikacin, kanamycin, streptomycin, capreomycin, and gatifloxacin have extensive kidney clearance, are nephrotoxic, and require significant dose reduction.

Antifungals

Amphotericin. Amphotericin use is limited by nephrotoxicity (see Chapter 55). Nephrotoxicity with crystalline amphotericin may be minimized with prehydration and administration by continuous infusion. Liposomal formulations have fewer infusion-related problems and are less nephrotoxic but more expensive. Oral amphotericin (used for its enteric effect and lozenges for oral thrush) is not absorbed and does not contribute to nephrotoxicity.

Azole antifungals. Most azole antifungals (ketoconazole, itraconazole, posaconazole, and voriconazole) are extensively metabolized and do not require dose reduction. Fluconazole is excreted by the kidney; after a loading dose, maintenance doses should be reduced in moderate to severe CKD, and it should be given after dialysis. Fluconazole is significantly excreted in urine and hence is often useful for fungal UTIs. The manufacturer recommends avoiding intravenous voriconazole in severe CKD because of possible accumulation of the intravenous vehicle (sulfobutyl betadex sodium). Voriconazole, ketoconazole, and itraconazole are potent inhibitors of CYP3A4 and P-glycoprotein that are involved in the metabolism and absorption of a variety of drugs, including cyclosporine, tacrolimus, sirolimus, everolimus, and statins. A twofold to 10-fold reduction of the concomitant drug may be required (guided by drug monitoring; see Table 78.2). Interactions between ketoconazole and calcineurin inhibitors (CNIs) or mammalian target of rapamycin (mTOR) inhibitors have been exploited as a cost-reducing immunosuppressantsparing strategy. Increased exposure to statins (except pravastatin) caused by CYP3A4 inhibition increases the risk for rhabdomyolysis-induced CKD. Fluconazole is a weak enzyme inhibitor, and although caution should be exercised, the need for preemptive dose reduction of concomitant drugs is less certain. Topical azoles, including bifonazole, clotrimazole, econazole, ketoconazole, tinidazole, and miconazole, are minimally absorbed and do not cause interactions.

Other antifungals. Absorption of nystatin from topical and oral preparations is minimal and safe in CKD. Terbinafine is hepatotoxic, and a 50% dose reduction is suggested in moderate to severe CKD. Griseofulvin, anidulafungin, and caspofungin can be given in usual doses. Flucytosine has extensive kidney clearance and requires significant dose reduction.

ANTIVIRALS

Many antivirals (or their active metabolites) have extensive kidney excretion and can cause nephrotoxicity (see also Chapter 70).

Guanine Analogs

Acyclovir, its prodrug valacyclovir, and famciclovir (a prodrug of penciclovir) have extensive kidney clearance, and doses must be reduced in proportion to the severity of CKD. These agents can also crystallize in tubules, causing obstructive nephropathy, especially when given intravenously. Where possible they should not be administered in low volumes of fluid, and the patient should be well hydrated. High concentrations cause severe CNS toxicity (cerebral irritation, ataxia, and myoclonus). Ganciclovir and its prodrug valganciclovir have extensive kidney clearance,22 and accumulation leads to severe bone marrow toxicity. Dose reduction based on kidney function is essential. These agents are freely dialyzed and should be given after hemodialysis (HD).

Hepatitis B and C

Pegylated interferon alfa-2a has a larger metabolic clearance than pegylated interferon alfa-2b, which has higher kidney clearance and requires dose reduction in CKD. Interferons can upregulate cell surface expression of class II histocompatibility antigens, which increases the potential for transplant rejection. Ribavirin and its metabolites rely on kidney excretion; accumulation causes severe anemia, making it contraindicated if GFR is below 50 mL/min; significantly reduced doses are sometimes used in lower levels of GFR. Newer direct-acting antivirals for hepatitis C (boceprevir, daclatasvir, ledipasvir, sofosbuvir, ombitasvir, paritaprevir, ritonavir, dasabuvir, simeprevir, telaprevir) are less dependent on kidney excretion and may be preferable in patients with CKD. Adefovir, entecavir, lamivudine, and telbivudine have extensive kidney excretion, and significant dose reduction is essential.

Neuraminidase Inhibitors

Oseltamivir is converted by hepatic esterases to its active metabolite, oseltamivir carboxylate, which is extensively (99%) removed through glomerular filtration and tubular secretion.23 The area under the curve (AUC) is increased 10-fold in severe CKD, and, although the drug is well tolerated, dose reduction is recommended. Oseltamivir carboxylate is cleared by hemodialysis, but in anuric patients plasma concentrations remain virtually unchanged in between hemodialysis sessions.

Patients on hemodialysis who have even small amounts of residual kidney function can clear oseltamivir carboxylate significantly faster than those who are anuric. Ideally, dosing in CKD would be guided by therapeutic drug monitoring, but this is not routinely available. Reducing the dose of oseltamivir in CKD used to be achieved by giving the same dose (75 mg) less frequently, but more recently it has been suggested it should be achieved by giving a lower dose (30-mg capsule) once or twice a day, depending on the degree of CKD. Giving a smaller dose from the outset delays the attainment of critical “therapeutic concentrations” because it takes approximately four times the prolonged half-life to achieve concentrations to maximize benefit. The initial dose should be 75 mg, and subsequent doses can be reduced either by reducing the dose size or prolonging the interval between doses.24 It may be wiser to use zanamivir whenever CrCl falls below 20 mL/min. Zanamivir is also removed by the kidney, but dose modification is not necessary because absorption from the inhaled formulation is very low (~2%).

Other Antivirals

Cidofovir and foscarnet have extensive kidney clearance and require dose reduction in CKD. Both are nephrotoxic, require close monitoring of kidney function, and should be administered with hydration.

Cidofovir is recommended to be administered with probenecid to slow kidney secretion and minimize nephrotoxicity. Tenofovir doses should also be reduced in moderate chronic kidney failure and avoided below 30 mL/min/1.73 m^2 and in combination with other nephrotoxins, such as adefovir. Agents active against HIV infection are also discussed in Chapter 58.

IMMUNOSUPPRESSANTS

Dosing of immunosuppressive agents used in kidney transplantation, as well as adverse effects, are discussed in Chapter 106. Initial and maintenance doses in individuals are highly variable and depend on

local protocol, concomitant therapy, rejection risk, drug concentrations, and response. Immunosuppression is required for the life of the transplant and should never be withheld except in exceptional circumstances (life-threatening infection or malignancy). Regimens should preferably be convenient (e.g., twice daily) to enhance compliance. In practice, the precise timing of doses or intake relative to time and food is not as important as consistency in relation to time and food because doses can be titrated to levels and response. Most immunosuppressants are hepatically metabolized and do not require dose modification based on altered excretion in CKD.
Immunosuppressants are prone to a range of significant drug interactions, which should be considered whenever a patient receiving these agents has a change in drug regimen. Significant interactions also can occur with “natural” or “herbal” medicines (e.g., St. John’s wort; see also Chapter 77 and Table 78.1). If these products are deemed essential, it is advisable to monitor response, kidney function, blood counts, and serum drug concentrations regularly but especially during initiation, dose alterations, and stopping the “natural” product. Therapeutic monitoring is recommended for several immunosuppressants25 (tacrolimus, cyclosporine, everolimus, sirolimus, and mycophenolate).
The target range may differ from center to center due to assay differences and may change with time posttransplant and immunosuppressive regimen. Reported concentrations should always be interpreted in the context of patient response and adverse effects.26

Calcineurin Inhibitors

CNIs are extensively metabolized to inactive metabolites. A major adverse effect of CNIs is nephrotoxicity (acute and chronic),27 and regular assessment of kidney function is essential. Nephrotoxicity may increase with concurrent use of mTOR inhibitors. Early detection of CNI nephrotoxicity on biopsy assists in planning maintenance therapy (see Chapters 106 and 109). Lower doses or temporary withdrawal may be used when CNIs have caused or are likely to cause nephrotoxicity (e.g., delayed graft function). Calcium channel blockers (CCBs) and blockers of the renin-angiotensin system may both reduce CNI nephrotoxicity. CNIs are substrates of P-glycoprotein and CYP3A4. Drugs that inhibit or compete as substrates for these can increase absorption and reduce metabolism of CNIs, causing increased serum concentrations and adverse effects. Drugs that induce these can reduce absorption and increase metabolism of CNIs, causing reduced serum concentrations, and increase the risk for rejection (Table 78.2). Tacrolimus trough concentrations (C0) show good correlation with drug effect/toxicity and are used to monitor therapy. Clinically, a combination of C0 (trough), C2 (concentration 2 hours after dose), and AUC0-4 (multipoint AUC, 0–4 hours) has been used to measure cyclosporin. Different assay methodologies (high-performance liquid chromatography [HPLC] and immunoassays) have differing abilities to differentiate parent compound from inactive metabolites. Specific HPLC methods are preferred, and physicians should be aware that results from different laboratories may differ due to assay specificity.

Corticosteroids

Corticosteroids are predominantly cleared by hepatic metabolism to inactive metabolites. Dose modification based on kidney function is not required.

Antiproliferative and Cytotoxic Agents

Various antiproliferative and cytotoxic agents are used to prevent transplant rejection (azathioprine and mycophenolate) and to suppress the immune system in patients with autoimmune and inflammatory kidney disorders (azathioprine, cyclophosphamide, chlorambucil, methotrexate, and mycophenolate). Their primary dose-limiting toxicity is bone marrow

Common Drug Dosing Recommendations in Chronic Kidney Disease Including Kidney Transplantation and Dialysis

TABLE 78.1

PREDOMINANT ELIMINATION PATHWAY
Drugs

Hepatic

Analgesics
Simple analgesics
Opioids

Acetaminophen

Kidney

Morphine
Pethidine (meperidine)
Fentanyl
Hydromorphone
Methadone
Oxycodone
Tramadol

NSAIDs
Neuropathic pain

Gabapentin
Pregabalin
Carbamazepine
Low-dose TCAs
Valproate

Antiinfectives
Aminoglycosides

Amikacin
Gentamicin
Tobramycin
Ertapenem
Doripenem
Imipenem
Cefotaxime
Ceftazidime
Cephalexin

Carbapenems

Cephalosporins

Ciprofloxacin
Norfloxacin

Reduce in severe impairment

Moxifloxacin
Glycopeptides

Macrolides

Teicoplanin
Vancomycin
Azithromycin
Clarithromycin
Roxithromycin
Erythromycin
Amoxycillin
Benzylpenicillin
Piperacillin
Ticarcillin/clavulanic acid

Penicillins

Sulfonamides and
trimethoprim
Tetracyclines

Tetracycline
Doxycycline
Minocycline

Antimycobacterials

Ethambutol
Isoniazid
Pyrazinamide
Rifampicin

Azole antifungals

Fluconazole
Ketoconazole

Normal dosing
Avoid/dose reduction
Avoid
Cautious normal doses
Cautious normal doses
Cautious normal doses
Cautious normal doses
Cautious normal doses
Avoid if possible
Significant dose reduction
Significant dose reduction
Normal dose
Normal dose
Normal dose
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Reduce in severe impairment
Dose reduction
Dose reduction
Dose reduction
Dose reduction
Normal dose
Normal dose
Reduce in severe impairment

Ceftriaxone
Fluoroquinolones

Dosing
Recommendations

Normal dose
Avoid/dose reduction
Avoid/dose reduction
Normal dose
Normal dose
Normal dose
Dose reduction
Normal dose
Dose reduction
Dose reduction
Dose reduction
Reduce high doses
Avoid
Normal dose
Normal dose
Dose reduction
Normal dose
Normal dose
Normal dose
Reduce maintenance doses
Normal dose

Comments

Metabolite kidney clearance
Metabolite kidney clearance

Potential nephrotoxicity
CNS adverse effects
CNS adverse effects

Nephrotoxicity
Nephrotoxicity
Nephrotoxicity

PO4 binders may impair
absorption
PO4 binders may impair
absorption
Nephrotoxicity and ototoxicity
Nephrotoxicity and ototoxicity
CYP3A4 interactions
CYP3A4 interactions

Falsely elevates creatinine

CYP3A4 interactions
CYP3A4 interactions
Continued

TABLE 78.1 Common Drug Dosing Recommendations in Chronic Kidney Disease Including
Kidney Transplantation and Dialysis—cont’d
PREDOMINANT ELIMINATION PATHWAY
Drugs

Hepatic

Kidney

Itraconazole
Voriconazole
Other antifungals

Acyclovir
Famciclovir
Ganciclovir
Valaciclovir
Entecavir
Ribavirin
Oseltamivir
Cidofovir
Foscarnet

Normal dose
Normal dose
Reduce maintenance doses
Normal dose
Normal dose
Dose reduction
Dose reduction
Dose reduction
Dose reduction
Avoid/dose reduction
Avoid/dose reduction
Dose reduction
Significant dose reduction
Significant dose reduction

Cyclophosphamide

Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Dose reduction

Terbinafine
Caspofungin
Griseofulvin

Guanine analogs

Other antivirals
Neuraminidase inhibitors
Other antivirals
Immunosuppressants
Calcineurin inhibitors

mTOR inhibitors
Antiproliferatives

Cyclosporin
Tacrolimus
Everolimus
Sirolimus
Azathioprine
Mycophenolate

Anticoagulants, Antiplatelet Agents, Thrombolytics, and Hemostatics
UFH
UFH
LMWHs
Dalteparin
Enoxaparin
Anticoagulants
Warfarin
Apixaban
Bivalirudin
Dabigatran
Danaparoid
Fondaparinux
Lepirudin
Melagatran
Ximelagatran
Rivaroxaban
Aspirin
Clopidogrel
Dipyridamole

Antiplatelets

Cardiovascular Drugs
ACE inhibitors
ARBs
β-Blockers

Atenolol
Sotalol
Carvedilol
Labetalol
Metoprolol
Pindolol
Propranolol

Dosing
Recommendations

Normal dose
Dose reduction
Dose reduction
Avoid/normal dose
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Avoid/dose reduction
Normal dose
Normal dose

Normal dose

Comments
CYP3A4 interactions
CYP3A4 interactions

CNS + nephrotoxicity
CNS + nephrotoxicity
Hematologic toxicity
CNS + nephrotoxicity
Hematologic toxicity
Nephrotoxic
Nephrotoxic
Nephrotoxic
Nephrotoxic

Hematologic toxicity

Bleeding risk
May promote vascular
calcification
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk
Bleeding risk

Titrate according to kidney
Potential nephrotoxicity
function and serum potassium
Potential hyperkalemia
Dose reduction
Dose reduction
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose

Common Drug Dosing Recommendations in Chronic Kidney Disease Including Kidney Transplantation and Dialysis—cont’d

TABLE 78.1

PREDOMINANT ELIMINATION PATHWAY
Drugs

Hepatic

CCB

Amlodipine
Diltiazem
Lercanidipine
Nifedipine
Verapamil
Nicorandil
Nitrates
Perhexiline
Atorvastatin
Rosuvastatin
Simvastatin

Antianginals

Statins

Kidney

Pravastatin
Fenofibrate
Digoxin
Disopyramide
Procainamide

Fibrates
Antiarrhythmics

Amiodarone
Flecainide
Mexiletine
Diuretics
Diabetes
Insulins
Biguanides
Sulfonylureas

DPP-4 inhibitors

Furosemide
Spironolactone
Insulin
Metformin
Gliclazide
Glibenclamide
Glipizide
Linagliptin
Saxagliptin

Sitagliptin
Vildagliptin
Dapagliflozin
Empagliflozin
Ertugliflozin
Exenatide

SGLT2 inhibitors

GLP-1 analogs

Thiazolidinediones
Gastrointestinal
H2 antagonists
PPIs

Dutaglutide
Liraglutide
Semaglutide
Pioglitazone
Rosiglitazone

Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Dose reduction
Reduce dose + monitoring
Dose reduction
Dose reduction
Normal dose
Normal dose
Normal dose
Dose increase
Avoid
Cautious dose titrations
Avoid
Normal doses
Avoid/dose reduction
Avoid/dose reduction
Normal dose
Avoid/dose reduction
Dose reduction
Dose reduction
Avoid eGFR <45 mL/min/1.73 m2
Avoid eGFR <30 mL/min/1.73 m2
Avoid eGFR <45 mL/min/1.73 m2
Avoid eGFR <30 mL/min/1.73
m2

Comments
CYP3A4 interactions

CYP3A4 interactions

Bradycardia

Hyperkalemia

Lactic acidosis
Active metabolites
Active metabolites

Associated with severe DKA

Normal dose
Normal dose
Normal dose
Avoid
Avoid
Ranitidine

Cimetidine
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole

Dosing
Recommendations

Normal dose
Avoid
Normal dose
Normal dose
Normal dose
Normal dose

Drug interactions
Acute interstitial nephritis may
occur (see Chapter 64)

Continued

TABLE 78.1 Common Drug Dosing Recommendations in Chronic Kidney Disease Including
Kidney Transplantation and Dialysis—cont’d
PREDOMINANT ELIMINATION PATHWAY
Drugs

Hepatic

Dopamine antagonists

Domperidone
Metoclopramide
Prochlorperazine
Ondansetron
Dolasetron
Tropisetron
Low potency:
Bisacodyl
Docusate
Lactulose
Sorbitol
High potency, including
phosphate containing
Atropine
Diphenoxylate
Loperamide

5-HT3 antagonists

Aperients and laxatives

Antidiarrheal agents

Musculoskeletal
Gout

Kidney

Allopurinol
Alendronate

CNS-Acting Drugs
Antiepileptics

SSRIs

Antipsychotics

Benzodiazepines

Comments

Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose

Extrapyramidal and CNS effects

at high dose with CKD

Normal dose
Normal dose
Normal dose
Normal dose
Avoid

Fluid and electrolyte
disturbances

Normal dose
Normal dose
Normal dose

Febuxostat
Bisphosphonates

Dosing
Recommendations

Reduce dose
Normal dose
Normal or reduced dose

Pamidronate
Risedronate
Zoledronate

Normal or reduced dose
Normal or reduced dose

Levetiracetam

Reduce dose
Normal dose
Normal dose + monitoring
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose
Normal dose

Carbamazepine
Phenytoin
Valproate
Citalopram
Paroxetine
Venlafaxine
Clozapine
Olanzapine
Risperidone
Clonazepam
Diazepam
Oxazepam
Temazepam

Active metabolite

Avoid in adynamic bone
disease
Rapid IV nephrotoxic

CYP3A4 interactions
CYP3A4 interactions

Enhanced CNS toxicity

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; H2, histamine-2; IV, intravenous; LMWH, low-molecular-weight heparin; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal antiinflammatory drug; PO4, phosphate; PPI, proton pump inhibitor; SGLT2, sodium-glucose cotransporter-2; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UFH, unfractionated heparin.

suppression, which is exacerbated by combined use with other bone marrow suppressants (e.g., ganciclovir, cotrimoxazole, and mTOR inhibitors). Regular blood monitoring is needed to guide dosage. Methotrexate relies on kidney clearance and should be avoided or used cautiously at a reduced dose in people with a low GFR. Kidney clearance is significant with cyclophosphamide, which can cause hemorrhagic cystitis via an active metabolite (acrolein) if it is allowed to dwell in the bladder for lengthy periods

(hence it should not be administered prior to bedtime), and chlorambucil, and dose modifications are required. Allopurinol and febuxostat significantly interfere with metabolism of the active metabolite of azathioprine (6-mercaptopurine), and coprescription can lead to life-threatening bone marrow suppression. The combination should be avoided by exchanging azathioprine with mycophenolate or by significant (75%) dose reduction of azathioprine or mercaptopurine.

mTOR Inhibitors

Although not nephrotoxic when used alone, mTOR inhibitors (sirolimus, everolimus) can potentiate the nephrotoxicity of CNIs. mTOR inhibitors are almost entirely hepatically metabolized to essentially inactive metabolites. Dosage is independent of kidney function and based on response, serum drug levels, and specific toxicities (especially hematologic and lipids). mTOR inhibitors are substrates of CYP3A4 and P-glycoprotein and susceptible to the same drug interactions as CNIs (Table 78.2). Bone marrow toxicity (neutropenia, anemia, and thrombocytopenia) is increased when they are used in combination with other myelosuppressants (azathioprine, mycophenolate, ganciclovir, and cotrimoxazole). Trough levels show good correlation with drug efficacy/toxicity and are used to monitor therapy. Different assay methodologies (HPLC vs. immunoassays) vary in their ability to detect parent drug from metabolites. Specific HPLC methods are recommended, and results from different laboratories or methods may not be interchangeable.

Immunosuppressant Antibodies

Antibodies used for immunosuppression include T cell–depleting antibodies (antithymocyte globulin, anti–interleukin-2 receptor (CD25) antibodies (basiliximab and daclizumab), and B cell–depleting antibodies (rituximab) (see Chapter 106). Dosage is independent of kidney function, and these agents should be administered after plasma exchange28 to avoid drug removal. They are not removed by HD.

CHEMOTHERAPY AND CYTOTOXIC AGENTS

Kidney function affects the outcomes of patients with cancer due to the impact on the anticancer drug selection and dosing.29 Alternative use of the second- or third-line agent may lead to reduced effectiveness; underestimation of kidney function may lead to inappropriate agent selection, dose reductions, underdosing, reduced effectiveness,

and failure of therapy. Conversely, overestimation of kidney function may lead to overdosing and toxicity from anticancer drugs cleared by the kidney. Cytotoxic agents are drugs with a narrow therapeutic index, hence a small change in plasma concentrations can lead to toxicity or loss of efficacy. Many anticancer drugs are excreted predominantly as unchanged drug or active metabolite in the urine and therefore require dose adjustment for kidney function (e.g., bleomycin, capecitabine, carboplatin, cisplatin, cyclophosphamide, erlotinib, etoposide, fludarabine, imatinib, methotrexate, mitomycin, pemetrexed).

Carboplatin dose is calculated based on the Culvert equation, which takes into consideration the target AUC and the patient’s kidney function:

$$\text{Dose (mg)} = \text{Target AUC} \times (\text{GFR} + 25)$$

Carboplatin dosing varies significantly on the estimate of GFR. The dose depends on the method used for estimation of GFR and whether a body surface area (BSA) indexed eGFR or absolute eGFR is used in the Culvert formula.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are novel small molecule targeted therapies administered orally and associated with improved outcomes and reduced toxicity compared with the conventional chemotherapy. Most of these agents do not require dose adjustment in mild and moderate CKD.30 The pharmacokinetics for some of these agents have not been studied in patients with severe CKD, and therefore their use has not been recommended in this patient population (e.g., alectinib, cabozantinib) or may be administered with caution (e.g., ceritinib, dabrafenib,

trametinib).
Some of these agents require dose adjustment in patients with severe CKD (e.g., afatinib, brigatinib, crizotinib, vandetanib). Crizotinib is an anaplastic lymphoma kinase 1 (ALK-1) inhibitor. It may act as a

Common CYP3A4/P-gp–Mediated Interactions With Transplant Immunosuppressants (Cyclosporine, Tacrolimus, Sirolimus, Everolimus)

TABLE 78.2
Drug Class

Drugs That Inhibit CYP3A4 and P-gp
Macrolide antibiotics

Azole antifungals

CCBs

Herbals, foods
Drugs That Induce CYP3A4 and P-gp
Antiepileptics

Antibiotics
Herbals, foods
CCB, Calcium channel blocker; P-gp, P-glycoprotein.

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Examples

Relative Potency

Azithromycin
Clarithromycin
Erythromycin
Roxithromycin
Fluconazole
Itraconazole
Ketoconazole
Voriconazole
Amlodipine
Nifedipine
Felodipine
Diltiazem
Verapamil
Grapefruit juice

–
+++
+++
+
+/–
++
+++
+++
+
+/–
+/–
++
+++
++

Carbamazepine
Phenytoin

Phenobarbitone
Rifampin
St. John’s wort

++
+++
++
+++
+++

competitive inhibitor of CrCl by the organic cation transporter 2 (OCT2) in the proximal tubule. This effect is similar to other drugs (e.g., trimethoprim, cimetidine), leading to the increase in serum creatinine that is not associated with true AKI (i.e., pseudo-AKI).

kidney function, eptifibatide and tirofiban are excreted by the kidney and have been associated with bleeding in this setting. Abciximab is cleared by platelet binding and is not associated with increased bleeding risk in patients with CKD.

ANTICOAGULANTS, ANTIPLATELET AGENTS, THROMBOLYTICS, AND HEMOSTATICS

Thrombolytics

Bleeding risk with anticoagulants, antiplatelet agents, and thrombolytics is generally increased in patients with CKD.31

Streptokinase, anistreplase, and alteplase are used as normal, but the high risk for hemorrhage should be considered. Urokinase and alteplase are also used to unclot dialysis catheters and occasionally to prevent catheter dysfunction.

Unfractionated Heparin

Hemostatics

Unfractionated heparin (UFH) is cleared via a saturable mechanism of the endothelium and reticuloendothelial system and a nonsaturable mechanism through the kidneys. Half-life is slightly prolonged (1.5-fold) in CKD, especially at higher doses. However, UFH is used at normal dose with titration based on activated partial thromboplastin time monitoring. In some centers, UFH is preferred in severe CKD because its duration of effect is shorter and more easily measured and reversed.

Tranexamic acid is highly (90%) dependent on clearance via the kidneys and requires dose reduction in moderate to severe CKD. Protamine and vitamin K are used as normal, as are fresh-frozen plasma and whole blood with critical bleeding.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) (enoxaparin, dalteparin) rely more on kidney clearance than UFH and in moderate to severe CKD can accumulate, increasing the risk for serious bleeding, especially following surgery. Consideration should be given to using UFH in this setting. In situations where LMWHs are preferred and there is doubt about clearance (or other kinetic issues), dosing should be guided by anti-Xa activity assay. Tinzaparin does not accumulate in patients with CrCl greater than 20 mL/min after at least 10 days of dosing and may be a useful option for bridging anticoagulation.

Other Parenteral Anticoagulants

Other parenteral anticoagulants that accumulate in CKD and that should be avoided or used with significant dose reduction include bivalirudin, danaparoid, fondaparinux, lepirudin, ximelagatran, and melagatran. Argatroban may be used at normal dose. Prostacyclin, used to prevent platelet aggregation in HD circuits, is rapidly hydrolyzed and not affected by CKD.

Oral Anticoagulants

The liver extensively metabolizes warfarin, and in CKD it is usually commenced at normal dose and titrated according to the international normalized ratio. Warfarin is highly protein bound, and with hypoalbuminemia there may be increased sensitivity to warfarin. Similarly, hepatic metabolism may be altered with CKD that results in increasing sensitivity. Warfarin may promote vascular calcification and should be avoided in advanced CKD unless absolutely necessary (e.g., those with a mechanical heart valve). Newer, directacting oral anticoagulants (DOACs) (rivaroxaban and apixaban) are partially dependent on kidney clearance. Dabigatran is very dependent on kidney clearance. Because these agents are difficult to monitor (assays not routinely available), they are dose reduced according to estimates of CrCl and are contraindicated (rivaroxaban <15 mL/min, apixaban <25 mL/min, and dabigatran <30 mL/min) in advanced CKD.

Antiplatelet Drugs

Commonly prescribed doses of oral antiplatelets (aspirin, clopidogrel, and dipyridamole) do not require adjustment, although patients with CKD are more prone to bleeding. Despite their efficacy in reduced

DIURETICS

Diuretics must reach the tubular lumen of the kidney in unbound form to exert an effect.32 Pharmacokinetic and pharmacodynamic properties of diuretics can change with proteinuria or CKD, usually causing a resistance to their effect. Diuretics in the immediate posttransplant setting may increase urine flow in native kidneys, giving a false impression of transplant function.

Thiazide Diuretics

Thiazide diuretics (chlorthalidone, hydrochlorothiazide, and indapamide) become less effective as diuretics when GFR is less than 30 mL/min/1.73 m2, although they may augment the effectiveness of a loop diuretic and retain their antihypertensive effects. Metolazone can maintain efficacy at a lower GFR.

Loop Diuretics

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) remain effective at low GFR and are generally preferred in patients with CKD, although higher doses are usually required because less reaches the site of action in the lumen as GFR falls.

Potassium-Sparing Diuretics

Potassium-sparing diuretics are the least effective diuretics and should be used cautiously in moderate to severe CKD because of the risk for hyperkalemia.

ANTIHYPERTENSIVES

Antihypertensives should be used cautiously to avoid kidney hypoperfusion.33 Hypotension during HD may require that doses be withheld or delayed on dialysis days.

ACE Inhibitors and ARBs

Although various ARBs and the active metabolites of ACE inhibitors are excreted by the kidney, they can be used effectively in CKD if initiated at moderate doses and titrated to response, kidney function, and serum potassium level. An increase in serum creatinine (up to 30% in the first 2 months) may be associated with blood pressure response. All ACE inhibitors and ARBs can cause AKI by inhibiting angiotensin II–mediated homeostatic vasoconstriction of the efferent renal arteriole during kidney hypoperfusion (e.g., with dehydration, hypotension, blood loss, and infection) or preexisting CKD (see also Chapter

70). Nephrotoxicity is more likely with coadministration of drugs that reduce kidney perfusion, including diuretics, antihypertensives, and NSAIDs.34 Hyperkalemia is more likely in those with CKD and those taking potassium-sparing diuretics or supplements. ACE inhibitors or ARBs also can worsen anemia by reducing erythropoietin production.

kidney patients. They can interfere with absorption and enterohepatic recirculation of various drugs, including mycophenolate.

β-Blockers

Statins

Calcium Channel Blockers

Most statins (hydroxymethylglutaryl–acetyl CoA [HMG-CoA] reductase inhibitors) are extensively metabolized and can be used effectively at normal doses in CKD and those who have undergone transplantation.37 Pravastatin is partially cleared via the kidneys. Rhabdomyolysis with AKI can occur, although the risk does not appear to be greatly increased with CKD. The risk increases with concomitant use of fibrates and drugs that inhibit the CYP3A4 metabolism of most statins. Patients commencing therapy should have kidney function and creatine kinase monitored regularly.

Most β-blockers (carvedilol, labetalol, metoprolol, pindolol, and propranolol) are hepatically metabolized and used at normal doses. Sotalol and atenolol are 90% removed and bisoprolol 50% removed by the kidney, and so dose reductions are often but not always required as they can be dosed to clinical effect. Atenolol can sometimes be given three times weekly after dialysis. β-Blockers may slightly elevate serum potassium.

Pharmacokinetics of CCBs are generally unaltered in CKD. These drugs are usually well tolerated and used in normal doses. Dihydropyridine CCBs (especially amlodipine) can cause edema in the lower limbs that is more likely due to “capillary leakage” than fluid retention, and it is less responsive to diuretics. This can aggravate the edema of CKD. To varying extents, CCBs inhibit CYP3A4 and P-glycoprotein, causing increased absorption and reduced elimination of various substrate drugs, including CNIs and mTORs. Verapamil and diltiazem are moderately potent inhibitors, and dose modification of the affected drug is required. This interaction has been exploited so that diltiazem and other, more potent CYP3A4 and P-glycoprotein inhibitors are used as immunosuppressant-sparing agents.35 36 Other CCBs do not usually cause clinically significant interactions.

Other Antihypertensives

Methyldopa, clonidine, prazosin, terazosin, doxazosin, and minoxidil can be initiated and titrated at conventional dosage but may be associated with a higher incidence of adverse effects in patients with CKD. In particular, minoxidil is relatively contraindicated in CKD because it can lead to volume expansion with the development of pericardial and pleural effusions; when used, additional diuretic therapy may be required. α-Blockers cause profound orthostatic hypotension. Nitroprusside must be used cautiously because the toxic metabolite thiocyanate may accumulate with CKD but can be removed by hemodialysis.

ANTIANGINAL AGENTS

Most antianginals (nitrates, CCBs, nicorandil, and perhexiline) can be used as normal.

ANTIARRHYTHMICS

Various antiarrhythmics (digoxin, flecainide, disopyramide, procainamide, and sotalol) rely on kidney excretion and require dose modification. Digoxin has significant kidney excretion and a narrow therapeutic window, so dose reduction is essential even in mild CKD. Because of reduced tissue protein binding and VD, some physicians use a smaller loading dose of digoxin than in patients with normal kidney function. Cautious monitoring and titration can prevent accumulation and toxicity. When possible, monitoring of antiarrhythmic drug concentrations and the electrocardiogram is recommended. Other agents (amiodarone, flecainide, metoprolol, mexiletine, and verapamil) are used at normal doses.

LIPID-LOWERING AGENTS

Bile Acid–Binding Resins

Bile acid–binding resins are now rarely used, and the large fluid volumes required to administer them limit their use in fluid-restricted

Fibrates

Fenofibrate but not gemfibrozil has extensive kidney clearance, and dose reduction is required. Combination of statins and fibrates significantly increases the risk for rhabdomyolysis and should be used only when benefits outweigh risks and with monitoring for muscle symptoms, creatine kinase, and alanine aminotransferase.

DIABETES

In addition to diabetes being a cause of CKD, the kidney also plays an important role in insulin metabolism, and thus kidney function influences glycemic control. Diabetes is common after transplantation because of resumed insulin metabolism by the functioning transplant and also the effect of tacrolimus and corticosteroids. Patients with CKD are at increased risk for hypoglycemia, and drugs should be initiated and titrated cautiously.[38] Various antidiabetic drugs depend on kidney excretion, and accumulation in CKD can cause adverse effects.[39] Management of diabetes in CKD is discussed in Chapter 33.

Diabetes Management in Peritoneal Dialysis

Patients receiving PD may have higher antihyperglycemic requirements because of the glucose load in PD fluid. If insulin is administered intraperitoneally, dosages may differ from intravenous requirements. Icodextrin solutions can significantly interfere with blood glucose monitoring because of metabolites (maltose, maltotriose, or maltotetrose) that falsely elevate blood glucose readings when monitors that use the enzyme glucose dehydrogenase pyrroloquinoline quinone reaction are used. This may lead to administration of insulin and the development of life-threatening hypoglycemia. A glucose-specific test strip is required to avoid interference.

Biguanides

Metformin is excreted almost entirely unchanged in urine, and accumulation can contribute to severe or fatal lactic acidosis (see Chapter 33),[40] although the association is inconsistent. Metformin should be temporarily discontinued in situations known to increase the risk for lactic acidosis or reduce kidney function (e.g., acute tissue hypoxia, dehydration, serious infection, or trauma) and 24 to 48 hours before anticipated surgery or use of iodinated radiocontrast media. Current Kidney Disease: Improving Global Outcomes guidelines recommend metformin as first-line therapy in CKD but to discontinue it where GFR is less than 30 mL/min/1.73 m^2. Even with low-dose use in patients with GFR less than 30 mL/min/1.73 m^2, there is still a risk for lactic acidosis, and an acute deterioration in kidney function can reduce drug clearance at any time. Patients on this regimen should be advised to seek early medical advice in any cases of acute deterioration in health.

Insulins

As GFR decreases, insulin clearance decreases in parallel, and so hypoglycemia may ensue if kidney function deteriorates and insulin regimens are not adjusted accordingly. Uremia, however, can cause peripheral resistance to insulin, requiring increased doses. Most insulin regimens can be used in patients with CKD or transplantation with cautious titration and monitoring.

Meglitinides

The nonsulfonylurea insulin secretagogues repaglinide and nateglinide can be used in patients with kidney failure without dose adjustment.

Sulfonylureas

Sulfonylureas are metabolized, and some (glibenclamide and glimepiride) have active metabolites that are excreted by the kidney. In moderate to severe CKD, the risk of hypoglycemia is increased.41 These agents should be initiated at a low dose and titrated to response. Gliclazide and glipizide are preferable because they do not have active metabolites. Regardless of which agent is used, the effect of sulfonylureas still may be increased because the insulin they release will itself have a prolonged action in CKD.

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin) depend on adequate kidney function to lower blood glucose levels and may be less effective at achieving this outcome in moderate or severe CKD. Nevertheless, trials suggest their independent renoprotective benefits by reducing proteinuria and delaying diabetic kidney disease.42 43 Dapagliflozin, empagliflozin, and ertugliflozin are currently not licensed for eGFR less than 45 mL/min/1.73 m2

Dipeptidyl Peptidase-4 Inhibitors

Many dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, vildagliptin) rely on kidney excretion and require significant dose reduction in CKD. No dose adjustment is required for linagliptin.

Glucagon-Like Peptide-1 Receptor Agonists

Several glucagon-like peptide 1 analogs (dulaglutide, liraglutide, semaglutide) may be used without dose adjustment even in severe CKD. However, exenatide should be used with caution when eGFR is less than 45 mL/min/1.73 m2 and is not recommended when eGFR is less than 30 mL/min/1.73 m2

Thiazolidinediones

Thiazolidinediones are extensively metabolized and excreted in bile. Their pharmacokinetics are not significantly altered by CKD and in fact show reduced exposure, possibly because of reduced protein binding. However, they can cause fluid retention and edema, exacerbating the difficulties of fluid management and heart failure and are generally best avoided in CKD. Thiazolidinediones have been associated with dilutional anemia because of an increase in plasma volume, which may complicate management of the anemia associated with CKD.

DRUGS FOR THYROID DISORDERS

Thyroid hormones generally do not require dose alteration in CKD.44 Doses should be initiated and titrated to thyroid-stimulating hormone levels and clinical effect. In circulation, thyroxine (T4) is 99.98% protein bound (0.02% free), and triiodothyronine (T3) is 99.8% bound (0.2% free). T3 and T4 bind partially, in slightly different proportions, to three different plasma proteins: thyroid-binding globulin, thyroid-binding prealbumin, and albumin. In protein-deficient states (e.g., nephrotic syndrome), there is the possibility of transient or permanent changes in thyroid hormone protein binding that may alter the free fraction of T3 and T4, leading to transient toxicity. Uremic toxins can inhibit enzymes associated with conversion of T4 to T3. Oral absorption of thyroid hormones is affected by coadministration with metallic phosphate binders and iron. Euthyroid patients with CKD may have abnormal thyroid function test results, possibly because of decreased peripheral conversion of T4 to T3, decreased clearance of reverse T3 generated from T4, or decreased binding of thyroid hormones to proteins. Antithyroid (carbimazole and propylthiouracil) can be used at usual doses.

MINERAL AND BONE DISORDERS

Prescribing for these disorders is further discussed in Chapter 88.

Phosphate Binders

Phosphate binders should be taken with meals for maximal efficacy. Patients can be educated to adjust phosphate binder dose to the phosphate content in each meal. Doses are not affected by kidney function, except that the requirement for phosphate binders tends to increase as GFR declines. Dosage is based on plasma phosphate concentration and the need to avoid biochemical abnormalities. Acid suppression may reduce the effectiveness of some phosphate binders but not sucroferric oxyhydroxide. Phosphate binders also may reduce gastrointestinal absorption of drugs, including thyroid hormones, fluoroquinolones, tetracyclines, digoxin, and immunosuppressants.

Vitamin D

In patients with CKD, inability of the kidneys to convert 25-hydroxycholecalciferol to the active 1,25 dihydroxycholecalciferol (calcitriol) may produce relative vitamin D deficiency and hypocalcemia, which requires treatment with the active vitamin D preparations calcitriol, paricalcitol, or alfacalcidol.

Calcimimetics

Cinacalcet dosage is independent of kidney function. When possible, cinacalcet should be administered with the evening meal to improve absorption and minimize side effects. Similarly, morning blood samples for parathyroid hormone levels should be drawn at least 12 hours after administration. Cinacalcet and etelcalcetide (a calcimimetic for parenteral use), are further discussed in Chapter 90.

DYSPEPSIA, GASTROESOPHAGEAL REFLUX DISEASE, AND PEPTIC ULCERS

Proton pump inhibitors, histamine-2 (H2) receptor blockers, and antacids are commonly used in patients with CKD (see Chapter 90).

Antacids

Alginates, magnesium trisilicate, and sodium bicarbonate are useful for symptom control, but the latter has high sodium content, which exacerbates hypertension and fluid status. Magnesium and aluminum salts can reduce the absorption of mycophenolate. Aluminum salts were widely used in the past as phosphate binders but are now often avoided in patients with advanced CKD due to the toxicity from absorbed aluminium (especially encephalopathy and bone toxicity).

H2 Antagonists

Most H2 antagonists are removed by the kidney but are relatively safe, so dose reduction is usually not required.[45] Protein binding and VD are unaltered; however, the bioavailability of nizatidine is reduced in CKD. Cimetidine should be avoided because accumulation produces CNS effects, and it causes significant interactions through the CYP450 system and falsely elevates serum creatinine levels.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are generally safe and well tolerated even at normal doses, although they have been associated with interstitial nephritis as well as with increased risk for CKD. As such, subjects with CKD should be evaluated for their need of PPIs or switched to H2 antagonists if possible.

ANTIEMETICS

Dopamine Antagonists

Domperidone, metoclopramide, and prochlorperazine are not significantly removed by the kidney; however, extrapyramidal and CNS effects may occur in CKD as well as QT prolongation, especially at high doses. Domperidone does not cross the blood-brain barrier and may be preferable for long-term management. Metoclopramide and domperidone increase gastric emptying, which may alter drug pharmacokinetics.

5-HT3 Antagonists

Most 5-HT3 antagonists are minimally excreted in urine and have a wide therapeutic window. Dolasetron, granisetron, ondansetron, and tropisetron are safe, and dose modification is not required.

APERIENTS AND LAXATIVES

Adequate fluid intake is important for normal bowel function, and fluid restrictions required in many end-stage kidney disease (ESKD) and dialysis patients are frequently accompanied by constipation as a consequence. Common low-potency agents, including docusate, bisacodyl, glycerin, lactulose, liquid paraffin, senna, and sorbitol, may be used for acute or chronic constipation. Normal doses should be titrated to effect while avoiding significant dehydration, fluid shifts, or electrolyte disturbances. High-potency laxatives and bowel preparations should be used cautiously, as they may cause significant fluid and electrolyte disturbances. Preparations containing high amounts of phosphate should be avoided. Despite the large fluid volumes required for administration, isoosmotic laxatives may be used for bowel preparation in patients with CKD and dialysis.

ANTIDIARRHEALS

Opioids or their derivatives should be used with the same caution as when they are used as analgesics. Loperamide and diphenoxylateatropine can be given in usual doses.

DRUGS FOR ERECTILE DYSFUNCTION

Phosphodiesterase-5 Inhibitors

The AUCs of sildenafil (2-fold), tadalafil (4-fold), and vardenafil (20%–30%) are increased in patients with severe CKD despite minimal dependence on kidney excretion. However, provided that relevant CV and drug contraindications are excluded, they can be used safely. They should be initiated at low doses and titrated to response. Shorteracting agents (sildenafil and vardenafil) may be preferable. Vardenafil can prolong the QT interval.

MUSCULOSKELETAL DRUGS

Nonsteroidal Antiinflammatory Drugs

NSAIDs can cause significant nephrotoxicity and should be avoided or used with extreme caution in patients with CKD.

Miscellaneous Arthritis Drugs

Gold salts and penicillamine are now rarely used for rheumatoid arthritis. Both were associated with nephrotic syndrome caused by membranous nephropathy. Glucosamine and fish oil can be used safely.

Gout and Hyperuricemia

Gout is common in CKD due to the impaired ability to remove urate.
In acute therapy, short courses of oral corticosteroids are safe and preferable to NSAIDs. Colchicine accumulation in CKD may cause diarrhea and hypoperfusion-induced CKD, as well as myelosuppression, and dosing should be reduced. In maintenance therapy, allopurinol is effective but should be initiated in low doses (50-100 mg/day) and then slowly increased over weeks, as initiation with higher disease has been associated with the allopurinol hypersensitivity syndrome (a StevensJohnson–like syndrome). The toxicity is greater in subjects who carry the HLA-B*58-01 allele, which is more common in Chinese (Han) and Korean peoples. Oxypurinol (the active metabolite) can also accumulate in patients with low GFR.46 Despite this, some patients with ESKD require and tolerate normal doses. Febuxostat is another xanthine oxidase inhibitor that is not affected by decreased kidney function but was associated with a higher risk for CV mortality than allopurinol in the CARES trial, although more recent studies did not confirm this finding. Allopurinol and febuxostat significantly interacts with azathioprine with a risk for severe myelosuppression. If the combination is unavoidable, the azathioprine dose should be reduced by 75% and blood counts monitored carefully. Uricosuric agents (e.g., probenecid) inhibit secretion of acids in the proximal tubule and prevent reabsorption of uric acid from the tubular lumen. They often become ineffective with diminishing kidney function and are best avoided if GFR is less than 40 mL/min/1.73 m2. Probenecid also interferes with the tubular secretion of many drugs, thereby increasing plasma concentrations.

Bisphosphonates

Bisphosphonates are extensively excreted in urine. The fraction not excreted is incorporated into bone, from which it slowly dissociates. In CKD, impaired clearance of the absorbed drug may increase the fraction available for incorporation into bone. The long terminal elimination half-life of these agents reflects rate-limiting dissociation from bone and may not be significantly altered in patients with CKD. Oral bisphosphonates appear to be safe in CKD stages 2 and 3. Their safety in CKD stages 4 and 5 is less well established, and they are contraindicated in adynamic bone disease. Rapid administration of intravenous bisphosphonates (pamidronate and zoledronic acid) without hydration has been associated with acute nephrotoxicity. Intravenous preparations should be administered slowly with hydration and kidney function assessed regularly. Oral bisphosphonate administration may be complicated by the volumes of fluid recommended. In addition, many patients with CKD are taking calcium-based phosphate binders or supplements that impair the absorption of oral bisphosphonates.

Intracavernosal Therapy

ANTIEPILEPTICS

Drugs given directly by intracavernosal injection do not achieve significant concentrations in the systemic circulation and can be used in patients with CKD.

Patients with CKD may be more prone to seizures (e.g., uremic encephalopathy and dialysis disequilibrium syndrome) and to the CNS effects of antiepileptics. Some antiepileptics (especially gabapentin and levetiracetam) are primarily cleared via the kidneys, and dose modification is essential. Some antiepileptics (barbiturates, phenytoin, and carbamazepine) are strong inducers of drug-metabolizing enzymes. Coadministration with drugs reliant on hepatic metabolism (e.g., immunosuppressants) can reduce exposure and efficacy of the concomitant drug. Therapeutic drug monitoring is available for many antiepileptics and should be used to guide dosage.

Benzodiazepines

See the “Psychotropic Drugs” section.

Carbamazepine

Carbamazepine is administered as normal and titrated to response and blood concentrations. It is a potent enzyme inducer, and care must be taken to account for important drug interactions.

Phenytoin

Caution should be exercised with phenytoin in CKD because of its erratic absorption, saturable metabolism, nonlinear pharmacokinetics, reduced protein binding, and increased VD. The concentration of free drug may be higher than in normal kidney function due to displacement from protein binding sites by uremic toxins. Ideally, the unbound (active) concentration of phenytoin should be assayed. A low total serum phenytoin level in CKD should not be mistaken as subtherapeutic and a reason to increase the dose. Nystagmus, cerebellar ataxia, and seizures can occur in overdose. Cautious titration based on effect and monitoring of free concentration is advised. Phenytoin is a potent enzyme-inducing agent, and care must be taken to account for drug interactions.

Other Antiepileptics

Levetiracetam, topiramate, and vigabatrin undergo significant kidney excretion, and dose modification is required. Valproate and lamotrigine are not significantly excreted by the kidney and do not cause enzyme induction or inhibition. Protein binding changes can increase the free fraction of valproic acid, predisposing to increased responsiveness.

effects (especially CNS effects).47 Slow titration and dose modifications are required. Adverse effects are not easily distinguished from symptoms of uremia. Despite being metabolized extensively by CYP450 enzymes, very few psychotropics cause clinically significant inhibition or induction of CYP3A4.

Selective Serotonin Reuptake Inhibitors

Most selective serotonin reuptake inhibitors (SSRIs) are extensively metabolized to compounds without significant SSRI activity.48 Normal doses of citalopram, fluvoxamine, paroxetine, and sertraline can be used with cautious dose titration. Fluoxetine is metabolized to an active metabolite (norfluoxetine), but single- and multiple-dose studies have shown little change in pharmacokinetics, even in dialysis patients. Patients with CKD may be more prone to the CNS toxicity of SSRIs and serotonin syndrome. SSRIs can cause the syndrome of inappropriate antidiuretic hormone secretion and platelet aggregation or hemorrhagic complications, which may increase the risk for bleeding in uremic patients who are already prone to bleeding complications. Although most SSRIs have some inhibitory effect on CYP3A4, this is usually not significant. Fluoxetine and fluvoxamine are more likely to interact than citalopram and sertraline, but all can be used in patients taking immunosuppressants. Cinacalcet can cause significant inhibition of CYP2D6-mediated metabolism of SSRIs and perhexiline. This may increase the possibility of serotonin syndrome or perhexiline toxicity, though this risk can be mitigated by extra monitoring.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are now infrequently used for depression but more for neuropathic pain and sleep, and their anticholinergic properties in urinary tract disorders. They are predominantly metabolized to metabolites with varying activity. Patients with CKD may be more prone to the common anticholinergic adverse effects, particularly urinary retention, orthostatic hypotension, confusion, and sedation.49 Some including amitriptyline can also prolong QT interval. Obstructive uropathy can occur from the anticholinergic properties. Cautious initial doses and titration of TCAs are recommended. Depending on response, many agents can be used at up to normal or maximal doses.

ANTIPARKINSONIAN DRUGS

Monoamine Oxidase Inhibitors

In addition to their use for Parkinson disease and hyperprolactinemia disorders, dopaminergic drugs are used to treat restless legs and other limb movement disorders in patients with CKD. Most are hepatically cleared and safe, although dopaminergic agents may exacerbate postural hypotension. Amantadine is highly dependent on kidney excretion, and dose modification is essential.

Monoamine oxidase inhibitors (MAOIs) are extensively metabolized by the liver. Although they are now rarely used, normal doses of reversible MAOIs (moclobemide) are preferred and can be titrated cautiously to full doses. MAOIs can cause peripheral edema, which is not usually associated with fluid retention and is unresponsive to diuretics. Prostatic hypertrophy and urinary retention also may occur.

ANTIMIGRAINE DRUGS

Simple analgesics (acetaminophen) are used as normal, although aspirin should be avoided at analgesic doses and opioids used cautiously (see discussion of analgesics). NSAIDs are best avoided because of potential nephrotoxicity. 5-HT1 agonists are effective in patients with CKD and transplantation. Naratriptan relies the most on kidney excretion (50%), and a lower maximum dose is recommended. Sumatriptan and zolmitriptan are preferred because they are less dependent on kidney excretion.

PSYCHOTROPIC DRUGS

Most psychotropics are fat soluble and nondialyzable, undergo significant hepatic metabolism, and are excreted as inactive compounds. Even so, kidney patients are often more susceptible to common adverse

Other Antidepressants

Venlafaxine dose should be initially reduced in patients with severe CKD because of reduced clearance of the active metabolite Odesmethylvenlafaxine and the potential for hypertension. Nefazodone is used at a normal dose.

Antipsychotics

Conventional antipsychotics cause a variety of side effects to which patients with CKD may be susceptible (sedation, confusion, and postural hypotension). Caution is advised for atypical antipsychotics that prolong the QT interval (e.g., pimozide, thioridazine, mesoridazine, droperidol, and ziprasidone). Newer atypical agents are more commonly used and better tolerated. Clozapine, olanzapine, quetiapine, and aripiprazole are commenced at normal doses and titrated to response. The clearances of risperidone and its active metabolite 9-hydroxyrisperidone are reduced by 60% in severe CKD. Lithium is

filtered and reabsorbed mainly in the proximal tubule. It has extensive kidney clearance and accumulates even in mild CKD, causing toxicity, and should be used with increased plasma monitoring if required.
Lithium is handled by the body like sodium, and any drug that affects plasma sodium concentration will likely affect plasma lithium concentration. Such drugs include diuretics that increase sodium loss, and the kidney “compensates” by retaining lithium and NSAIDs. HD is efficient in removal of lithium and can be used in overdose; however, multiple dialysis treatments are usually required because plasma concentrations rebound soon after HD. Chronic lithium nephrotoxicity is discussed further in Chapter 65

Benzodiazepines

Benzodiazepines are extensively metabolized by the liver to a range of active and inactive metabolites. Enhanced CNS toxicity, especially sedation, is the main concern in kidney patients. Because of the potential for accumulation, chronic use should be discouraged. Shorter-acting benzodiazepines are preferred, and the dose should be titrated cautiously according to response. The dose of midazolam should be reduced because of changes in plasma protein binding. Hemoperfusion and dialysis are not useful in patients with benzodiazepine intoxication. Flumazenil may be used as an antidote in patients with overdose, at doses similar to those with normal kidney function.

ANEMIA DRUGS

Erythropoiesis-Stimulating Proteins

The pharmacokinetics of erythropoiesis-stimulating agents (ESAs) are not affected by kidney function per se. However, as kidney function decreases, dose requirements may increase to account for reduced endogenous erythropoietin production. Use of ESAs is discussed in detail in Chapter 86

Iron Therapy

Oral supplements may be sufficient in early-stage CKD or PD patients who do not have the same degree of regular blood loss as HD patients. The most iron that can be absorbed from the gut is likely approximately 20 mg/day, and many iron tablets contain much more than this (generally 80–100 mg). Patients with severe iron deficiency

including those on HD often require intravenous supplementation (see Chapter 86).

ANTIHISTAMINES

Normal doses of sedating antihistamines generally can be used. They should be used cautiously in patients with bladder outflow obstruction because of their anticholinergic adverse effects that may cause or aggravate urinary frequency or retention. Newer, less sedating antihistamines are better tolerated and have a wider therapeutic window, and accumulation rarely causes significant complications. Cetirizine relies more on kidney clearance, and dose reduction is suggested. Loratadine and desloratadine have active metabolites but are safe. Fexofenadine is safe; however, terfenadine should be avoided because of the risk for arrhythmias.

VACCINES

Live vaccines (BCG [bacillus Calmette-Guérin], oral poliovirus, rubella, typhoid, yellow fever, and varicella) in immunosuppressed patients are contraindicated because of the potential for causing disease. Attenuated vaccines (diphtheria-tetanus, hepatitis B, influenza, meningococcal, and pneumococcal) may be used, but impaired response in immunocompromised individuals may lead to inadequate protection. Hepatitis B may need more doses for seroconversion to be achieved in patients on HD. Immunization should preferably occur at least 1 month before initiation of immunosuppression. After transplantation, the immune response may be inadequate for at least 6 to 8 months, meaning that vaccination should be withheld until then.50

VITAMIN SUPPLEMENTATION

Patients with CKD may become vitamin deficient as a result of poor dietary intake and the effect of dialysis on removal of watersoluble vitamins. Administration of vitamin supplements (B, C, and folic acid) is recommended after dialysis. In contrast, liposoluble vitamin A (retinol, beta-carotene) may accumulate in patients on dialysis, causing hypervitaminosis A, and supplementation is not required.51

SELF-ASSESSMENT QUESTIONS

1. Which of the following drugs require(s) clinically significant dose modification in patients with significantly reduced kidney function?
A. Enoxaparin
B. Gabapentin
C. Amoxicillin
D. Amlodipine
E. Famciclovir
2. Which of the following drugs is/are the most likely to cause clinically significant drug interactions with calcineurin inhibitors?
A. Fluconazole
B. Clarithromycin
C. Vancomycin
D. Acyclovir
E. Roxithromycin

3. Which of the following drugs require(s) dose modifications in chronic kidney disease because of a metabolite that is substantially removed by the kidney?
A. Olanzapine
B. Allopurinol
C. Atenolol
D. Amlodipine
E. Pethidine (meperidine)
4. Which of the following drugs is/are likely to be removed by hemodialysis and should therefore be dosed after dialysis?
A. Pregabalin
B. Amiodarone
C. Levetiracetam
D. Pantoprazole
E. Acyclovir

REFERENCES

1. Cervelli MJ, ed. The Renal Drug Reference Guide. Adelaide: MJC Pharma; 2007. www.renaldrugreference.com.au.
2. Ashley C, Dunleavy A, eds. The Renal Drug Handbook. 5th ed. Oxford: CRC Press; 2018. https://renaldrugdatabase.com.
3. Aronoff GR, Berns JS, Brier ME, et al., eds. Drug Prescribing in Renal Failure (Dosing Guidelines for Adults and Children). 5th ed. Philadelphia: American College of Physicians; 2007.
4. Johnson CA. Dialysis of Drugs. Verona, WI: CKD Insights; 2009.
5. Kurella M, Bennett WM, Chertow GM. Analgesia in patients with ESRD: a review of the available evidence. Am J Kidney Dis. 2003;42:217–228.
6. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004;28:497–504.
7. Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. J Emerg Med. 1995;13:797–802.
8. Mirkov S. Reducing clinical risks associated with the pharmacological treatment of acute gout attacks. Drugs Ther Perspect. 2018;34:377–385.
9. Perazella M, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. Am J Med. 2001;111:64–67.
10. Blum RA, Comstock TJ, Sica DA, et al. Pharmacokinetics of gabapentin in subjects with various degrees of renal function. Clin Pharmacol Ther. 1994;56:154–159.
11. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol. 2003;43:277–283.
12. St Peter WL, Redic-Kill KA, Halstenson CE. Clinical pharmacokinetics of antibiotics in patients with impaired renal function. Clin Pharmacokinet. 1992;22:169–210.
13. Decker BS, Molitoris BA. Manifestations of and Risk Factors for Aminoglycoside Nephrotoxicity. UpToDate; 2009.
14. Mirkov S, Lyseng-Williamson KA. Appropriate drug dosages in obese patients. Drugs Ther Perspect. 2018;34:344–349.
15. Ahern JW, Possidente CJ, Hood V, Alston WK. Cefazolin dosing protocol for patients receiving long-term hemodialysis. Am J Health Syst Pharm. 2003;60:178–181.
16. Kroll MH, Hagengruber C, Elin RJ. Reaction of picrate with creatinine and cepha antibiotics. Clin Chem. 1984;30:1664–1666.
17. Fillastre JP, Leroy A, Moulin B, et al. Pharmacokinetics of quinolones in renal insufficiency. J Antimicrob Chemother. 1990;26(suppl B):51–60.
18. Decker BS, Molitoris BA. Vancomycin dosing and serum concentration monitoring in adults. UpToDate. Online 2009; version 17.1.
19. Phillips ME, Eastwood JB, Curtis JR, et al. Tetracycline poisoning in renal failure. Br Med J. 1974;5:149–151.
20. Dijkmans BA, van Hooff JP, de Wolff FA, Mattie H. The effect of cotrimoxazole on serum creatinine. Br J Clin Pharmacol. 1981;12:701–703.
21. Launay-Vacher V, Izzedine H, Deray G. Pharmacokinetic considerations in the treatment of tuberculosis in patients with renal failure. Clin Pharmacokinet. 2005;44:221–235.
22. Czock D, Scholle C, Rasche FM, et al. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. Clin Pharmacol Ther. 2002;72:142–150.
23. Karie S, Launay-Vacher V, Janus N, et al. Pharmacokinetics and dosage adjustment of oseltamivir and zanamivir in patients with renal failure. Nephrol Dial Transplant. 2006;21:3606–3608.
24. Jones TE. Oseltamivir - current dosing recommendations reduce the therapeutic benefit in patients with mild to moderate kidney function and/or large body mass: a review of the literature with recommendations to optimize dosing, including the use of therapeutic drug monitoring. Ther Drug Monit. 2021;43(1):103–107.
25. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24:330–350.
26. Morris RG. Immunosuppressant drug monitoring: is the laboratory meeting clinical expectations? Ann Pharmacother. 2005;39:119–127.

27. Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4:481–508.
28. Ibrahim RB, Liu C, Cronin SM, et al. Drug removal by plasmapheresis: an evidence-based review. Pharmacotherapy. 2007;27:1529–1549.
29. Hendrayana T, Wilmer A, Kurth V, Schmidt-Wolf IG, Jaehde U. Anticancer dose adjustment for patients with kidney and hepatic dysfunction: from scientific evidence to clinical application. Sci Pharm. 2017;85(1):8.
30. Zhao D, et al. Dose adjustment for tyrosine kinase inhibitors in non-small cell lung cancer patients with hepatic or kidney function impairment (Review). Oncol Rep. 2020.
31. Grand'Maison A, Charest AF, Geerts WH. Anticoagulant use in patients with chronic renal impairment. Am J Cardiovasc Drugs. 2005;5:291–305.
32. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. J Am Soc Nephrol. 2002;13:798–805.
33. Carter BL. Dosing of antihypertensive medications in patients with renal insufficiency. J Clin Pharmacol. 1995;35:81–86.
34. Thomas MC. Diuretics, ACE inhibitors and NSAIDs—the triple whammy. Med J Aust. 2000;172:184–185.
35. McDonald SP, Russ GR. Associations between use of cyclosporinsparing agents and outcome in kidney transplant recipients. Kidney Int. 2002;61:2259–2265.
36. Jones TE, Morris R, Mathew TH. Diltiazem-cyclosporin pharmacokinetic interaction – dose response relationship. Br J Clin Pharmacol. 1997;44:499–504.
37. Strippoli GFM, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. Br Med J. 2008;336:645–651.
38. Management of diabetes in chronic renal failure. Indian J Nephrol. 2005;15(suppl 1):S23–S31.
39. Yale JF. Oral antihyperglycemic agents and renal disease: new agents, new concepts. J Am Soc Nephrol. 2005;16:S7–S10.
40. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006;25:CD002967.
41. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea induced hypoglycemia in diabetic patients with end stage renal disease. Am J Kidney Dis. 2000;35:500–505.
42. Toto RD. SGLT-2 inhibition: a potential new treatment for diabetic kidney disease? Nephron. 2017;137:64–67.
43. Kelly MS, Lewis J, Huntsberry AM, et al. 'Efficacy and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease'Postgrad. Med. 2019;131(1):31–42.
44. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol. 2009;160:503–515.
45. Manlucu J, Tonelli M, Ray JG, et al. Dose-reducing H2 receptor antagonists in the presence of low glomerular filtration rate: a systematic review of the evidence. Nephrol Dial Transplant. 2005;20:2376–2384.
46. Day RO, Graham GG, Hicks M, et al. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46:623–644.
47. Cohen LM, Tessier EG, Germain MJ, Levy NB. Update on psychotropic medication use in renal disease. Psychosomatics. 2004;45:34–48.
48. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet. 1997;32(suppl 1):1–21.
49. Lieberman JA, Cooper TB, Suckow RF, et al. Tricyclic antidepressant and metabolite levels in chronic renal failure. Clin Pharmacol Ther. 1990;37:301–307.
50. Cohn J, Blumberg EA. Immunizations for renal transplant candidates and recipients. Nat Clin Pract Nephrol. 2009;5:46–53.
51. Kosmadakis G, Correia E, Carceles O, et al. Vitamins in dialysis: who, when and how much? Kidney Failure. 2014;36(4):638–650.

79

Herbal and Over-the-Counter Medicines and the Kidney

Mark S. Segal, Xueqing Yu

The use of herbal medicines and dietary supplements continues to increase globally. An estimated one-third of adults in wealthy countries and more than 80% of the population in many low- and middleincome countries use herbal and folk medicines to promote health and manage a number of common maladies, such as colds, hay fever, indigestion, and constipation, as well as liver cirrhosis, cancer, heart disease, acquired immunodeficiency syndrome (AIDS), and diabetes.1

With the expanding legalization of medicinal and recreational marijuana, this use is poised to increase even further. In Africa, up to 80% of the population depends on traditional medicine for primary health care; in China, herbal preparations account for up to 50% of the total consumption of pharmaceutical agents; and there has been a surge in the popularity of herbal medicine in the West. For instance, the U.S. herbal medicine market increased from $1.6 billion in 1994 to $9.6 billion in 20191 2; complementary and alternative medicines, including Chinese herbal medicines and herbal plants, have been used by about 50% of Australians.1

Germany and France are the leaders in sales of over-the-counter (OTC) herbal medicines in Europe and also have large markets for prescription herbal preparations (Fig. 79.1).3 The European Union has taken steps to regulate herbal remedies with the Traditional Herbal Medicinal Products Directive (also known as Directive 2004/24/EC), which was implemented in May of 2011. This mandates that all herbal medicinal products must obtain an authorization to market within the European Union and that herbal medicines must be manufactured under Good Manufacturing Practice.

There are at least 11,000 species of plants for medicinal use, and about 500 of them are commonly used by various ethnic groups.1 4 These herbal plants may be used either in their primary forms or in mixtures. However, the source and composition of botanical medicines vary depending on the prevalent local practices. Herbal remedies are not tested for efficacy and safety, their ingredients are largely unknown, and there is no standardization of dosage and route of administration. Organ toxicity caused by traditional medicines is directly related to a combination of poor education, poverty, lack of medical facilities, weak or absent legislation, and widespread belief in indigenous systems of medicine in rural areas. Problems related to herbal medicines arise as a result of intrinsic toxicity, adulteration, contamination, substitution, misidentification, mistaken labeling, and unfavorable herb-drug interactions.1 4

Increasing evidence for both adverse drug reactions and poisoning events associated with the use of herbal medicines has been reported worldwide. Herbal medicines have been found to be adulterated with synthetic drugs and other potentially toxic compounds. On the other hand, coadministration of herbal medicines with conventional drugs raises the potential for herb-drug interactions, which may cause altered drug elimination, undertreatment, and/or toxicity.1 4 5

HERBAL MEDICATIONS AND THE KIDNEY

The kidneys are particularly vulnerable to toxic injury because of their high blood flow rate, large endothelial surface area, high metabolic activity, active uptake by tubular cells, medullary interstitial concentration, and low urine pH. Kidney tubules are involved in active transport and urinary concentration, and therefore the local concentration of these toxins is potentially high, leading to direct injury to tubular cells. Herbal medicines may be nephrotoxic via one or more common pathogenic mechanisms, including alterations in intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Furthermore, potentially nephrotoxic exogenous substances such as paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulfate, and potassium permanganate are often added to herbal compounds. Drug-related nephrotoxicity is becoming more common, as more people have comorbidities that require multiple medications and more diagnostic and therapeutic procedures, all with the potential to harm kidney function. Patient-related risk factors for drug-induced nephrotoxicity include age greater than 60 years, underlying glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2, volume depletion, diabetes, heart failure, and sepsis.6 These same risk factors also may make individuals susceptible to kidney toxicity from herbal medicines.

An overview of the potential kidney side effects of herbal medicines is shown in Table 79.1

ARISTOLOCHIC ACID NEPHROPATHY

Aristolochic Acids

Aristolochic acids (AAs) are a family of structurally related nitrophenanthrene carboxylic acids found in herbal medicines such as Aristolochia spp., including A. fangchi, A. clematitis, and A. manshuriensis (Table 79.2). The predominant AAs are AAI (8-methoxy-6-nitro-phenanthro-[3,4-d]-1,3-dioxolo-5-carboxylic acid) and AAII (6-nitro-phenanthro-[3,4-d]-1,3-dioxolo-5-carboxylic acid). AAs are activated by human NAD(P)H:quinone oxidoreductase (NQO1)7 and react with DNA to form covalent 7-(deoxyadenosin-N6-yl)aristolactam I (dA-AA) and 7-(deoxyguanosin-N2-yl)aristolactam(dG-AA) adducts. These aristolactam adducts are mutagenic.8 After even a single dose, AAI is stably detected in the kidneys. Human aristolochic acid nephropathy (AAN) is reproducible in rodents with AA intoxication, resulting in tubular atrophy and interstitial fibrosis, leading to kidney failure.9 The progressive tubular atrophy is related to impaired regeneration and apoptosis of proximal tubular epithelial cells, which is considered a possible mechanism of tubular epithelial cell deletion. The resident fibroblast activation plays a critical role in the process of kidney fibrosis during AA toxicity.10 The nephrotoxic and carcinogenic

Distribution of Over-the-Counter
Herbal Medicine Use in Europe
2.06 billion

Germany
France

1.13 bilion

Italy

543 million

Poland

252 million

United Kingdom

211 million

Spain

170 million

TABLE 79.2 Botanicals Known or
Suspected to Contain Aristolochic Acid and
Their Common Names
Botanical Name

Common or Other Names

Aristolochia spp.

Aristolochia, Guan Mu tong, Guang Mu
tong
Oval leaf Dutchman’s pipe

Aristolochia acuminata (syn. A.
tagala)
Aristolochia bracteata
Aristolochia clematitis
Aristolochia contorta

Switzerland

93 million

Austria

88 million

Aristolochia cymbifera
Aristolochia debilis (syn. A.
longa, A. recurvilabra, A.
sinarum)

The Netherlands

81 million

Aristolochia fangchi

Czech Republic

76 million

Belgium

127 million

Sales of over-the-counter herbal medicines (U.S. dollars)

Fig. 79.1 Distribution of the $4.96 billion European market for overthe-counter herbal medicines in 2003. (Data from De Smet PA. Herbal medicine in Europe—relaxing regulatory standards. N Engl J Med. 2005;352:1176–1178.)

Kidney Syndromes Induced by Herbal Medicines

TABLE 79.1
Syndrome

Herbal Medicine

Hypertension

Glycyrrhiza spp. (Chinese herbal teas, gancao, boui-ougi-tou)
Ephedra spp. (ma huang)
Traditional African medicine: toxic plants (Securidaca longepedunculata, Euphoria matabelensis, Callilepis laureola, Cape aloes), or adulteration by dichromate
Chinese medicine: Taxus celebica
Morocco: Takaout roumia (paraphenylenediamine)
Peruvian medicine (Uña de Gato)
Tung Shueh pills (adulterated by mefenamic acid)
Chinese herbs containing AAs (Akebia spp., bouiougi-tou, Mokutsu)
Chinese herbs adulterated by cadmium
Chinese herbs adulterated by phenylbutazone
Chinese herbs or Kampo containing AAs (Aristolochia spp., Akebia spp., Mu Tong, Boui, Mokutsu)
Datura spp., Rhododendron molle (atropine, scopolamine)
Ma huang (ephedrine)
Cranberry juice (oxalate)
Chinese herbs containing AAs

Acute tubular necrosis

Acute interstitial nephritis
Fanconi syndrome

Papillary necrosis
Chronic interstitial kidney fibrosis
Urinary retention
Kidney stones
Urinary tract carcinoma

AA, Aristolochic acids.
From Isnard Bagnis C, Deray G, Baumelou A, et al. Herbs and the

kidney. Am J Kidney Dis. 2004;44:1–11.

Ukulwe
Birthwort
Ma Dou Ling (fruit), Bei Ma Dou Ling (root),
Tian Xian Teng (herb)
Mil homens
Ma Dou Ling (fruit), Tian Xian Teng (herb),
Qing Mu Xiang (root), Sei-Mokkou
(Japanese), Birthwort, Long birthwort,
Slender Dutchman's pipe
Guang Fang ji (root), Fang ji, Fang
chi, Makuboi (Japanese), Kou-boui
(Japanese), Kwangbanggi (Korean)
Han Fang Ji
Indian birthwort (root), Yin Du Ma Dou Ling
Yellowmouth Dutchman's pipe, Zhu Sha
Lian

Aristolochia heterophylla
Aristolochia indica
Aristolochia kaempferi (syn.
A. chrysops, A. feddei, A.
heterophylla, A. mollis, A.
setchuenensis, A. shimadai, A.
thibetica, Isotrema chrysops,
Isotrema heterophylla,
Isotrema lasiops)
Aristolochia macrophylla (syn.
Dutchman's pipe
A. sipho)
Aristolochia manshuriensis (syn. Manchurian birthwort, Manchurian
Hocquartia manshuriensis,
Dutchman's pipe (stem), Guan Mutong
Isotrema manshuriensis)
(stem), Kan-Mokutsu (Japanese),
Mokubai (Japanese), Kwangbanggi
(Korean)
Aristolochia maxima (syn.
Maxima Dutchman's pipe, Da Ma Dou Ling
Howardia hoffmannii)
Aristolochia mollissima
Wooly Dutchman's pipe, Mian Mao Ma
Dou Ling
Aristolochia moupinensis
Moupin Dutchman's pipe, Huai Tong
Aristolochia sarpentaria (syn. A. Virginia snakeroot, Serpentaria, Virginia
serpentaria)
serpentary
Aristolochia triangularis
Triangular Dutchman's pipe, San Jiao Ma
Dou Ling
Aristolochia tuberosa
Tuberous Dutchman's pipe, Kuai Jing Ma
Dou Ling
Aristolochia tubiflora
Tubeflower, Dutchman's pipe, Guan Hua
Ma Dou Ling
Aristolochia versicolar
Versicoloraus Dutchman's pipe, Bian Se
Ma Dou Ling
Asarum canodense (syn. A.

Wild ginger, Indian ginger, Canada
acuminatum, A. ambiguum,
snakeroot, false coltsfoot, colic root,
A. canadense, A. furcatum,
heart snakeroot, Vermont snakeroot,
A. medium, A. parvifolium, A.
Southern snakeroot, Jia Na Da Xi Xin
reflexum, A. rubrocinctum)
Asarum himalai(y)cum
Tanyou-saishin (Japanese)
Asarum splendens
Do-saishin (Japanese)

From Djukanović L, Marinković J, Marić I, et al. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol Dial Transplant. 2008;23(12):3932–3938.

Fig. 79.2 Traditional Chinese Pharmacy. A pharmacy selling traditional herbal remedies (left) including Fang Chi (right). The true incidence of aristolochic acid nephropathy (AA) is largely unknown and probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in India and Eastern Asia. (From Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: A worldwide problem. Kidney Int. 2008;74:158–169.)

effects of AAs have been reported in animals; exposure to AA causes a progressive interstitial fibrosis associated with urothelial malignancy. Similar toxicities are observed in humans.

Aristolochic Acid Nephropathy

The association of kidney disease with long-term consumption of A. fangchi was first reported in Belgium in nine young women taking slimming preparations.11 Since then there have been case reports and series from around the world.12 Even though this disease may affect millions worldwide, high-quality epidemiologic data on the incidence and prevalence of AAN are lacking because of the absence of internationally agreed on diagnostic criteria and low awareness of the disease.12 Increasing evidence supports that it is the AAs in the herbs that are responsible for their kidney toxicity (Figs. 79.2 and 79.3).9 This syndrome was initially referred to as Chinese herb nephropathy and is now known by the more specific, mechanistic name of AAN.13 The kidney toxicity of AA depends on the dosage and the duration of administration.14 It is now clear that Balkan endemic nephropathy (BEN), a condition known for several decades without a known cause, is a form of AAN, in which there is contamination of wheat (flour) by A. clematitis.9

A

Definition

AAN is characterized by tubulointerstitial nephritis that progresses to fibrosis with deterioration of kidney function, ultimately leading to end-stage kidney disease (ESKD), sometimes within months after first exposure. There is a high associated risk for uroepithelial malignancy.

Epidemiology

Soon after its initial description, AAN was recognized as a global health problem.9,11,12,14,15 Since the publication of the index cases, new cases of AAN have been reported, not only in Belgium but also worldwide.9–16 The true incidence of AAN remains unknown and is probably underestimated because numerous ingredients known or suspected to contain AA are used in traditional medicine in China, Japan, and India (see Fig. 79.3).9 AAN affects thousands of people living in discrete areas in Bulgaria, Bosnia, Croatia, Romania, and Serbia along the Danube River basin (Fig. 79.4), and was formerly known as BEN there.15,17 This form of AAN typically presents in the fourth or fifth decade of life and is rarely seen in individuals younger than 20 years, presumably reflecting low-grade chronic exposure to AA.

B

Fig. 79.3 Chinese Herb or Aristolochic Acid Nephropathy. (A) Guang Mu Tong, a Chinese herb that contains aristolochic acids. (B) Extensive paucicellular interstitial fibrosis and tubular atrophy typically found in Chinese herb or aristolochic acid nephropathy. The same pathologic appearances are seen in Balkan endemic nephropathy. (From Debelle

FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008;74:158–169. Courtesy Dr. Bojan Jelaković.)

Areas Where Balkan
Nephropathy Is Prevalent

Austria

Hungary

Slovenia

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Serbia

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Macedonia
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Greec

Fig. 79.4 Areas Where Balkan Nephropathy is Prevalent. The endemic areas are in red. (From Djukanović L, Marinković J, Marić I, et al. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol Dial Transplant. 2008;23[12]:3932–3938.)

Clinical Manifestations

The initial presentation of AAN is usually silent, with the kidney disease only discovered by routine blood testing. Occasional patients present with Fanconi syndrome or with acute kidney injury (AKI) caused by acute tubular necrosis.[18] The urinary sediment is unremarkable, and the urinalysis is initially negative for albuminuria. However, urinary excretion of low molecular weight proteins (e.g., β_2-microglobulin, cystatin C) is markedly increased, and the ratio of urinary low molecular weight protein to albumin is higher than in glomerular diseases.[19]

When there is prospective monitoring in endemic areas, tubular proteinuria is usually the first manifestation. Other manifestations of tubular dysfunction include impaired acidification, decreased ammonia, increased uric acid excretion, and urine-concentrating defects with salt wasting, which may precede the decrease in GFR. The disease progresses to ESKD. Other hallmarks are that the severity of the anemia is disproportionate to the degree of kidney function impairment and that the blood pressure is usually in the normal range until the development of ESKD.

The increased incidence of uroepithelial carcinomas is characteristic of AA exposure. A case series identified upper tract urothelial carcinoma as a potent risk factor for bladder urothelial carcinoma after kidney transplantation for AAN, indicating that long-term follow-up for recurrent malignancy is potentially important (see “Treatment” section).[20]

Pathology

AAN is characterized by extensive interstitial fibrosis and tubular atrophy, which generally decreases in severity from the outer to the inner cortex (see Fig. 79.3). Early in the disease, the glomeruli are relatively spared, although at later stages there is some collapse of the capillaries and wrinkling of the basement membrane. There is endothelial cell swelling with consequent thickening of interlobular and afferent arterioles.[9,21] There are no immune deposits.

Pathogenesis

The striking association between AA exposure and uroepithelial abnormalities was first noted in nephroureterectomy specimens from

individuals with AAN removed at the time of transplantation, demonstrating moderate atypia and atypical hyperplasia (see Fig. 79.3).[9,22] An early and massive interstitial inflammation characterized by activated monocytes and macrophages and cytotoxic CD8+/CD103+ T lymphocytes seen in experimental AAN[23,24] suggests that the pathophysiology includes an immunologic element. The persistence of AA-DNA adducts in the kidneys of the Belgian women cohort is consistent with their postulated role of DNA adducts in urothelial cancer. Of AAN patients, 40% to 45% develop multifocal high-grade transitional cell carcinomas, mainly in the upper urinary tract.[16] There is a strong association between DNA adduct formation, mutation pattern, and tumor development. In animal models, oral ingestion of AA is followed by extensive formation of AA-DNA adducts in the forestomach, accompanied by the development of tumors.20 A genome-wide search in a series of cancers from Taiwan (where a significant fraction of the population is prescribed herbal medicines containing AA) demonstrated the presence of AA-DNA adducts and other DNA signatures of AA exposure in cancers of the upper urinary tract. Of additional concern was the presence of AA-DNA adducts in cancers of the liver and kidney.25 Transitional cell cancers from patients with AAN contain AA and a characteristic pattern of tumor protein 53 (TP53) mutations, 89% occurring at A:T pairs and 78% of these being A:T to T:A transversions. These types of transversions are not seen in transitional cell carcinomas of the renal pelvis in the absence of AA exposure. Molecular epidemiologic evidence relates urothelial carcinoma in patients with AAN to dietary exposure to AA.26

The link between AA and BEN, which confirmed that BEN is a form of AAN, came from the insight that in endemic regions, bread is a dietary staple and is traditionally prepared from flour made from locally grown wheat. The seeds of A. clematitis, a plant native to the region, were found interspersed with the harvested wheat grain, and dA-aristolactam and dG-aristolactam DNA adducts were found in the kidney cortex of patients with BEN but not in those with other chronic kidney diseases (CKDs).26 27 Aristolactam-DNA adducts have been found in 70% of people in endemic areas with dietary exposure to AA and in 94% of patients with specific A:T to T:A mutations in TP53. Neither aristolactam-DNA adducts nor specific mutations were detected in tissues of those from nonendemic regions. Because AAN occurs only in a fraction of those individuals exposed to AA within the endemic region, it is assumed that a genetic susceptibility puts some individuals with a dietary exposure to AA at risk for AAN and urothelial carcinoma.9 12

Diagnosis

Diagnostic criteria for AAN are shown in Box 79.1. An analysis of 182 patients in Serbia showed that proteinuria, urine α1-microglobulin, and kidney size are significant predictors of AAN, whereas kidney failure and several tubular disorders (urine specific gravity, increased fractional sodium excretion, and reduced tubular phosphate reabsorption) had a nonsignificant predictive value.15 28

Treatment

There have been no randomized trials of treatment for AAN. However, a pilot study in 35 AAN patients with CKD demonstrated a significant reduction in the number of patients reaching ESKD after 1 year of corticosteroid therapy.29 Corticosteroid therapy was later confirmed, in a larger cohort with historical controls, to slow the progression of kidney failure.30 It is suggested that corticosteroids, 1 mg/kg of predniso(ol)ne for 4 weeks followed by a maintenance dose of 0.1 mg/kg tapered every 2 weeks, be initiated in those with biopsy-proven AAN (including cases discovered in endemic regions) and estimated GFR (eGFR) greater than 20 mL/min per 1.73 m2. It is recommended to discontinue steroid

Diagnostic Criteria for Aristolochic Acid Nephropathy, Including Balkan Endemic Nephropathy

BOX 79.1

- Epidemiologic pattern
- Known exposure to aristolochic acid–containing medicines or living in endemic Balkan settlements
- Clinical features
- Glomerular filtration rate (GFR) decrease
- Proteinuria usually less than 1 g/24 h
- Bland urinary sediment
- Markers of kidney tubular damage (glycosuria, increased urinary excretion of β2-microglobulin or α1-microglobulin, and N-acetyl-β d glucosaminidase)
- Typical kidney histology showing hypocellular cortical interstitial fibrosis decreasing from the outer to the inner cortex (if kidney biopsy feasible)
- Exclusion of other known kidney disease (e.g., chronic pyelonephritis [obstructive and atrophic], adult dominant polycystic kidney disease, glomerulonephritis)

Modified from Djukanović L, Marinković J, Marić I, et al. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol Dial Transplant. 2008;23(12):3932–3938; and Luciano RL, Perazella MA. Aristolochic acid nephropathy: epidemiology, clinical presentation, and treatment. Drug Saf. 2015;38(1):55–64.

therapy after 6 months if the eGFR continues to decrease. Although renin-angiotensin system blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is important in managing CKD, there is no evidence that this strategy improves kidney function or delays progression in AAN.[12 28]

Because patients with AAN are at increased risk for uroepithelial malignancies, all patients with AAN should undergo biannual cytologic evaluation of urine. In those patients with AAN who do not yet require kidney replacement therapy (KRT), yearly surveillance is suggested with computed tomography imaging and ureteroscopy. In addition, prophylactic bilateral nephroureterectomy is strongly recommended for all patients with ESKD caused by AAN who are going to be recipients of a kidney transplant and subsequent immunosuppression.[31]

KIDNEY INJURY CAUSED BY OTHER MEDICINALS

Aside from AAs, the use of other herbal therapy may lead to kidney injury or various toxic insults, especially in patients with kidney disease. Various kidney syndromes have been reported after the use of medicinal plants, including acute tubular necrosis, acute interstitial nephritis, Fanconi syndrome, hypertension, papillary necrosis, chronic interstitial nephritis, and nephrolithiasis.[6 32] Herbal plants reported as the cause for kidney injury include Securidaca longepedunculata (or violet tree), Euphorbia matabelensis, Crotalaria laburnifolia, Uncaria tomentosa (cat's claw), Lepidium meyenii (common name: maca), Tripterygium wilfordii (Lei Gong Teng), licorice root (Glycyrrhiza glabra), irumban puli (Averrhoa bilimbi), cape aloe, Callilepis laureola (Impila), mushrooms, and djenkol beans (Pithecellobium). In addition, the medicinal grass carp (Ctenopharyngodon idellus) gallbladder has been noted to cause hepatitis and acute kidney failure.[1 32–36]

ACUTE KIDNEY INJURY

T. wilfordii Hook F (TWHF) is a Chinese herbal medicine that has been used for over 2000 years. When made into a cream, it is used externally for treatment of arthritis and inflammatory swelling. Extracts of TWHF have been found to have immunosuppressive effects, which could successfully treat rheumatoid arthritis, lupus, minimal change disease, and other autoimmune disorders. The adverse effects of TWHF include gastrointestinal (GI) upset, infertility, and leukopenia. In addition, it has been reported that AKI, profound hypotension, and shock may occur after ingestion of an extract of TWHF. In rats, daily intragastric ingestion of an effective compound extracted from TWHF for 16 days led to proximal tubular dysfunction.32 33 Despite the known risks of the herbal medication, Tripterygium glycosides, the active compound extracted from TWHF, is being investigated for treatment of diabetic nephropathy.

Cat’s claw, or Uña de Gato, is a Peruvian herbal preparation made from Uncaria, a woody vine found in the Amazon basin. It has been used for treatment of cirrhosis, gastritis, gonorrhea, cancers of the female genital tract, and rheumatism. The oxindole alkaloids from the root bark of cat’s claw are thought to invoke its putative antiinflammatory effects, but other unknown substances contribute to the overall effect of cat’s claw extracts. A case of reversible acute interstitial nephritis after the use of this preparation has been reported, likely an idiosyncratic allergic reaction to the remedy.34

Mushrooms

Most kidney diseases associated with mushrooms are a consequence of kidney failure resulting from mushroom-induced hepatic failure. However, throughout Europe and North America, there are a variety of nephrotoxic mushrooms that can be confused with edible mushrooms and can cause AKI. The Cortinarius spp. (C. callisteus, C. cinnamomeus group, C. gentilis, C. orellanus, C. rainierensis, C. speciosissimus, C. splendens, and C. semisanguineus group) are the most notorious (Fig. 79.5). The most common nephrotoxic mushroom is probably C. gentilis. In 2016 there were 6421 mushroom exposures reported in the United States and its territories, with two fatalities. The type of mushroom is unknown in over 80% of cases.35 The history of mushroom ingestion may be remote, particularly with Cortinarius spp Although GI symptoms are usually noted at the time of ingestion, they may not be severe enough for patients to seek medical attention, and symptoms of kidney failure may not manifest until 1 to 3 weeks after exposure. Presentation with a shorter latent period suggests a more severe toxicity and greater risk for severe kidney failure. Improvement in kidney function may occur within several weeks to months, but patients may require chronic dialysis or kidney transplantation.

A more recently described mushroom syndrome involves Amanita smithiana (U.S. Pacific Northwest) or Amanita proxima (France, Italy, Spain) It is thought that the toxin is 2-amino-4,5-hexadienoic acid.36 Although it causes acute tubular necrosis within hours of ingestion, the clinical outcome is usually good.

Diagnosis of Acute Kidney Injury Induced by Folk Remedies

An accurate assessment of the contribution of herbs to AKI is made difficult by failure to elicit a history by the physician unfamiliar with these risks or denial by the patients because of fear of stigmatization or social pressure. It is often difficult to discount the contribution to AKI of the original illness for which the herbal medicine was prescribed. AKI may be either the sole manifestation or part of a multisystem and metabolic involvement.

Treatment

Management of AKI is usually supportive and includes volume replacement and correction of metabolic abnormalities. KRT is offered for the usual indications. About 60% of all folk remedy related AKI cases need KRT, with 25% to 75% mortality. Charcoal hemoperfusion is effective in clearing alfa-amanitin from circulation in those with poisoning from Amanita mushrooms.37

A

D

C

B

E

F

G

Fig. 79.5 Examples of the Cortinarius Species of Mushrooms. (A) C. callisteus. (B) C. cinnamomeus. (C) C. gentilis. (D) C. orellanus. (E) C. speciosissimus. (F) C. splendens. (G) C. semisanguineus. (All images are from Wikimedia Commons. A is attributed to Amadej Trnkoczy at Mushroom Observer. B is attributed to James Lindsey at Ecology of Commanster. C is attributed to Irene Anderson. D is attributed to Thomas Pruß. E is attributed to Rand Workman at Mushroom Observer. F is attributed to Thomas Stjernegaard Jeppesen.)

OTHER KIDNEY COMPLICATIONS OF HERBAL REMEDIES

Hypertension

Ma huang is an ephedra-containing herbal preparation used in the treatment of bronchial asthma, cold and flu symptoms, fever and chills, headaches and other aches, edema, and lack of perspiration. In Western countries, ephedrine and herbal ephedra preparations are used to promote weight loss and enhance athletic performance. Dietary supplements that contain ephedra alkaloids have been reported to induce hypertension, palpitations, tachycardia, and stroke. Prescribed ephedrine was not associated with a substantially increased risk for adverse cardiovascular outcomes in a registry-based case-crossover study.[38,39] However, ephedra may pose a serious health risk to some users, such as patients with kidney disease who are prone to hypertension.

The dried roots of the licorice plant (G. glabra) have been consumed for over 6000 years and are used as flavoring and sweating agents, as demulcents and expectorants in the Western world, and as antiallergic and anti-inflammatory agents in Asian countries, including China, Japan, and Korea. Licorice contains glycyrrhizin. After oral administration of licorice preparations, glycyrrhizinic acid is hydrolyzed by intestinal bacteria into glycyrrhetic acid. Glycyrrhetic acid can inhibit distal tubule 11-β-hydroxysteroid dehydrogenase-2 (11-BOHD-2), which converts the corticosteroid hormone cortisol to cortisone. Decreased activity of 11-BOHD-2 leads to an excess of cortisol and an overstimulation of the mineralocorticoid receptor, leading to sodium and water retention and increased excretion of potassium. Large doses of glycyrrhizinic acid over a prolonged period can cause pseudoaldosteronism, with hypokalemia, hypernatremia, edema, and hypertension, as well as arrhythmia and other cardiac disorders.[1] To minimize the adverse effects, it is recommended that licorice not be ingested for longer than 4 to 6 weeks.[40]

Crystalluria and Nephrocalcinosis

Many health drinks that are well tolerated by individuals with normal kidney function can cause serious problems in patients with kidney disease. One example is star fruit (carambola) juice, which can contain as much as 800 mg of oxalate in 100 mL and can provoke oxalate crystalluria. It should be noted that star fruit should also be avoided in dialysis patients and those with advanced kidney insufficiency because caramboxin, the neurotoxin found in star fruit, is excreted by the kidney and if ingested in large enough amounts can cause paresthesias, seizures, coma, and death. Sour carambola juice is a popular beverage in Taiwan. Although preparation of commercial carambola juice, by pickling and dilution, markedly reduces oxalate content, fresh juice or only mildly diluted postpickled juice may contain high quantities of oxalate. Cranberry concentrate tablets also can lead to an increase in oxaluria. Ingestion of ma huang drinks have been reported to lead to kidney stones, and the use of ephedrine and guaifenesin individually or in combination causes more than 35% of urinary stones that are related to pharmaceutical metabolites and 0.1% of all urinary stones.41

Hyperkalemia

Dietary potassium restriction is often recommended for people with chronic kidney disease, especially because hyperkalemia is a side effect of many medications used to slow the progression of kidney disease. Common foods high in potassium include oranges, bananas, tomatoes, avocadoes, and potatoes. However, some health drinks are also very high in potassium. Noni juice, often taken to increase energy, contains more potassium than any other fruit juice. The legume alfalfa (Medicago sativa) and the plants dandelion (Taraxacum officinale), stinging nettle (Urtica dioica), and horsetail (Equisetum arvense) all contain significant amounts of potassium42 and may induce hyperkalemia in persons with CKD.

Urinary Obstruction

Djenkol beans or Jering (Pithecellobium jiringa) are broad, round, reddish beans that grow during monsoon season in Myanmar, Indonesia, and Malaysia and are considered a delicacy. The Jering seeds are extolled for their supposed ability to prevent diabetes and high blood pressure. In addition, the seeds have bladder spasmodic properties and are used as a remedy to eliminate stones from the bladder. Jering poisoning or djenkolism is characterized by spasmodic suprapubic and/or flank pain, urinary obstruction, and AKI.[42] Chronic djenkol bean consumption is associated with a fourfold higher risk for nonglomerular hematuria. The djenkol bean contains a large amount of djenkolic acid in the range of 0.3 to 1.3 g/100 g wet weight; 93% of the acid exists in a free state. Djenkolic acid crystals may lacerate kidney tissue and cause bleeding or obstruction. Obstruction of the kidney tubules by crystals of djenkol acid is a possible mechanism of acute tubular necrosis. Mild djenkolism requires pain control and hydration. Severe djenkolism, manifested by anuria and AKI, is usually managed with analgesia, aggressive hydration, and alkalinization of the urine with sodium bicarbonate to increase the solubility of djenkolic acid. Some cases of severe djenkolism with anuria do not respond to conservative therapy and require surgical intervention.[43]

Kidney Toxicity From Contaminants in Herbal Medicines

Herbal medicines may be contaminated with excessive or banned pesticides, microbial products, heavy metals, or chemical toxins or adulterated with orthodox drugs. These contaminants are related to the source of these herbal materials, whether grown in a contaminated environment, contaminated during collection, or contaminated during storage, sometimes intentionally. The presence of orthodox drugs is often a result of the intentional adulteration of the herbal remedy by the manufacturers.[44] A report found undeclared pharmaceuticals or heavy metals in 32% of Asian medicines sold in California. These included ephedrine, chlorpheniramine, methyltestosterone, phenacetin, sildenafil, corticosteroids, and fenfluramine; 10% to 15% contained lead, mercury, or arsenic. Of more than 500 Chinese drugs, approximately 10% contained undeclared drugs or heavy metals.[4] Several case reports link these adulterations with kidney injury. The first report was a 73-year-old Malaysian woman who presented with kidney failure and bilateral papillary necrosis after having consumed 2 tablets daily of a traditional herbal preparation, freely available from Chinese medical halls, for 10 years for osteoarthritis. She denied the consumption of any other analgesics, but the analysis of the herbal preparation showed 120 mg of phenylbutazone in each tablet. The second report concerned a 34-year-old housewife taking a mixture of Chinese herbs who presented with Fanconi syndrome and nephrogenic diabetes insipidus. She had a urinary excretion of cadmium 50 times greater than normal. In another report, a patient presented with AKI with marked albuminuria, pyuria, and hematuria after a 4-week treatment with Tung Shueh pills for arthralgias. The cause was acute interstitial nephritis, and the Tung Shueh pills were found to contain both diazepam and mefenamic acid. In Morocco, the traditional el badia, a powder made of the seeds of Tamarix orientalis, is used as hair dye; however, in times when the T. orientalis seeds are scarce, they are replaced with Takaout roumia, which contains paraphenylenediamine. Inadvertent ingestion of paraphenylenediamine is an issue in a number of African countries; for example, in Morocco it is responsible for about 10% of all cases of AKI, 50% of all cases of rhabdomyolysis, 25% of intensive care unit admissions for poisonings, and two-thirds of poisoning-related deaths.[4,6]

In Thailand and other parts of Southeast Asia and India, there are reports of contamination of herbal remedies with cadmium and/or

mercury. In South Africa, about 15% of herbal remedies are contaminated with uranium. In the United States, ginseng dietary supplements have been shown to contain the pesticides quintozene and hexachlorobenzene or to exceed the standard for lead content.

Herb-Drug Interactions Resulting in Adverse Kidney-Related Effects

Herbs with potential for pharmacokinetic and/or pharmacodynamic herb-drug interactions are often taken concomitantly with therapeutic drugs, without the prescribing physician’s knowledge. Pharmacokinetic herb-drug interactions are caused by altered absorption, metabolism, distribution, and excretion of drugs. A frequent underlying mechanism of altered drug concentrations by concomitant herbal medicines is the induction or inhibition of hepatic and intestinal cytochrome P-450 enzymes (CYPs). There are reports of 32 drugs interacting with herbal medicines in humans. These drugs include anticoagulants (warfarin, aspirin, and phenprocoumon), sedatives and antidepressants (midazolam, alprazolam, and amitriptyline), oral contraceptives, antiretroviral agents (indinavir, ritonavir, and saquinavir), immunosuppressants (cyclosporine and tacrolimus), anticancer drugs (imatinib and irinotecan), and digoxin. Most of them are substrates for CYPs and/or P-glycoprotein, and many have narrow therapeutic indices. Toxicity arising from drug-herb interactions may be minor, moderate, or even fatal, depending on a number of factors associated with the patients, herbs, and drugs.1

St. John’s wort, derived from the plant Hypericum perforatum, has been used since ancient times for depression and anxiety. It is the most common antidepressant used in Germany. St. John’s wort induces a hepatic enzyme through activation of the CYP system, leading to decreased serum levels of a wide range of prescribed drugs, with possible clinically serious consequences. For example, St. John’s wort ingested for 10 days by a group of healthy volunteers reduced the bioavailability of digoxin by an average of 25%. St. John’s wort ingested for 2 weeks reduced the total absorption of indinavir by 50%, which is large enough to cause treatment failure. Other reports indicated significant increases in the metabolism of warfarin, theophylline, oral contraceptives, and cyclosporine. Use of St. John’s wort in transplant recipients is associated with both toxicity and underdosage of calcineurin inhibitors as a result of phytochemically triggered activity changes of isoenzyme CYP3A4 metabolism and drug transport proteins.45,46

Gingko biloba is one of the most popular plant extracts in Europe and is approved in Germany for the treatment of dementia. G. biloba is composed of several flavonoids, terpenoids (e.g., ginkgolides), and organic acids believed to act synergistically as free radical scavengers. G. biloba should not be administered with concomitant anticoagulation or in patients with bleeding disorders. Concomitant use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), as well as anticoagulants such as warfarin and heparin, should be avoided. Spontaneous hyphema and spontaneous bilateral subdural hematomas have been observed in patients taking G. biloba and are attributed to ginkgolide B, a potent inhibitor of platelet-activating factor needed to induce arachidonate-independent platelet aggregation. Hemorrhagic complications were observed often in patients administered concomitant anti-aggregate or anticoagulant therapy. However, the exact mechanism of the interaction of G. biloba with aspirin, warfarin, and NSAIDs remains unclear. Experimental data from rats suggest that a G. biloba diet markedly increased the content of CYP and activity of glutathioneS-transferase and markedly induced the level of CYP2B1/2, CYP3A1, and CYP3A2 messenger RNA in the liver.47

Most information about the toxicity of herbal medicines is found only in case reports, and precise identities of the culprit substances, toxicologic characteristics, and pathogenic mechanisms of herbal medicines remain largely unknown. Although many herbs have been used for centuries without evidence of acute kidney damage, insidious damage caused by long-term use is a concern because many herbs have not been rigorously tested for toxicity.

OVER-THE-COUNTER MEDICINES AND THE KIDNEY

In addition to the increasing popularity of OTC health foods, nutritional supplements, and medicinal products from plants or other natural sources, there is increasing consumption in many countries of pharmaceutical products bought OTC, particularly analgesics and agents for treatment of dyspepsia.

Analgesics

OTC analgesics used for fever and minor musculoskeletal symptoms are one of the most widely used classes of drugs in the developed world. NSAIDs are also used to treat inflammatory conditions; and aspirin is used prophylactically as an anticoagulant in thrombosis-related disorders. Acetaminophen (paracetamol), aspirin, ibuprofen, and naproxen are available OTC in many countries, sometimes in combinations.

Although studies on the association between the long-term use of aspirin, NSAIDs, and other analgesics and ESKD have given conflicting results, many studies suggest an association between chronic ingestion of analgesics and kidney disease.

Because analgesic use is widespread, even a small percentage of increased risk for kidney disease may have major public health implications.

NSAIDs inhibit cyclooxygenase and may inhibit lipoxygenase, decreasing the production of prostaglandins and leukotrienes, which account for many NSAID-induced effects on the kidney. In patients with volume depletion, renal perfusion depends on circulating prostaglandins to vasodilate the afferent arterioles, allowing more blood flow through the glomerulus. So the contribution of prostaglandins to renal homeostasis is most critical in elderly patients and those with circulatory disturbances, such as kidney or liver dysfunction, congestive heart failure, or volume depletion.48

Patients who warrant chronic therapy with analgesics and NSAIDs should be monitored by regular screening with dipstick urinalysis and serum creatinine for early evidence of kidney injury. Specifically, lowrisk patients should be monitored within 3 months and have studies repeated every 6 to 12 months and high-risk patients should be monitored within 1 to 3 weeks and have studies repeated every 3 to 6 months. Early detection and removal of the offending agent could halt or even reverse analgesic-induced kidney injury. There is a pressing need for multicenter prospective studies to assess the true incidence of this problem and study the effects of various analgesic agents (alone and in combination) in at-risk populations.

Analgesic Nephropathy

Analgesic nephropathy, resulting from the habitual consumption over several years of compound analgesics, is characterized by renal papillary necrosis and chronic interstitial nephritis. It is an increasingly rare condition because phenacetin (the analgesic most implicated as a causative agent) is banned in many countries. Phenacetin alone was not the cause of analgesic nephropathy (in fact, phenacetin was never marketed as a single agent); it was the use of phenacetin in combination analgesics that caused the problem. A retrospective cohort study using data from the Australia and New Zealand Dialysis and Transplant Registry showed that among 31,654 patients receiving KRT over the previous 35 years, 10.2% had analgesic nephropathy, but the incidence was less than 3.5% in 2005.49 Analgesic nephropathy is discussed further in Chapter 65.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs), such as omeprazole, are now available OTC in many countries and can be associated with granulomatous allergic interstitial nephritis (see Chapter 64). Use of PPIs has been linked epidemiologically to an increased risk for CKD in the general population.

Cannabis and Synthetic Cannabinoids

With the legalization of cannabis in Canada in 2018 and the decriminalization and legalization of recreational and/or medicinal use of cannabis in some states in the United States, cannabis is now the most commonly used psychotropic drug in the United States, second only to alcohol. In herbal cannabis, the dried flowers, fruits, leaves, and stems from the female hemp plant Cannabis sativa, and its subspecies, there are over 100 phytocannabinoids. The major active phytocannabinoids are cannabidiol (CBD), a nonpsychoactive phytocannabinoid, and delta 9-tetrahydrocannabinol (THC), a psychoactive phyotcannaminoid.[50] Phytocannabinoids, synthetic cannabinoid analogs, and endocannabinoids, such as anandamide and 2-arachidonoylglycerol, are all ligands of the cannabinoid receptor type 1 and 2 (CB1 and CB2, respectively). The principal location of CB1 is in the central nervous system, where they have an inhibitory effect on γ-aminobutyric acid (GABA). Activation of CB1 results in the neuropsychiatric effects of synthetic cannabinoids, such as elation, irritability, and anxiety. The principal location of CB2 is in tissues related to the immune system, and these receptors are suggested to have a role in the control of emesis and pain. Both CB1 and CB2 are also expressed in human podocytes and other cells of the glomerulus. Endocannabinoids, such as anandamide, activate the CB1 receptor and increase the GFR and renal blood flow in rodents, independent of changes in blood pressure. In addition, anandamide stimulates nitric oxide production and leads to inhibition of sodium transport in the thick ascending limbs of the loop of Henle.[51]

CBD is metabolized by cytochrome P450 (CYP)3A4 and CYP2C19 and is suspected to be a potent inhibitor of these pathways. All drugs metabolized by this system (Table 79.3; including tacrolimus) would have a prolonged half-life in the presence of CBD, and there have been case reports of CBD oil affecting tacrolimus levels.

Synthetic cannabinoids, like many herbal supplements, are manufactured in unregulated laboratories and accidental or purposeful contamination may occur by the manufacturers and/or distributors. The synthetic cannabinoids are solubilized, applied to dried, plant material, and sold as “synthetic marijuana,” “herbal incense,” “spice,” and potpourri. Some synthetic cannabinoids are more powerful than THC and a number of cases of AKI have been attributed to smoking synthetic cannabinoids.[52] Although AKI may be secondary to a contaminant or nephrotoxin present in a single batch of drug, a number of the reported AKI patients used a product that was known to contain a novel fluorinated synthetic cannabinoid (XLR-11) or its metabolites were found in clinical samples of the patients.[52]

Many of the touted therapeutic benefits of CBD are for symptoms that are common in people with advanced CKD, such as pain, nausea, anxiety, and insomnia. At this time, the evidence supporting using nonsynthetic cannabinoids for symptom management is limited to the treatment of chronic neuropathic pain, with a potential to treat uremic pruritus. However, nonsynthetic cannabinoids, particularly smoked cannabis, can pose significant health risks; thus the limited substantiated therapeutic benefit of cannabis must be weighed against these risks.[53]

TABLE 79.3 Metabolism of Medications Affected by CBD

Cytochrome P450 Isoenzyme	Drugs Metabolized
CYP2C19	Amitriptyline, carisoprodol, citalopram, cyclophosphamide, diazepam, hexobarbital, imipramine, indomethacin, clomipramine, lansoprazole, mephenytoin, mephobarbital, moclobemide, nelfinavir, nilutamide, omeprazole, pantoprazole, phenobarbital, phenytoin, primidone, progesterone, proguanil, propranolol, rabeprazole, temazepam, teniposide, valproic acid, (R)-warfarin, zidovudine
CYP3A4	Acetaminophen, codeine, ciclosporin (cyclosporin), diazepam, and erythromycin, alfentanil, alprazolam, amiodarone, amlodipine, amitryptyline, aprepitant, aripiprazole, astemizole, atorvastatin, buspirone, carbamazepine, cerivastatin, chlorpheniramine, cilostazol, cisapride, clarithromycin, codeine cyclosporine A, dapsone, dexamethasone, dextromethorphan, diazepam, digoxin, diltiazem, docetaxel, domperidone, eplerenone, ergotamine, erythromycin, estradiol, etoposide, ethynylestradiol, felodipine, fentanyl, finasteride, fluoxetine, gleevec, haloperidol, halothane, hydrocortisone, indinavir, irinotecan, ivabradine, ketoconazole, lercanidipine, levonorgestrel, lidocaine, loratadine, lovastatin, methadone, metronidazole, midazolam, mifepristone, nateglinide, nelfinavir, nifedipine, nisoldipine, nitrendipine, ondansetron, omeprazole, paracetamol, pimozide, propranolol, progesterone, quetiapine, quinidine, quinine, risperidone, ritonavir, saquinavir, salmeterol, sildenafil, simvastatin, sufentanyl, tacrolimus (FK506), taxol, tamoxifen, terfenadine, testosterone, theophylline, trazodone, triazolam, valproate, warfarin, venlafaxine, verapamil, vincristine, zaleplon, ziprasidone, zolpidem

CBD, Cannabidiol.

From Tomaszewski P, Kubiak-Tomaszewska G, Pachecka J. Cytochrome P450 polymorphism: molecular, metabolic, and pharmacogenetic aspects. II. Participation of CYP isoenzymes in the metabolism of endogenous substances and drugs. Acta Pol Pharm. 2008;65(3);307–318.

SELF-ASSESSMENT QUESTIONS

1. A very slender 25-year-old international fashion model presented with kidney failure, minimal hypertension, and mild albuminuria. Kidney function deteriorated, and the patient received a kidney transplant. Six months later, she developed bilateral urogenital tract tumors. What was the most likely cause of her kidney disease?

A. Analgesic nephropathy
B. Aristolochic acid nephropathy
C. Anorexia nervosa
D. Heavy metal intoxication

2. A 30-year-old recent emigrant from Romania presents with a 3-month history of fatigue, dyspnea on exertion, anorexia, and nausea. On physical examination, she is thin and appears chronically unwell. Blood pressure is 160/100 mm Hg, with otherwise normal physical examination findings. Laboratory workup is significant for hematocrit 22, serum potassium 5.7 mmol/L, serum bicarbonate 19 mmol/L, serum glucose 90 mg/dL, blood urea nitrogen 80 mg/

dL, and serum creatinine 4 mg/dL. Urinalysis shows 1+ glucose, 2+ protein, 20 to 30 leukocytes per high-power field. Urine culture is negative for bacteria and acid-fast bacilli. Urine protein was 500 mg/24 h; kidney ultrasound, right kidney, 9.8 cm; left kidney, 9.6 cm; and no hydronephrosis. What is the most likely cause of her impaired kidney function?
A. Acute kidney failure from tubular necrosis
B. Chronic glomerulonephritis

C. Chronic tubulointerstitial nephritis (Balkan endemic nephropathy)
D. Occult diabetic nephropathy
3. A previously noncompliant patient with stage 4 chronic kidney disease secondary to hypertension comes into your office saying he has changed his ways. He has lost weight, is taking all of his medications, and is drinking homemade star fruit (carambola) juice for its antioxidant properties. His serum creatinine is 5.1 mg/dL (previously 2.4 mg/dL). In the figure, which picture are you most likely to see on urinalysis?
A. Cystine crystal
B. Urate crystal
C. Triple phosphate
D. Oxalate crystal
4. A 52-year-old woman 5 years after kidney transplantation is taking mycophenolate mofetil and cyclosporine with stable transplant function. She reports that she just came back from a health spa and that she feels wonderful. She said she was diagnosed with depression and was started on St. John’s wort by the herbalist. Which of the following transplant-related problems are you are most concerned about?
A. Acute rejection
B. Crystal formation in the graft
C. Cyclosporine toxicity
D. Hypertension

REFERENCES

1. Zhou SF, Xue CC, Yu XQ, Wang G. Metabolic activation of herbal and dietary constituents and its clinical and toxicological implications: an update. Curr Drug Metab. 2007;8:526–553.
2. May T, Eckl G, Reynolds VCM. US sales of herbal supplements increase by 8.6% in 2019. HerbalGram. 2020;127:54–69.
3. De Smet PA. Herbal medicine in Europe—relaxing regulatory standards. N Engl J Med. 2005;352:1176–1178.
4. Jha V, Rathi M. Natural medicines causing acute kidney injury. Semin Nephrol. 2008;28:416–428.
5. Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician. 2008;78:743–750.
6. Isnard Bagnis C, Deray G, Baumelou A, et al. Herbs and the kidney. Am J Kidney Dis. 2004;44:1–11.
7. Martinek V, Kubickova B, Arlt VM, et al. Comparison of activation of aristolochic acid I and II with NADPH:quinone oxidoreductase, sulphotransferases and N-acetyltranferases. Neuroendocrinol Lett. 2011;32(suppl 1):57–70.
8. Schmeiser HH, Janssen JW, Lyons J, et al. Aristolochic acid activates ras genes in rat tumors at deoxyadenosine residues. Cancer Res. 1990;50:5464–5469.
9. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008;74:158–169.
10. Pozdzik AA, Salmon IJ, Debelle FD, et al. Aristolochic acid induces proximal tubule apoptosis and epithelial to mesenchymal transformation. Kidney Int. 2008;73:595–607.
11. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet. 1993;341:387–391.
12. Gökmen MR, Cosyns JP, Arlt VM, et al. The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. Ann Intern Med. 2013;158(6):469–477.
13. Gillerot G, Jadoul M, Arlt VM, et al. Aristolochic acid nephropathy in a Chinese patient: time to abandon the term “Chinese herbs nephropathy”. Am J Kidney Dis. 2001;38:E26.
14. Lai MN, Lai JN, Chen PC, et al. Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid. Nephrology (Carlton). 2009;14:227–234.
15. Djukanović L, Marinković J, Marić I, et al. Contribution to the definition of diagnostic criteria for Balkan endemic nephropathy. Nephrol Dial Transplant. 2008;23(12):3932–3938.
16. Nortier JL, Vanherweghem JL. Renal interstitial fibrosis and urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). Toxicology. 2002; 181-182:577–580.
17. Lincoln T. Toxicology: danger in the diet. Nature. 2007;448:148.
18. Kong PI, Chiu YW, Kuo MC, et al. Aristolochic acid nephropathy due to herbal drug intake manifested differently as Fanconi’s syndrome and endstage renal failure—a 7-year follow-up. Clin Nephrol. 2008;70:537–541.
19. Kabanda A, Jadoul M, Lauwerys R, et al. Low molecular weight proteinuria in Chinese herbs nephropathy. Kidney Int. 1995;48:1571–1576.
20. Lemy A, Wissing KM, Rorive S, et al. Late onset of bladder urothelial carcinoma after kidney transplantation for end-stage aristolochic acid nephropathy: a case series with 15-year follow-up. Am J Kidney Dis. 2008;51:471–477.
21. Depierreux M, Van Damme B, Vanden Houte K, Vanherweghem JL. Pathologic aspects of a newly described nephropathy related to the prolonged use of Chinese herbs. Am J Kidney Dis. 1994;24:172–180.
22. Cosyns JP, Jadoul M, Squifflet JP, et al. Chinese herbs nephropathy: a clue to Balkan endemic nephropathy? Kidney Int. 1994;45:1680–1688.
23. Pozdzik AA, Salmon IJ, Husson CP, et al. Patterns of interstitial inflammation during the evolution of renal injury in experimental aristolochic acid nephropathy. Nephrol Dial Transplant. 2008;23:2480–2491.

24. Wang Y, Meng F, Arlt VM, et al. Aristolochic acid-induced carcinogenesis examined by ACB-PCR quantification of H-Ras and K-Ras mutant fraction. Mutagenesis. 2011;26:619–628.

25. Rosenquist TA, Grollman AP. Mutational signature of aristolochic acid: clue to the recognition of a global disease. DNA Repair (Amst). 2016;44:205–211.
26. Jelaković B, Karanović S, Vuković-Lela I, et al. Aristolactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. Kidney Int. 2012;81:559–567.
27. Grollman AP, Shibutani S, Moriya M, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. Proc Natl Acad Sci USA. 2007;104:12129–12134.
28. Luciano RL, Perazella MA. Aristolochic acid nephropathy: epidemiology, clinical presentation, and treatment. Drug Saf. 2015;38(1):55–64.
29. Vanherweghem JL, Abramowicz D, Tielemans C, Depierreux M. Effects of steroids on the progression of renal failure in chronic interstitial renal fibrosis: a pilot study in Chinese herbs nephropathy. Am J Kidney Dis. 1996;27:209–215.
30. Martinez MC, Nortier J, Vereerstraeten P, Vanherweghem JL. Steroid therapy in chronic interstitial renal fibrosis: the case of Chinese-herb nephropathy. Nephrol Dial Transplant. 2002;17:2033–2034.
31. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). N Engl J Med. 2000;342:1686–1692.
32. Asif M. A brief study of toxic effects of some medicinal herbs on kidney. Adv Biomed Res. 2012;1:44.
33. Dan H, Peng RX, Ao Y, Liu YH. Segment-specific proximal tubule injury in Tripterygium glycosides intoxicated rats. J Biochem Mol Toxicol. 2008;22:422–428.
34. Hilepo JN, Bellucci AG, Mossey RT. Acute renal failure caused by ‘cat’s claw’ herbal remedy in a patient with systemic lupus erythematosus. Nephron. 1997;77:361.
35. Brandenburg WE, Ward KJ. Mushroom poisoning epidemiology in the United States. Mycologia. 2018;110(4):637–641.
36. Saviuc P, Danel V. New syndromes in mushroom poisoning. Toxicol Rev. 2006;25:199–209.
37. Splendiani G, Zazzaro D, Di Pietrantonio P, Delfino L. Continuous renal replacement therapy and charcoal plasmaperfusion in treatment of amanita mushroom poisoning. Artif Organs. 2000;24:305–308.
38. Bennett S, Hoffman N, Monga M. Ephedrine- and guaifenesin-induced nephrolithiasis. J Altern Complement Med. 2004;10:967–969.
39. Hallas J, Bjerrum L, Støvring H, Andersen M. Use of a prescribed ephedrine/caffeine combination and the risk of serious cardiovascular events: a registry-based case-crossover study. Am J Epidemiol. 2008;168:966–973.
40. de Klerk GJ, Nieuwenhuis MG, Beutler JJ. Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. BMJ. 1997;314:731–732.
41. Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics. New York: John Wiley & Sons; 1996.
42. Segasothy M, Swaminathan M, Kong NC, Bennett WM. Djenkol bean poisoning (djenkolism): an unusual cause of acute renal failure. Am J Kidney Dis. 1995;25:63–66.
43. Bunawan NC, Rastegar A, White KP, Wang NE. Djenkolism: case report and literature review. Int Med Case Rep J. 2014;7:79–84.
44. Chan K. Some aspects of toxic contaminants in herbal medicines. Chemosphere. 2003;52:1361–1371.
45. Yang XX, Hu ZP, Duan W, et al. Drug-herb interactions: eliminating toxicity with hard drug design. Curr Pharm Des. 2006;12:4649–4664.
46. Ernst E. The risk-benefit profile of commonly used herbal therapies: gingko, St john’s wort, ginseng, echinacea, saw palmetto, and kava. Ann Intern Med. 2002;136:42–53.
47. Shinozuka K, Umegaki K, Kubota Y, et al. Feeding of Gingko biloba,

extract (GBE) enhances gene expression of hepatic cytochrome P-450 and attenuates the hypotensive effect of nicardipine in rats. Life Sci. 2002;70:2783–2792.
48. Schlondorff D. Renal prostaglandin synthesis. Sites of production and specific actions of prostaglandins. Am J Med. 1986;81:1–11.
49. Chang SH, Mathew TH, McDonald SP. Analgesic nephropathy and renal replacement therapy in Australia: trends, comorbidities and outcomes. Clin J Am Soc Nephrol. 2008;3:768–776.

References

50. Grotenhermen F, Russo E. Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential. Binghamton, NY: The Haworth Press; 2002.
51. Chua JT, Argueta DA, DiPatrizio NV, et al. Endocannabinoid system and the kidneys: from renal physiology to injury and disease. Cannabis Cannabinoid Res. 2019;4(1):10–20.
52. Centers for Disease Control and Prevention. Acute kidney injury associated with synthetic cannabinoid use— multiple states. 2012. Morb Mortal Wkly Rep (MMWR). 2013;62:6.

53. Ho C, Martinusen D, Clifford Lo Canadian Journal of Kidney Health and Disease. Rev Cannabis Chronic Kidney Dis Sympt Mangt. 2019;6:1–14.
54. Tomaszewski P, Kubiak-Tomaszewska G, Pachecka J. Cytochrome P450 polymorphism: molecular, metabolic, and pharmacogenetic aspects.
II. Participation of Cyp isoenzymes in the metabolism of endogenous substances and drugs. Acta Poloniae Pharmaceutica. Drug Res. 2008;65(3):307–318.

80

Epidemiology of Chronic Kidney Disease and Dialysis

Morgan E. Grams, Stephen P. McDonald

The global average life expectancy is now 73.4 years—an enormous increase from 61.7 years in 1980, due in part to declining mortality from communicable, maternal, neonatal, and nutritional disease.1,2 On the other hand, with the aging of the population, chronic kidney disease (CKD) has become one of the most common noncommunicable diseases in the world, as well as a leading cause of mortality. Half of the people in the United States are expected to develop CKD during their lifetime.3 Associated with huge health system costs, particularly with kidney failure, CKD has come into focus as a common, morbid, and often preventable disease.4

DEFINING CHRONIC KIDNEY DISEASE

Chronic Kidney Disease Staging

Over the past decade, the definition of CKD has evolved to incorporate advances in knowledge about prognosis.5 The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines published in 2002 classified CKD into five stages on the basis of glomerular filtration rate (GFR) and signs of kidney damage (pathologic abnormalities or markers of damage in blood, urine, or imaging studies).6 This staging system was modified in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines to reflect the independent contributions of GFR, albuminuria, and cause of CKD.7 The two-dimensional “heat map” that classifies CKD in GFR categories (G stages) and albuminuria categories (A stages) has been widely accepted and robustly validated, but less is known about the third dimension, as routine reporting on the cause of CKD is relatively uncommon (Fig. 80.1).8

Classification Based on Estimated Glomerular Filtration Rate

Serum creatinine is the most commonly used filtration marker for the estimation of GFR, and GFR estimating equations incorporating serum creatinine, as well as age and sex, generate precise and accurate assessments of kidney function in the vast majority of both CKD and non-CKD populations.9,9a In North America, the best available GFR estimating equation is that developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).10 The accuracy of GFR estimation also has benefited from universal standardization of the creatinine laboratory assay (see Chapter 3).11 Serum cystatin C is an additional filtration marker used in the estimation of GFR, with an equation that uses both cystatin C and serum creatinine recognized as being the most accurate.9a

Classification Based on Albuminuria

Multiple techniques exist to estimate urine albumin excretion. The semiquantitative dipstick method is most common, followed by spot and 24-hour urine protein or albumin excretion assessments. All are subject to limitations. Dipstick testing is inexpensive, but the diagnostic accuracy can be low,12,13 particularly for moderately increased levels of albuminuria. Although a full day’s collection of urine albumin is the gold standard for albuminuria estimation, the process is tedious and imposes substantial burden on the patient. Thus, the KDIGO guideline recommends a spot collection of urine, with early morning timing preferred, as the initial screening test.7 Urine albumin is recommended over urine protein assessment given the superiority of the laboratory assay and standardization, as well as the relative importance in prognosis. Spot samples are standardized to urine creatinine to normalize to 24-hour excretion and account for any differences in concentration (e.g., albumin-to-creatinine ratio [ACR]). Abnormalities in GFR or albuminuria must persist for more than 3 months to meet the definition of CKD (see Chapter 3).

Classification Based on Chronic Kidney Disease Cause

The cause of kidney disease (the “C” in the KDIGO CGA staging) is the least studied aspect of the CKD definition. The proposed KDIGO classification categorizes disease by the presence of underlying systemic disease and the location of the abnormality (see Fig. 80.1). For example, diabetic nephropathy might be classified as a systemic disease affecting the glomerulus, and obstructive nephropathy as a primary kidney disease affecting the tubulointerstitium. Limitations of this approach include the infrequent use of kidney biopsy, the gold standard for assessment of pathologic location of kidney abnormalities.

On the other hand, decisions not to perform kidney biopsies are often driven by the uncertain benefit of precise localization of pathologic abnormalities in terms of prognostic implications—a vicious circle begetting sparse evidence.

Rationale for the Chronic Kidney Disease Definition

Associations With Adverse Outcomes

The cut-points of GFR and albuminuria used to define CKD (<60 mL/min/1.73 m^2 and ≥30 mg/g, respectively) have been rigorously

Chronic Kidney Disease Classification According to Glomerular Filtration Rate and Albuminuria
Persistent albuminuria categories
description and range

GFR categories (mL/min/1.73 m 2)
description and range
G1

Normal or high

G2

Mildly decreased

60-89

G3a

Mildly to moderately decreased

45-59

G3b

Moderately to severely decreased

30-44

G4

Severely decreased

15-29

G5

Kidney failure

𝑜90

𝑛15

A1

A2

A3

Normal to mildly
increased

Moderately
increased

Severely
increased

𝑛30 mg/g
𝑛3 mg/mmol

30-300 mg/g
3-30 mg/mmol

瓈300 mg/g
瓈30 mg/mmol

Classification of CKD based on presence or absence of systemic disease and location within the kidney
Presence of systemic disease
affecting the kidney

Primary kidney diseases
Glomerular diseases
Tubulointerstitial diseases
Vascular diseases

Cystic and congenital diseases

Fig. 80.1 Depiction of Chronic Kidney Disease (CKD) Classification: G Stages and A Stages. The cube denotes how the three components of the CKD classification scheme (glomerular filtration rate [G], albuminuria [A], and underlying kidney disease) interact to influence the risk of progression to kidney failure. This risk is represented in qualitative terms (lowest to highest) by green, yellow, orange, and red colors.

Odds of Laboratory Abnormalities
by Estimated Glomerular Filtration Rate
64

Anemia
Acidosis
Hyperphosphatemia
Hypocalcemia
Hyperparathyroidism
Hyperkalemia

Adjusted odds ratio

32
16
8
4
2
1
.5
15

30

45

60
75
90
105
120
eGFR, mL/min/1.73 m2

Fig. 80.2 Odds of laboratory abnormalities according to estimated glomerular filtration rate (eGFR) among people from the general US population. (From the continuous National Health and Nutrition Examination Survey [1999–2010].)

examined. Each represents a higher risk state compared with normal levels for a variety of outcomes. For example, the relationship between GFR and the prevalence of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hyperparathyroidism demonstrates a continuous increase in risk with GFR less than 60 mL/min/1.73 m^2 (Fig. 80.2).14 Furthermore, the risk for future kidney outcomes, including acute kidney injury (AKI), CKD progression, and kidney failure, all exhibit graded associations with lower GFR.15 Although relationships with progression to kidney failure with kidney replacement therapy (KRT) are strongest, both lower eGFR and more severe albuminuria are independently associated with cardiovascular mortality and

all-cause mortality as well (Fig. 80.3).8 For example, for a given value of GFR, more severe albuminuria is associated with higher risk for adverse events compared with albuminuria levels less than 30 mg/g.4

Persistent Relationships Within Subgroups

Although there remains some controversy about the use of different thresholds for different groups of people,16 the risk relationships between eGFR and ACR with adverse outcomes are remarkably robust in different subgroups, including older and younger adults and men and women. For example, while reduced GFR is more common among older individuals compared to younger individuals, it remains a strong

Hazard Ratio of Adverse Outcomes Associated With
Estimated Glomerular Filtration Rate and Albuminuria
4

4

All-cause mortality
Cardiovascular mortality

3
Adjusted HR

Adjusted HR

3

2
1.5

All-cause mortality
Cardiovascular mortality

2
1.5
1
.8

1
15

A

30

45
60
75
90
105 120
1
3
10
30
100
300
1000
B
ACR, mg/g
eGFR, mL/min/1.73 m2

Fig. 80.3 Hazard ratios (HRs) of adverse outcomes associated with estimated glomerular filtration rate (eGFR) (A) and albuminuria (B) among people from the general US population. ACR, Albumin-to-creatinine ratio. (From the National Health and Nutrition Examination Survey III [1988–1994] and the continuous National Health and Nutrition Examination Survey [1999–2010].)

Hazard Ratio of Adverse Outcomes
Associated With Estimated Glomerular
Filtration Rate, by Sex

risk factor for KRT compared with higher levels of GFR.17 Similarly, the risk relationships between ACR and adverse outcomes appear fairly consistent in women compared with men, counter to the proposed sex-specific definitions that assign a higher ACR threshold in women (Fig. 80.4).18

RISK FACTORS FOR CHRONIC KIDNEY DISEASE

Age

Many risk factors have been implicated in the development of CKD. Age is a strong risk factor for GFR less than 60 mL/min/1.73 m2, and so population aging is almost inevitably associated with an increase in CKD burden. Interestingly, although incidence rates of KRT tend to be highest among persons older than 65 years, older age is often associated with a lower risk for developing KRT in multivariable-adjusted analyses.4 24 In other words, for the same level of kidney function, a

Adjusted HR

Accurate estimations of CKD prevalence are difficult because tests for filtration markers and albuminuria are not uniformly performed; however, many believe the global burden of CKD to be large and increasing.19 The best estimates are derived from nationally representative samples, such as the National Health and Nutrition Examination Survey (NHANES) in the United States; estimates based on populations receiving health care may overestimate (or, in some cases, underestimate) disease prevalence.20 In the United States, estimates of CKD prevalence based on a one-time measurement of serum creatinine recently placed the proportion of the population with stage G3 or G4 CKD at 6.9%; using a definition of ACR greater than 30 mg/g or eGFR less than 60 mL/min/1.73 m2, the prevalence of any CKD was 14.2%.21 This definition likely overestimates prevalence because the persistence of albuminuria was not taken into account. Publications from countries in Europe show wide variation in CKD prevalence, from 3.3% in Norway to 17.3% in northwest Germany, but this may reflect differences in sampling strategy rather than true population-level differences.22 Estimates in lower-income countries are less available, but most place the global population burden between 8% and 16%, affecting nearly 500 million adults worldwide in 2010.23

Female
Male

16
8
4
2
1
2.5

5

10

30

300

1000

ACR

Fig. 80.4 Hazard ratios (HR) of adverse outcomes associated with albuminuria, by sex. ACR, Albumin-to-creatinine ratio. (From Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a metaanalysis. BMJ. 2013;346:f324.)

younger person is at higher risk for progression to end-stage kidney disease (ESKD) than an older person. This observation may be due in part to the fact that mortality is lower in younger persons and that younger persons may be more likely to accept or be prescribed a replacement therapy (dialysis or transplantation) compared with older persons.

Sex and Race/Ethnicity

Risk for CKD differs by other demographic factors as well. Women are generally at higher risk for incident CKD but lower risk for incident KRT than men.2 In the United States, Black individuals have a higher prevalence of KRT than White individuals. Much of the difference in CKD burden stems from long-standing and pervasive structural racism resulting in differences in socioeconomic status and access to health care.

Differences in the frequency of specific genetic variants also partially underlie this disparity. Sickle cell trait and the APOL1 high-risk genotype, present in 7% and 13% of persons of African descent, respectively, confer higher risk for CKD and KRT.25 26 The presence of sickle cell trait may confer risk via subclinical sickling in the oxygen-poor medulla, leading to impairments in concentrating ability and hematuria over time. The mechanism of the APOL1 high-risk genotype is as yet uncertain, but it appears to be mediated through the development of albuminuria. Other racial/ethnic groups also have higher risk of KRT, including persons of Hispanic ethnicity and Indigenous Americans/Alaskan Natives in the United States, as well as indigenous people in many other countries.27

Social Determinants

Socioeconomic factors play an important role in CKD risk. People with lower socioeconomic status face greater burden of CKD and rapid GFR decline in the United States, and this finding has been replicated in many other developed countries.4 7 Socioeconomic status is often lower in racial and ethnic minorities, and several studies have demonstrated attenuation or elimination of racial disparities in kidney outcomes with accounting for differences in income and the presence of health insurance, including risk for AKI, eGFR decline, and delay in transplantation in children.28

Comorbid Conditions

Diabetes mellitus and hypertension are often cited as the major attributable causes of CKD in the developed world, and recent studies suggest similarities in the developing world.4 Nearly half of the population with kidney failure has diabetes. Persons with diabetes and CKD merit concern, not only for the risk for albuminuria and CKD progression, but also for heightened risk for many other adverse outcomes, particularly cardiovascular disease. Risk for CKD among those with diabetes mellitus may be managed through tight control of blood glucose and blood pressure and the use of specific therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium-glucose cotransporter-2 inhibitors. Hypertension also has shown a graded association with the risk for KRT in observational studies, although the relationship with kidney disease is more complex than that of diabetes and CKD because hypertension is thought to be both a cause and a consequence of CKD. Obesity may confer increased risk for CKD over the long term, possibly mediated through the development of diabetes and hypertension, and smoking has also been linked to higher KRT risk.29

ISSUES WITH IDENTIFYING CHRONIC KIDNEY DISEASE

Lack of Awareness

Generally, a silent disease until the most advanced stages, CKD is largely underrecognized by providers and patients. Fewer than 10% of people with laboratory-confirmed CKD in the NHANES survey reported being aware that they had kidney disease, a finding corroborated in other regions.4 Provider awareness may not be much higher; only 12% of patients with CKD had an associated diagnostic code in Stockholm health care.30 Low awareness of disease may lead to low testing and referrals, with only 27% of patients with eGFR less than 60 mL/min/1.73 m^2 tested for albuminuria and 23% referred to a nephrologist. Albuminuria testing is also low in persons with diabetes. In the Stockholm cohort, 38% of patients with diabetes were evaluated for albuminuria, very similar to the testing frequency among US Medicare patients with diabetes.4

Imperfect Biomarkers

Another issue in CKD identification is the occasional fallibility of existing biomarkers. Serum creatinine, the most widely used

filtration marker to estimate GFR, has non-GFR determinants, including diet and muscle mass. As a consequence, amputees and persons with reduced muscle mass may have a falsely elevated eGFR when creatinine is used. Thus, the KDIGO guidelines recommend a confirmatory measurement performed for persons in whom measuring creatinine may be less accurate.7 To confirm diagnosis, KDIGO recommends obtaining a cystatin C–based eGFR or clearance measurement, or measuring GFR with an exogenous filtration marker when treatment decisions are at stake. Of note, cystatin C has its own non-GFR determinants, including body mass index and inflammation. For this reason, for the general population the most accurate estimating equation uses both creatinine and cystatin (see Chapter 3).31

Errors in Urine Albumin Assessment

Variability in albumin excretion and measurement can confound CKD identification. In clinical practice, spot samples are usually assessed and standardized to urine creatinine to correct for error induced by differences in hydration status. However, urine albumin and creatinine excretion are thought to follow a circadian rhythm, additionally varying with posture, exercise, and diet.32 Moreover, many providers instead quantify urine protein, a less sensitive and specific marker of glomerular permeability. Urine protein measurement is hampered by interlaboratory variation in methods and calibration and the lack of a reference measurement protocol.7 For these reasons, urine albumin assessment is generally preferred over urine protein assessment, and repeated 24-hour collections offer the most accurate estimation of true albuminuria.

OUTCOMES OF CHRONIC KIDNEY DISEASE

Associations With Adverse Outcomes

The public health implications of CKD are enormous because of the strong associations with adverse outcomes—in particular, cardiovascular disease, kidney failure, and mortality. Some have argued that CKD should be considered a coronary heart disease risk equivalent, much like diabetes, and some guidelines recommend preventive statin use for all patients with CKD older than 50 years.33 The independent associations of GFR and albuminuria with adverse outcomes has been demonstrated in general, high-risk, and CKD populations, as well as in separate geographic regions.8,34

Variation in Absolute Risk for Adverse Outcomes

Increasingly, risk scores are used to inform patient counseling and treatment decisions. Guidelines encourage the incorporation of kidney failure risk prediction in kidney replacement therapy planning, and several risk scores now exist.7 The kidney failure risk equation is the most widely used and has been globally validated.24 The absolute risk for progression to kidney failure was observed to be slightly lower in non–North American countries, a difference that was not explained by differences in demographic or clinical characteristics. Variation in absolute risk for KRT thus might suggest differences in treatment availability, patient or provider acceptance, or differences in the competing risk for death.

DIALYSIS EPIDEMIOLOGY

The number of people receiving chronic KRT (dialysis or kidney transplantation) worldwide has progressively increased over the 50 years since these treatments became available, and this increase continues. Initially available only to selected patients in restricted centers in some countries, both long-term dialysis and kidney transplantation

Global Prevalence of Treated ESKD
Rate per million population (pmp), age ≥ 18 years
<433.0 pmp

433.0–759.0 pmp

759.1–1048.0 pmp

>1048.0 pmp

Data not reported

Fig. 80.5 Patients receiving kidney replacement therapy in 2010. ESKD, End-stage kidney disease. (From Bello A, et al. Global Kidney Health Atlas: A Report by the International Society of Nephrology on the Global Burden of End-Stage Kidney Disease and Capacity for Kidney Replacement Therapy and Conservative Care Across Countries and Regions. International Society of Nephrology; 2019.)

have become progressively more available not just in high-income countries but also in many low-income countries. Approximately 2.5 million people were estimated to be receiving chronic KRT in 2010[35]; absolute rates are high in North America, but the highest prevalent rates (people currently receiving KRT) per million population are in Taiwan and Japan (Fig. 80.5), where the vast majority of people receive long-term dialysis. Good data are available throughout the developed world because of the existence of regional and national dialysis registries; conversely, information such as this is less commonly available in lower-income countries.[36] These registries typically report rates, outcomes, and practice patterns of dialysis at a national level; many also have a major role in provision of hospital-specific information and other safety and quality reporting, as well as providing a substantial resource for clinical research.

Incidence and Prevalence of Chronic Dialysis

Incidence rates (the number of new KRT patients) comprise patients starting chronic or long-term dialysis and a small number of people receiving preemptive kidney transplants. Incidence rates are highest in Taiwan, Mexico, and the United States, followed by various other Asian countries. There is substantial variation among countries in every region around the world (Fig. 80.6). Diabetic kidney disease (DKD) has been the main factor in the increase in incidence rates in almost all countries. In most countries, DKD is attributed as the cause for kidney failure in 40% to 60% of cases.

The trends in incidence rates vary across different regions. In many Asian countries (e.g., Korea, Singapore, Malaysia, Thailand), rates continue to increase. However, in the United States, Canada, Western Europe, Australia, and New Zealand, incidence rates have generally stabilized over the last 5 to 10 years. Nevertheless, in these countries the prevalent numbers and rates of dialysis continue to increase because the number of people leaving dialysis programs (deaths and transplant recipients) is smaller than the incident number.

Not every person with kidney failure receives dialysis or transplantation. In some situations (particularly those with substantial comorbidities or limited life expectancy), dialysis may not be clinically appropriate, or a decision is made for a conservative (nondialysis) approach to treatment (see Chapter 95). Registries typically report rates of KRT, which is synonymous with ESKD, a US administrative term meaning treatment with dialysis or kidney transplantation for chronic kidney failure.

Estimating the “total burden” of kidney failure requires incorporation of both the number of people commencing KRT and the number of people dying of kidney failure without treatment. This has been examined using data linkage (of registry data with death certificates) in Australia[37] and in cohort studies, most notably in Alberta, Canada.[37] These studies suggest that among older age groups (over 75 years), dialysis therapy is used in

Incidence Rate of Kidney Replacement Therapy by Country, 2014

Taiwan
United States
Jalisco [Mexico]
Thailand
Singapore
Rep. of Korea
Japan
Malaysia
Greece
Portugal
Hungary
Canada
Guatemala
Brazil
Israel
Belgium, French sp.
Belgium, Dutch sp.
Romania
Philippines
Hong Kong
Chile
Uruguay
France
Argentina
Macedonia
Bulgaria
Poland
Saudi Arabia
Italy
Spain
Kuwait
Turkey
Indonesia
Austria
Denmark
Slovakia
Qatar
Sweden
United Kingdom*
New Zealand
Australia
Netherlands
Bosnia and Herzegovina
Lithuania
Norway
Scotland
Finland
Switzerland
Serbia
Iceland
Latvia
Estonia
Albania
Iran
Colombia
Peru
Jordan
Russia
Bangladesh

Belarus
Ukraine
South Africa

493
355
346
333

378

311
296
259
251
236

Country

200
197
194
191
188
187
175
172
171
169
166
165
165
164
161
149
145
145
142
141
140
135
133
128
128
123
121
120
119
117
117
113
107
106
106
102
101

222

92
89
88
85
81

81
80
71
60
58
51
51
32
22

0

100

200

300

400

500

ESKD incidence rate (per million population/year)

Fig. 80.6 Incidence rate of kidney replacement therapy (per million population per year), by country for 2014. *Includes England, Wales, and Northern Ireland. ESKD, End-stage kidney disease. (From US Renal Data System. International Comparisons. USRDS 2018 Annual Data Report. Vol. 2. Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.)

fewer than 50% of people with kidney failure. Consistent with this is evidence suggesting that among older patients with comorbidities, there is little or no survival advantage of dialysis therapy.38

Dialysis is a resource-intensive therapy, and there is a relationship between the provision of (and access to) dialysis and the overall economic development of a country (Fig. 80.7). As with other chronic diseases, there is also a gradation seen within many societies in rates of

incident kidney failure, with higher rates seen among those at the lower end of the socioeconomic spectrum.39 40 Gradients with income and education are also seen among predialysis patients.41

Incidence rates vary with sex, with rates generally lower among women than men.42 Incidence rates increase with older age, up to 75 to 80 years old. There have been progressive changes differing across age-specific incidence rates over many years, with increasing incidence

Prevalence of Patients Receiving Kidney Replacement
Therapy as a Function of Per Capita Gross
Domestic Product
Low-income country
Middle-income country
High-income countries

KRT prevalence (pmp)

1,750
1,500

Log (all)

1,250

R2 = 0.5963

1,000
750
500
250
0
0

10,000

20,000

30,000

40,000

50,000

60,000

GDP per capita (international $)
Fig. 80.7 Prevalence of patients receiving kidney replacement therapy (KRT) as of December 31, 2002, and gross domestic product (GDP) per capita. PMP, Per million population. (From White SL, Chadban SJ, Jan S, et al. How can we achieve global equity in provision of renal replacement therapy? Bull World Health Organ. 2008;86:229–237.)

Age-Specific Incident KRT Rates in Australia

per million per year

500
400
300
200
100
0
1970

1980

1990

Year

2000

2010

2020

Age (years)
0–24
65–74

25–44
75–84

45–64
85+

Fig. 80.8 Age-specific kidney replacement therapy (KRT) incidence rates in Australia. (From ANZDATA Registry: 43rd Annual Report, 2020.)

rates of progressively older age groups over a long period followed by stabilization in more recent years. An example of this (from Australia, but typical of that seen in high-income countries) is shown in Fig. 80.8 Some ethnic groups experience particularly high rates of kidney failure and dialysis. Indigenous peoples in Australia, New Zealand, Canada, and the United States have very high rates of kidney disease, poorer outcomes, and less access to transplantation.43 The causes underlying this are complex, but common elements appear to include

very high rates of diabetes, metabolic syndrome, and hypertension driving high rates of CKD.

Dialysis Practice Patterns

Dialysis practice patterns vary widely across countries, with different usage of PD, HD, and home HD. For prevalent patients, the regions with the highest proportion of PD are Hong Kong (72% of prevalent patients) and the Jalisco region of Mexico (47% of prevalent patients).44

Mortality Among Prevalent Australian Dialysis Patients
vs General Population
Male

Annual death rate (95% Cl)

Female
.6
.4
.2
.1

.01

.001

20

40

60

80

20

40

60

80

Age
General population
Dialysis patients

Fig. 80.9 Death rates of prevalent dialysis patients versus general population. CI, Confidence interval. (From ANZDATA Registry: 43rd Annual Report, 2020.)

Home HD is most commonly used in New Zealand and Australia, where 18% and 9%, respectively, of prevalent KRT patients are treated with this modality. Practice patterns also vary in the application of various techniques of HD; for example, dialysis sessions are generally longer in Japan, with slower blood flow rates.

Outcomes

The rationale for dialysis is to prevent death from uremia, and hence the outcome for dialysis treatment is usually reported as mortality rate. Other important outcomes commonly reported include cause-specific mortality rates, hospitalizations, and technique failure. Patientreported outcomes (including measures of quality of life and functional ability) are also extremely important.

Crude mortality rates vary widely; a multinational observational study (Dialysis Outcomes and Practice Patterns Study) reported rates from 6.6% per year in Japan to 21.7% in the United States.45 Mortality rates among dialysis patients are substantially higher than in the general population, a differential particularly marked among younger age groups (Fig. 80.9). The excess mortality is primarily driven by cardiovascular and infectious causes. There is also a modest (approximately 3-fold) excess risk for cancer among dialysis patients, even after exclusion of cancers directly related to the cause of kidney disease (see Chapter 92).46 An issue unique to categorization of deaths among the dialysis cohort is assignment of deaths as a result of withdrawal from therapy. There is a wide range in reported frequency of withdrawal, from less than 5% to more than 20% of all deaths.47 These differences may in part reflect different coding mechanisms but are also likely to reflect differences in practice patterns in the commencement of therapy among older patients with higher levels of comorbidity.

There is variation in mortality over time, with the highest rates seen in the first 3 months after commencing dialysis, particularly among older age groups (Fig. 80.10). After this period, mortality rates approximate the longer-term rates. There are a number of possible contributors to this, including the risk associated with commencement of dialysis (such as the placement of central venous catheters) and increased severity of comorbidities associated (or causing) the deterioration of kidney function.

Multiple observational studies have compared mortality between PD and HD, but no definitive randomized controlled trials (RCTs) have been completed despite several attempts. Results from observational studies have varied across countries; common elements are the presence of multiple interactions such that the comparison depends on comorbidities and patient age, the length of follow-up, and selection biases and local/regional outcomes of each technique.

For PD (and to a lesser extent home HD), “technique survival” is a common metric. This refers to the proportion of people continuing on PD at various time points. It is a combined end point, with patient death and transfer to HD considered failures. Typically, 30 days of HD is considered to be a permanent transfer to HD. It is important to ensure consistency of definitions in comparisons of technique survival; alternative duration definitions have substantial effects on the calculated technique survival.

The use of patient-reported outcomes (PROMs) is growing, supported by evidence that patient priorities around dialysis treatment differ from those of clinicians.48 However, there are significant limitations to the uptake of PROMs. First, the resources required for implementation of PROMs in routine practice can be a substantial barrier.49 Second, despite the conceptual simplicity, there is limited evidence to date about how measuring PROMs may affect quality of life.

EPIDEMIOLOGIC CONCEPTS

Epidemiologic factors influence the reported rates of KRT; understanding the potential biases is a necessary part of interpretation of these data.

The prevalent number of KRT patients at any point in time receiving a form of KRT reflects both the rate of people starting treatment (for overall KRT numbers, the incidence rate) and the rate of people ceasing treatment (the mortality rate). These rates can be considered transition probabilities among various states. This concept can be applied to the overall number of people receiving KRT, the number receiving dialysis or transplantation, and other subgroups. For example, the determinants of the prevalent number of people receiving dialysis at any point in time can be determined from the existing population plus the number of new patients (incidence rate plus the number of people who have lost graft function) less the number of deaths (mortality rates during dialysis) and kidney transplants.

This form of multistate model is often known as a Markov model. Use of these models to estimate future trends can be used by health

Mortality Rates by Age Among Hemodialysis Patients
45
All patients

40

Age <65 years

Mortality rate*

35

Age >65 years

30
25
20
15
10
5
0
0

30

60

90

120

150

180

210

240

270

300

330

360

Days after start of dialysis
Mortality rate during the first 360 days of HD treatment
0-30 31-60 61-90 91-120 121-150 151-180 181-210 211-240 241-270 271-300 301-330
331-360
All patients
Age <65 years
Age >65 years

29.3
13.3
41.2

28.9

12.6
41.2

24.9
13.5
33.7

23.8
11.6
33.5

20.4
10.7
28.2

17.9
10.4
24.0

16.2
10.2
21.1

17.0
9.1
23.6

15.7
9.3
21.0

16.5
9.7
21.9

16.8
8.9
23.5

14.4
8.7
19.2

Fig. 80.10 Overall mortality rates among hemodialysis patients by age. *Number of deaths per 100 patientyears. HD, Hemodialysis. (From Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. Kidney Int. 2014;85:158–165.)

services and others in predicting the future number of people receiving KRT. This can be done under existing conditions and under various hypothetical scenarios to model the effects of various interventions.

The incidence rates reported for ESKD typically exclude dialysis for AKI. Definitions of the start point of KRT vary across registries and data collections. In many cases, an “intent” definition is used (i.e., dialysis is commenced with the intention of long-term treatment, underpinned by a diagnosis of irreversible kidney failure). The other approach (used by the US registry and some other registries) is to use day 90 after dialysis start as the point at which patients are deemed to require “chronic” dialysis. Although this approach eliminates uncertainty around people with prolonged acute (or acute on chronic) kidney injury who may or may not recover, it does prevent analysis of early mortality.

Selection bias affects incidence rates. There may be constrained provision of dialysis services that affects ability to access dialysis services.

There have also been changes in clinical practice over time affecting the propensity to treat in certain situations (especially among older and more frail patients). These factors will influence observed rates; differences in these selection biases will be relevant to comparisons of disease incidence among groups and also to the same group between different times. This is likely to have contributed to the increasing dialysis rates among progressively older people observed in the 1970s to late 1990s.

Lead time bias occurs when the time point of observation differs between groups. One example of this is the comparison of PD and HD cohorts. Patients commencing KRT with PD typically do so at a higher eGFR than those commencing with HD; current UK data suggest this mean difference is around 0.5 mL/min/1.73 m2 50 Although small, this may amount to 2 to 3 months of difference in starting point of analyses.

Competing risks arise when an illness may lead to multiple possible outcomes, but the occurrence of one precludes another. For example,

changes in cardiovascular mortality may affect the incidence rate of KRT because patients who survive despite significant heart disease may avoid premature death that would preclude dialysis treatment.

Another example is the influence of kidney transplantation in evaluation of survival of a dialysis cohort: increased occurrence of transplantation may lead to higher mortality in a dialysis cohort.

Immortal time bias arises when an inappropriate time point is chosen for comparators. An example of this might be comparison of mortality after coronary angiography performed as a pretransplant assessment between those transplanted and not transplanted; the transplanted group will accumulate “immortal” follow-up time between angiography and transplantation, in contrast to the nontransplanted group.

EVIDENCE QUALITY

There is a relative dearth of RCTs supporting practice in the area of dialysis compared with other disciplines. Most large-scale trials examining dialysis-specific interventions have yielded negative or inconclusive results; for example, the use of non–calcium-containing phosphate binders,51 increased dialysis dose,52 use of statins in dialysis patients,53 and hemodiafiltration.54 In response to this, clinical trials networks with a focus on nephrology have been established in several countries to catalyze the conduct of trials (particularly where there is limited commercial interest). Examples of this approach currently underway are multicenter randomized trials examining issues such as dialysate sodium concentration and the effect of differing phosphate targets.

The outcomes examined in trials also have been critically examined. Due to the time delay and multiple contributing factors to mortality, many trials have used surrogate outcomes. Given the association of many biochemical abnormalities with increased mortality, their use appears logical. However, as in other areas of medicine, use of surrogate outcomes in trials and evidence generation in nephrology has been problematic, with changes in surrogates not reflected by reduction in mortality or other hard endpoints. An example of this is the use of phosphate (and parathyroid hormone) as a surrogate to assess

the effectiveness of cinacalcet. Partly as a response to this, initiatives have been instituted to develop and standardize the outcomes for trials.55 An important element of this is also the inclusion of input from patients and consumers of services in setting research priorities.

SELF-ASSESSMENT QUESTIONS

1. The KDIGO CKD classification includes all of the following in the staging of CKD except:
A. the severity of hypertension.
B. the severity of albuminuria.
C. the level of GFR.
D. the cause of disease.
2. Which statement is true?
A. Low GFR is unimportant in older adults.
B. Higher albuminuria is worse for men than women.
C. Higher albuminuria is associated with acute kidney injury.
D. Assays for proteinuria are more accurate than assays for albuminuria.
3. Racial disparities in kidney failure incidence are in part attributable to:
A. the higher prevalence of APOL1 genetic risk variants in those of European descent.
B. lower socioeconomic status and poorer access to health care among Black individuals.
C. greater rates of smoking among Black individuals.
D. lipoxins.

4. Which statement is most true about rates of new dialysis patients?
A. They are highest in Eastern European countries.
B. An increase in rates of glomerulonephritis is the major driver.
C. Rates are highest among young people.
D. Rates are higher among men than women.
E. Rates are generally lower among groups with lower socioeconomic status.
5. Which statement is true regarding competing risks in comparison of rates of new dialysis patients between groups?
A. Competing risks refers to higher rates seen among health systems in which funding is allocated on a competitive grants basis.
B. Men more than women are affected because testosterone leads to greater competitive drive.
C. Competing risks from transplantation will not be a factor if measured covariates are included and adjustment is made for them.
D. Incident dialysis rates might be higher if vascular mortality associated with CKD were lower.
E. Propensity score matching can largely address the problems raised by competing risks.

REFERENCES

1. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–1544.
2. Global Health Estimates: Life Expectancy and leading causes of death and disability. World Health Organization. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates.
3. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis. 2013;62:245–252.
4. United States Renal Data System. 2016 USRDS annual data report: epidemiology of kidney disease in the United States. In: National Institutes of Health National Institute of Diabetes and Kidney Diseases. ; 2016.
5. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081.
6. National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative. Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.
7. Kidney Disease: improving Global O. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
8. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081.
9. Padala S, Tighiouart H, Inker LA, et al. Accuracy of a GFR estimating equation over time in people with a wide range of kidney function. Am J Kidney Dis. 2012;60:217–224.
9a. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–1749.
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–612.
11. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the laboratory working group of the national kidney disease education program. Clin Chem. 2006;52:5–18.
12. Lim D, Lee D-Y., Cho SH, et al. Diagnostic accuracy of urine dipstick for proteinuria in older outpatients. Kidney Res Clin Pract. 2014;33:199–203.
13. Sumida K, Ndakarni GN, Grams M, et al. Conversion of urine proteincreatinine ratio or urine dipstick protein to urine albumin-creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant-based meta-analysis. Ann Intern Med. 2020;173(6):426–435.
14. Inker LA, Coresh J, Levey AS, et al. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol. 2011;22:2322–2331.
15. Grams ME, Sang Y, Ballew SH, et al. A Meta-analysis of the Association of Estimated GFR, albuminuria, age, race, and sex with acute kidney injury. Am J Kidney Dis. 2015.
16. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. J Am Soc Nephrol. 2002;13:1034–1039.
17. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. JAMA. 2012:2349–2360.
18. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 2013;346:f324.
19. Thomas B, Matsushita K, Abate KH, et al. Global cardiovascular and renal outcomes of reduced GFR. J Am Soc Nephrol. 2017.
20. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease

in the United States. JAMA. 2007;298:2038–2047.
21. Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med. 2016;165(7):473–481.

22. Bruck K, Stel VS, Gambaro G, et al. CKD Prevalence varies across the European general population. J Am Soc Nephrol. 2016;27:2135–2147.
23. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int. 2015;88:950–957.
24. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315:164–174.
25. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329:841–845.
26. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA. 2014;312:2115–2125.
27. United States Renal Data System. Annual Data Report. End Stage Renal Disease: Incidence, Prevalence, Patient Characteristics, and Treatment Modalities. https://adr.usrds.org/2020/end-stage-renal-disease/1incidence-prevalence-patient-characteristics-and-treatment-modalities.
28. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social determinants of racial disparities in CKD. J Am Soc Nephrol. 2016;27:2576–2595.
29. Hsu CY, Iribarren C, McCulloch CE, et al. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med. 2009;169:342–350.
30. Gasparini A, Evans M, Coresh J, et al. Prevalence and recognition of chronic kidney disease in Stockholm healthcare. Nephrol Dial Transplant. 2016;31:2086–2094.
31. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20–29.
32. Hansen HP, Hovind P, Jensen BR, Parving HH. Diurnal variations of glomerular filtration rate and albuminuria in diabetic nephropathy. Kidney Int. 2002;61:163–168.
33. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012;380(9844):807–814.
34. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative metaanalysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514–525.
35. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385:1975–1982.
36. Bello AK, Levin A, Lunney M, et al. ISN Global Kidney Health Atlas. Brussels: International Society of Nephrology; 2019.
37. Sparke C, Moon L, Green F, et al. Estimating the total incidence of kidney failure in Australia including individuals who are not treated by dialysis or transplantation. Am J Kidney Dis. 2013;61:413–419.
38. Chandna SM, Da Silva-Gane M, Marshall C, et al. Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. Nephrol Dial Transplant. 2011;26:1608–1614.
39. Grace BS, Clayton P, Cass A, McDonald SP. Socio-economic status and incidence of renal replacement therapy: a registry study of Australian patients. Nephrol Dial Transplant. 2012;27:4173–4180.
40. Hommel K, Rasmussen S, Kamper A-L., Madsen M. Regional and social inequalities in chronic renal replacement therapy in Denmark. Nephrol Dial Transplant. 2010;25:2624–2632.
41. Morton RL, Schlackow I, Mihaylova B, et al. The impact of social disadvantage in moderate-to-severe chronic kidney disease: an equityfocused systematic review. Nephrol Dial Transplant. 2016;31:46–56.
42. Hecking M, Bieber BA, Ethier J, et al. Sex-specific differences in hemodialysis prevalence and practices and the male-to-female mortality rate: the Dialysis Outcomes and Practice Patterns Study (DOPPS). PLoS Med. 2014;11:e1001750.

43. Yeates KE, Cass A, Sequist TD, et al. Indigenous people in Australia, Canada, New Zealand and the United States are less likely to receive renal transplantation. Kidney Int. 2009;76:659–664.
44. United States Renal Data System. International comparisons. USRDS 2016 annual data report. Atlas of End-Stage Renal Disease in the United States. Vol. 2. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
45. Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol. 2003;14:3270–3280.

References

46. Vajdic CM, McDonald SP, McCredie MRE, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006;296:2823–2831.
47. Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. Kidney Int. 2014;85:158–165.
48. Evangelidis N, Craig JC, Tong A. Song Executive Committee and Investigators. Standardised Outcomes in Nephrology-Haemodialysis (Song-HD): using the Delphi method to gain consensus on core outcomes for haemodialysis trials. J Ren Care. 2015;41(4):211–212.
49. Morton RL, Lioufas N, Dansie KB, et al. Use of patient-reported outcome measures and patient-reported experience measures in renal units in Australia and New Zealand: a cross-sectional survey study. Nephrology. 2020;25(1):14–21.
50. Gilg J, Caskey F, Fogarty D. UK Renal Registry 18th Annual Report: UK renal replacement therapy incidence in 2014: national and centre-specific analyses. Nephron. 2016;132(suppl 1):9–40.

51. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int. 2007;72:1130–1137.
52. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–2019.
53. Wanner C, Krane V, Marz W, et al. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. Kidney Blood Press Res. 2004;27:259–266.
54. Nistor I, Palmer SC, Craig JC, et al. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. Cochrane Database Syst Rev. 2015;5:CD006258.
55. Evangelidis N, Tong A, Manns B, et al. Developing a set of core outcomes for trials in hemodialysis: an international Delphi survey. Am J Kidney Dis. 2017;70(4):464–475.

81

Pathophysiology of Disease Progression in Proteinuric and Nonproteinuric Kidney Disease

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Chronic kidney disease (CKD) is a worldwide threat to public health and has a risk-multiplier effect on major noncommunicable diseases, including cardiovascular diseases.1 More than 697 million individuals are currently affected by CKD worldwide,2 and the number of patients with end-stage kidney disease (ESKD) treated with renal replacement therapy with dialysis or transplantation globally exceeds 2.6 million people.3 Independent of the initial insult, progression to ESKD is relatively common in chronic nephropathies. Many forms of progressive noncystic kidney disease are glomerular in origin, and yet it is the intensity of the accompanying or evolving injury of the tubulointerstitial compartment, rather than the extent of glomerular changes, that predicts the overall decline in kidney function.4 Although genetic factors contribute to susceptibility and progression of kidney disease, increased glomerular capillary flow and pressure consistently leading to increased urinary protein traffic have been claimed as independent factors of progression and poor kidney outcomes in nondiabetic and diabetic kidney disease.5 6 The Ramipril Efficacy in Nephrology (REIN) study was the first trial to formally test the role of proteinuria in the progression of kidney disease.7-9 The trial showed that in 352 patients with proteinuric nephropathies from different etiologies, higher proteinuria at inclusion was associated with faster glomerular filtration rate (GFR) decline and progression of ESKD on follow-up.5 10 Notably, in the REIN trial, larger proteinuria reduction and less residual proteinuria at follow-up were both associated with slower GFR decline and more effective protection against progression to ESKD, independent of treatment allocation.11 Greater proteinuria reduction predicted slower progression, as in the patients with type 2 diabetes with overt nephropathy included in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)6 study and Irbesartan Diabetic Nephropathy Trial (IDNT).12 The predictive pathogenic role of proteinuria was confirmed by a pooled analysis of 2387 CKD patients included in 11 trials, which showed that, irrespective of treatment, short-term changes in proteinuria were strongly consistent with long-term outcomes, whereas no effect on proteinuria predicted no long-term benefit.13 Thus, efforts to dissect the mechanisms and mediators underlying disease progression in proteinuric nephropathies are of utmost importance to help design novel medications to further improve the efficacy of current renoprotective interventions.

FROM GLOMERULAR HEMODYNAMIC CHANGES TO LOSS OF CHARGE- AND SIZE-SELECTIVE PROPERTIES

Under normal conditions, the kidney filtration barrier prevents the passage of macromolecules from the blood into the urinary space. The ability to retain proteins in the glomerular capillary is influenced by the intrinsic permeability and selectivity properties of the three distinct but interacting layers: fenestrated glomerular endothelial cells, the glomerular basement membrane (GBM), and podocytes with their foot processes and slit diaphragms.14-16 The glomerular barrier properties allow for high filtration rate of water and nonrestricted passage of small and middle-size molecules while maintaining charge and size selectivity for serum albumin and larger proteins.

The luminal surface of glomerular endothelial cells is covered by the glycocalyx, a thin, negatively charged layer of membrane-bound glycoproteins, proteoglycans, and glycosaminoglycans.17 The negative charges prevent the transmural passage of anionic circulating proteins, such as albumin, by acting as an electrostatic barrier. Therefore, although endothelial fenestrae are much larger than albumin (about

60 nm in diameter compared with the albumin’s radius of only 3.6 nm), negatively charged circulating macromolecules stay away from the endothelial surface due to electrical repulsion and remain within the circulation. It is now evident that the first restriction to albumin filtration across the glomerular capillary wall consists in the endothelial surface layer, and its role is to substantially decrease protein concentration in the fluid that enters the GBM layer.17 The thickness of the glycocalyx layer appears to be importantly affected by shear stress. In particular, increased fluid shear stress is associated with glycocalyx formation and reorganization on the cell surface in contact with fluid flow.18 Thus, pathologic conditions in which changes in glomerular capillary flow (i.e., reduced flow) may occur are expected to decrease glycocalyx formation, thereby reducing the retention of anionic proteins within the bloodstream. It has been demonstrated that disruption of the endothelial glycocalyx increases glomerular albumin filtration even in the presence of only minor changes in both the GBM and glomerular epithelial cells.

The epithelial filtration slit of podocytes is a major component of the glomerular barrier that also contributes to restrict protein transport. As shown from animal models in the early 1980s, a variety of insults ultimately lead to a common pathway of glomerular capillary hyperperfusion and hypertension, followed by increased permeability with excess passage of proteins across the glomerular capillary wall and progressive glomerular injury.19 Enhanced intraglomerular capillary pressure stretches the glomerular wall, which, in addition to directly injuring glomerular cells,20 impairs the selective function of the glomerular capillary, an effect explained by the appearance of very large pores that exceed the sizes observed in normal conditions and allow increased filtration of plasma proteins (Fig. 81.1).21 Mechanical strain also increases angiotensin II (Ang II) production and expression of Ang II type 1 (AT1) receptors in podocytes.22 Independent of its hemodynamic effects, Ang II may directly impair the glomerular barrier sieving function, possibly through inhibition of podocyte expression of nephrin, the essential protein component of the glomerular slit diaphragm (Fig. 81.2).23 This observation has been confirmed in studies in diabetic animals showing that blockade of Ang II synthesis/activity preserved the expression of nephrin in the glomeruli and prevented

Wistar
40 wk

Fractional pore area (%)

Proteinuric Rats Have Large Pores in the Slit Diaphragm,
Allowing the Passage of Proteins
30

25.5

25
20

17.7
12.8 11.8

15
10
5

Fractional pore area (%)

0.50

30

Fractional pore area (%)

4.1

2.1

1.00

1.50

2.00

2.50

3.00

3.50

4.00

4.50

27.5

25

21.4

20
14.9

15
10

8.1

7.8

5

5.9

5.8
1.5

0
0

MWF
60 wk

5.8

0
0

MWF
40 wk

7.8

6.7

5.8

0.50

1.00

1.50

1.1

2.00

1.2

1.4

0.7

2.50

1.6

3.00

1.6
3.50

4.00

4.50

30
25
20

13.1 14.2

15
8.6

10
5

11.0

14.1
10.7
7.4

2.1

0

5.4

3.4

2.8

2

1.1

2.5

2.50
2.00
3.00
3.50
4.00
Pore area (×10 3 nm2)

Fig. 81.1 Proteinuric Munich Wistar Frömter (MWF) Rats Have Large Pores in the Glomerular Capillary Slit Diaphragm That Exceed the Size Observed in Normal Animals. Distribution of fractional pore area (the fraction of the total pore area for given pore area interval) calculated for slit pores in 40-week-old normal Wistar rats and in 40- or 60-week-old proteinuric MWF rats. (From Gagliardini E, Conti S, Benigni A, Remuzzi G, Remuzzi A. Imaging of the porous ultrastructure of the glomerular epithelial filtration slit. J Am Soc Nephrol. 2010;21[12]:2081–2089.)

0

0.50

1.00

1.50

overt proteinuria.24 Thus, in the setting of diabetes, after the initial insult of hyperglycemia and intraglomerular hypertension, Ang II plays a relevant role in sustaining glomerular injury via persistent activation of Notch1 and Snail signaling in the podocyte, eventually resulting in persistent downregulation of nephrin expression.25 The consistency of the findings in Zucker diabetic fatty rats with overt nephropathy and in patients with type 2 diabetes and established nephropathy provides a robust reason to infer an important role for the Ang II Notch1/Snail axis in perpetuating loss of glomerular size–selective properties. A recent experimental study points to protective actions of mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH), a protein located on the inner mitochondrial membrane, against podocyte injury and progression of diabetic kidney disease.26 In particular, mGPDH expression was found to be downregulated in podocytes of mice and patients with diabetic nephropathy. Podocyte-specific mGPDH knockout mice showed exacerbated diabetes-induced proteinuria, podocyte damage and glomerulosclerosis. Inhibition of the receptor for the advanced glycation end-product (RAGE) abrogated mGPDH-induced podocyte injury and glomerular disease, suggesting that the effects of this mitochondrial protein were exerted through the regulation of the

1.6
4.50

RAGE signaling pathway. Restoration of mGPDH expression in mice with established glomerular injury resulted in renoprotection, making mGPDH a potential therapeutic target for ameliorating diabetic kidney disease.26

Given the abundant evidence that podocyte injury underlies most, if not all, proteinuric kidney diseases, new technologies, including ultrahigh-resolution imaging and genetically engineered models of human disease, were used to develop a biophysical theoretical model of glomerular ultrafiltration.27 28 According to this model, remarkable intraluminal hydrostatic pressure exerts physical forces on the capillary wall that are counteracted by the GBM and by podocytes. When podocytes are injured, they take on a simplified, effaced phenotype, and the slit diaphragm length is much reduced. Concomitantly, the capacity of podocyte foot processes to provide compressive forces to counteract a transmembrane pressure of 40 mm Hg is decreased, thereby reducing the compression of GBM, with eventual increase in the permeability to albumin.27 28 However, this hypothesis does not account for the role played by the subpodocyte space (SPS) which surrounds the filtration membrane and increases under pathologic conditions.29 30 Indeed, evidence from studies that used Munich Wistar Frömter (MWF) rats, an

Glomerular Hypertension Predisposes to
Proteinuria and Renal Disease Progression
Glomerular hypertension

Mechanical strain

2.0
1.5
1.0
0.5
0

*

1.2
Ang II
(pg per μg of cell lysate)

AT1R level
(adjusted for tubulin)

2.5

Ctr

1.0
0.8
0.6
0.4
0.2
0

MS

Durvasula et al.,
Kidney Int, 2004

Ctr

MS

Durvasula et al.,
Kidney Int, 2004
Pore dimension
Proteinuria

Disease progression

Fig. 81.2 Schematic Process Linking Glomerular Capillary Hypertension to Proteinuria and Kidney Disease Progression. After the original disease process causes an initial loss of nephron units, enhanced intraglomerular capillary pressure stretches the glomerular wall, impairing its size-selective function. Mechanical strain also increases angiotensin II (Ang II) production and expression of Ang II type 1 receptors (AT 1R) in podocytes, eventually directly contributing to loss of the glomerular barrier sieving function through inhibition of podocyte slit diaphragm nephrin expression. *P < .05 vs control. Ctr, Control; MS, mechanical strain.
(From Durvasula RV, Petermann AT, Hiromura K, et al. Activation of a local

tissue angiotensin system in podocytes by mechanical strain. Kidney Int. 2004;65[1]:30–39.)

experimental model of spontaneous proteinuria and glomerulosclerosis,31 indicates that loss of glomerular filtration function depends strongly on abnormal rearrangement of podocytes, which causes an expansion of the SPS, an increase in its hydraulic resistance to filtered water, and an increased force acting within the SPS, which tends to detach podocytes from the capillary membrane.32 This evidence is further corroborated by the finding that angiotensin-converting enzyme (ACE) inhibition preserves podocyte structure, reducing the spatial extension of SPS and restoring the hydrodynamic detaching forces which act on podocytes, eventually normalizing water filtration and glomerular barrier function.32

Podocyte Response to Protein Trafficking

Besides being affected by mechanical stress, podocytes are also damaged by excessive protein load resulting from alteration of glomerular permeability to macromolecules.33

Protein uptake by podocytes may occur through binding to megalin, a receptor for albumin and immunoglobulin light chains that is endocytosed after ligand binding, as shown in cultured murine podocytes.34 Excessive protein uptake by podocytes also induces transforming growth factor-β (TGF-β) production, which contributes to cell apoptosis, an additional cause of podocyte loss in proteinuric glomerulopathies.35

Finally, podocytes possess a fully functional endothelin (ET) system, and evidence has highlighted the role of ET-1 in promoting structural and functional alteration of these cells in kidney disease.36 This possibility is supported by the beneficial effects of ET receptor antagonists on the development of proteinuria and glomerular injury in type 1 diabetic animals, partially attributed to attenuation of podocyte loss.24 Although the mechanism of podocyte preservation by ET receptor antagonism remains ill defined, recent observations indicate that ET-1 induces an epithelial-to-mesenchymal transition-like event associated with increased podocyte motility.37 This is dependent on the activation of ETA receptor, which recruits β-arrestin 1, leading to epithelial growth factor receptor translocation and β-catenin phosphorylation, in turn promoting the expression of migratory genes.37

Furthermore, the preservation of podocyte structure under ET receptor antagonism could be secondary to a reduction in the protein load reaching the cells, as suggested by recent findings in diabetic apoE knockout mice.38 In this model, the ETA receptor antagonist atrasentan restored the structural integrity of glomerular endothelial glycocalyx normalizing the barrier against the excessive traffic of albumin through the capillary wall up to podocytes.38

Crosstalk of Podocytes With Mesangial and Endothelial Cells

The mesangial cells are a critical part of the glomerular functional unit, interacting closely with podocytes.39 Alterations in one cell type can produce changes in the others. Whether cytokines generated by podocytes influence mesangial cells has yet to be clearly defined, but

Mechanisms of Progressive Glomerular Injury
GLOMERULAR DISEASE
Proliferation/
extracellular
matrix deposition

Nephron loss
Glomerular
capillary
hypertension

Mesangial
cells
Mechanical
stretching

Endothelial
cells
Podocytes

Glomerular
permeability to
proteins

Proteinuria

GLOMERULOSCLEROSIS

Podocyte protein
accumulation

Ang II
synthesis
Gene
activation

TGF-β

Cytoskeleton
rearrangement/loss of
differentiated phenotype

Slit diaphragm
dysfunction

Foot process
effacement

Fig. 81.3 Mechanisms of Progressive Glomerular Injury. A reduction in the number of nephrons as a consequence of various glomerular diseases results in compensatory glomerular hemodynamic changes that are ultimately detrimental. By mechanical stretching, the increased glomerular capillary pressure directly injures glomerular cells. Glomerular hypertension also impairs the glomerular capillary size-selective function, which causes excessive protein ultrafiltration and, eventually, podocyte injury and proteinuria. Ang II, Angiotensin II; TGF-β, transforming growth factor-β.

the observation that podocyte injury frequently results in mesangial cell proliferation supports the existence of such cytokine crosstalk.[39] Moreover, podocyte abnormalities are accompanied by upregulation of TGF-β messenger RNA and enhanced production of the related protein,[40] which ultimately induces differentiation of mesangial cells into myofibroblasts, abnormal extracellular matrix (ECM) deposition, and glomerulosclerosis.[41,42]

Loss of podocytes secondary to protein-induced cell injury may lead to reduced production of vascular endothelial growth factor (VEGF), a molecule constitutively expressed and secreted by podocytes,[43] influencing the formation of glomerular endothelial fenestrae and eventually promoting endothelial cell apoptosis.[44] How VEGF reaches endothelial cells against the urine flow is not yet known, however. Conversely, in vitro evidence has shown that blockade of VEGF in glomerular endothelial cells enhanced the release of ET-1, which induced nephrin shedding from podocytes,[45] leading to further dysfunction of glomerular protein permeability (Fig. 81.3).

Activation of Parietal Epithelial Cells

Changes in glomerular perm-selective function, as it occurs in proteinuric glomerulopathies, elevate the filtered load of plasma albumin and consequently its concentration in Bowman’s space (Fig. 81.4).[46] Evidence shows that the abnormally filtered albumin impairs the mechanism underlying regeneration of damaged podocytes.[47] Indeed, although podocytes have limited capacity to divide, they are potentially replaced by differentiation of a population of kidney progenitor cells localized within Bowman’s capsule.[48] In vitro, albumin overload blocked the differentiation of human kidney progenitor cells into podocytes expressing podocin and other functional molecules. The albumin-dependent block of relevant gene transcription and of progenitor differentiation was explained by specific binding and sequestration of retinoic acid, which is endogenously synthesized by the cells from retinol (see Fig. 81.4).[47]

The abnormal concentration of proteins in the ultrafiltrate also can lead to activation and accumulation of parietal epithelial cells (PECs) within Bowman’s space as a common response to glomerular injury,[49] as shown in several human proliferative glomerulonephritides. This possibility is supported by findings in MWF rats, which are genetically programmed to undergo kidney damage characterized by excessive migration and proliferation of parietal progenitor cells, leading to their accumulation into cellular lesions and glomerulosclerosis.[50] Along Bowman’s capsule in the adult MWF rats, a population of PECs expressing the neural cell adhesion molecule (NCAM), a marker of metanephric mesenchyme,[51] together with CD24, a mouse and human kidney stemness marker, has been identified.[50] Double-staining of NCAM with the podocyte marker WT1 identified three cell populations lining Bowman’s capsule: immature progenitor cells expressing NCAM, transitional cells expressing markers from progenitor cells and podocytes (NCAM+WT1+), and more differentiated epithelial cells, the parietal podocytes (NCAM WT1+). NCAM+ PECs in vitro differentiate into podocytes, confirming their progenitor nature.[50] We investigated the behavior and role of NCAM+ PECs in the evolution of glomerular lesions in MWF rats that showed early lesions consisting of bridges between the parietal and visceral epithelium, followed by hyperplastic lesions that eventually evolve to sclerosis.[50] The majority of cells in glomerular lesions were claudin+ PECs of Bowman’s capsule, whereas there were few podocytes. In old MWF animals, the

Albumin Concentration in Bowman’s Space
and Regeneration of Damaged Podocytes
Control

Proteinuric glomerulopathy
1206

1.9

178

31
362

0.6

Albumin
concentration
(μg/mL)

A

3000
300
30
3

2698
μg/mL

33
μg/mL

Renal progenitor

Renal progenitor

RARE

RARE

Bowman’s
space
acid

B

Differentiation

Albumin

No differentiation/proliferation

Fig. 81.4 Albumin Concentration in Bowman’s Space and Regeneration of Damaged Podocytes. (A) In the proteinuric glomerulopathies, changes in glomerular perm-selective function results in a high concentration of albumin in Bowman’s space. Color-coded representation of estimated albumin concentration along the entire nephrons in two animal groups (control and kidney mass ablation

model). Numbers represent local group average albumin concentration in micrograms per milliliter. (B) In vitro albumin overload, prevented the differentiation to podocytes from human kidney progenitor cells by sequestering retinoic acid, thus impairing retinoic acid response element (RARE)-mediated transcription of podocyte-specific genes. After early podocyte injury, retinol is lost through the injured glomerular filtration barrier and transformed into retinoic acid. Albumin overload also promotes proliferation and migration of kidney progenitor cells into Bowman's space. (A, Modified from Sangalli F., Carrara F., Gaspari F., et al. Effect of ACE inhibition on glomerular permselectivity and tubular albumin concentration in the renal ablation model. Am J Physiol Renal Physiol. 2011;300[6]:F1291–F1300. B, Modified from Peired A, Angelotti ML, Ronconi E, et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. J Am Soc Nephrol. 2013;24[11]:1756–1768.)

claudin+ PECs increased in number, proliferated, and accumulated in Bowman's space, whereas parietal podocytes decreased. These findings suggested dysregulation of PECs' ability to differentiate into podocytes and to repair injury.50 PECs expressing the progenitor cell marker also have been reported to proliferate and accumulate into the multilayered cellular lesions in patients with glomerulonephritides characterized by extracellular capillary proliferation.52 Upregulation of the CXCR4 chemokine receptor on these progenitor cells was found to be accompanied by high expression of its ligand, SDF-1, in podocytes.52 Moreover, PEC proliferation was associated with increased expression of the AT1 receptor. Reninangiotensin system blockade normalized CXCR4 and AT1 receptor expression on parietal progenitor cells concomitant with regression of

crescentic lesions.52 Together these findings suggest that the glomerular hyperplastic lesions derive from the proliferation and migration of kidney progenitor cells in response to injured podocytes and that the Ang II/AT1 receptor pathway may contribute, together with SDF-1/CXCR4 axis, to the dysregulated response of PEC precursors. A recent study highlighted the key role of complement components C3 and C3a in determining podocyte dysfunction and loss leading to PEC activation.53 Proliferation and migration of PECs in response to activated complement contribute to the development of glomerular sclerotic lesions.53 Consistently, studies on kidney biopsy samples from patients with proteinuric nephropathies and PEC activation showed concomitant glomerular C3 and C3a deposition, indicating its key role in the development of glomerular lesions.53

PROXIMAL TUBULAR CELL INJURY

detected in biopsy specimens from patients with primary focal segmental glomerulosclerosis (FSGS), and a positive correlation was documented between proteinuria and incidence of tubular cell apoptosis.[57] Proximal tubular cell apoptosis has been shown to contribute to tubuloglomerular disconnection and atrophy in response to proteinuria in animal models of proteinuric nephropathies.[56] When passive PHN rats were given the ACE inhibitor lisinopril, which limits proteinuria, tubular atrophy and disconnection were remarkably prevented.[56] PHN animals that did not respond to ACE inhibition in terms of reduction of proteinuria had a glomerular population consisting mainly of atubular glomeruli and glomeruli connected with atrophic tubules, which again is consistent with the possibility that excessive protein tubular handling favors disconnection.[56]

Glomerular ultrafiltration of excessive amounts of plasma protein–associated factors incites tubulointerstitial damage and further promotes the effects of glomerular disease on the tubulointerstitial compartment. The harmful substances in the proteinuric ultrafiltrate may incite tubular epithelial injury with tubular apoptosis, secondary generation of inflammatory mediators, and peritubular inflammation.[41] The mechanisms by which increased urinary protein concentration leads to toxic injury are multifactorial and involve complex interactions among numerous pathways of cellular damage.

Tubular Cell Apoptosis

Kidney proximal tubular cells have a remarkable ability to reabsorb large quantities of albumin through clathrin- and megalin receptor–mediated endocytosis.[54] Kidneys in rats with albumin overload proteinuria[55] or passive Heymann nephritis (PHN)[56] showed increased numbers of terminal deoxynucleotidyl transferase nick-end labeling-positive apoptotic cells in the tubulointerstitial compartment. In tubules, most of the positive cells expressed Ang II type 2 (AT2) receptors.[55] Findings of reduced phosphorylation of extracellular signal-regulated kinase and Bcl-2 suggested an AT2 receptor–mediated mechanism underlying tubular cell apoptosis.[55] Similarly, apoptotic cells expressing both proximal and distal tubular phenotypes were

Tubular Cell Phenotypic Changes

Excessive protein uptake at the apical pole of the proximal tubular cells is associated with phenotypic changes characteristic of an activated state. Insights into specific mechanisms linking protein uptake to cell activation have come from in vitro studies using polarized tubular cells to assess the effect of apical exposure to proteins. Collectively, they show that protein overload induces a proinflammatory phenotype (Fig. 81.5).[58] Indeed, upregulation of inflammatory and fibrogenic genes and production of related proteins have been reported after a challenge of proximal tubular cells with plasma proteins. They

Tubular Cell Phenotype Induced by Proteins

C3

Albumin
RANTES
MCP-1
IL-8
Fractalkine

Endothelin 1

Transferrin
IgG

C3
mRNA
↑C3 convertase

C3

mRNA
Bb

TNF
IL-6

↑C3b
↑C3a
mRNA

C5b-9
C3a
Factor H

C3aR
Heparan sulfate

Fractalkine
TGF- β
Collagen I, IV
Laminin
Fibronectin

↑Heparanase

↓Heparan sulfate
↓Factor H binding
Fig. 81.5 Tubular Cell Phenotypic Changes Induced by Proteins. Protein overload of proximal tubular cells
as a consequence of increased glomerular permeability to proteins activates intracellular signals that promote
cell apoptosis or cause increased production of inflammatory and vasoactive mediators and growth factors.
IgG, Immunoglobulin G; IL-6, interleukin-6; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein-1;
RANTES, regulated upon activation, normal T cell expressed and secreted; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

include cytokines, chemokines, and vasoactive substances, such as monocyte chemotactic protein-1 (MCP-1); regulated upon activation, normal T cell expressed and secreted (RANTES); interleukin-8; fractalkine; and ET-1.58 Moreover, levels of the profibrogenic cytokine TGF-β and its type I receptor, tissue inhibitors of metalloproteinase (TIMP-1 and TIMP-2), as well as membrane surface expression of the αvβ5 integrin, were also highly increased in vitro on stimulation by plasma proteins.58 Investigation of the molecular mechanisms underlying chemokine and growth factor upregulation in proximal tubular cells on protein challenge has focused on the activation of the transcription factor nuclear factor-κB (NF-κB).58 In this context, a recent study showed that albumin is capable of inducing chromatin modification, making the promoter region of the gene encoding miR184, which plays a key role in tubulointerstitial nephritis of diabetic rats, more accessible to NF-κB inducing the miR-184 transcription.59 Other studies confirmed the role of the NF-κB pathway and revealed reactive oxygen as a second messenger.60 The link of excessive protein reabsorption to tubular cell activation has been confirmed by in vivo studies in animal models. Evidence of early activation of proximal tubule cells during nonselective proteinuria was derived from experiments in megalin knockout/NEP25 mice treated with the immunotoxin LMB2, a model of nephrotic syndrome, FSGS, and tubulointerstitial injury.61 Megalin-deficient proximal tubule cells reabsorbed fewer proteins in vivo and expressed fewer tubular injury markers, such as MCP-1 and heme-oxygenase.61 Moreover, a report using podocin knockout mice as a model of FSGS demonstrated that increased reabsorption of abnormally filtered albumin and other proteins in proximal tubule cells was associated with massive increase of lysosomal proteolysis.62 However, high expression of proinflammatory and profibrotic mediators (MCP-1 and TGF-β) in the kidney also occurred almost simultaneously with the increase in tubular content of megalin ligands.62 This suggests that, despite the effective degradation of endocytosed proteins by lysosomes in this model, the excessive protein uptake by tubule cells was still capable of activating phenotypic changes by upregulation of proinflammatory and growth factor encoding genes.

With proteinuria, a putative key factor in tubular cell activation and damage is the excess glomerular filtration of plasma-derived complement C3, the central molecule in the complement system that exerts proinflammatory potential. Kidney tubule epithelial cells appear more susceptible to luminal attack by the C5b-9 membrane attack complex because of the relative lack of membrane-bound complement regulatory proteins, such as membrane cofactor protein (CD46), decay-accelerating factor, or CD55 and CD59 on the apical surface.63 In rats with reduced kidney mass, C3 colocalized with proximal tubular cells engaged in high protein uptake. By limiting the transglomerular passage of proteins, treatment with ACE inhibitors was an effective manner to reduce the C3 load of tubular cells in remnant kidneys.64 C3 and other complement proteins are also found in proximal tubules in kidney biopsy material from patients with nephrosis.65 Furthermore, proximal tubular cells are able to synthesize C3 and other complement factors and to upregulate C3 in response to serum proteins in vitro.66 Studies in C3-deficient kidneys transplanted into wild-type mice have helped clarify that ultrafiltered C3 contributes more to tubular damage induced by protein overload than locally synthesized C3.67

INTERSTITIAL INFLAMMATION AND FIBROSIS

In proteinuric kidney disease, progressive inflammation and injury to the kidney interstitium are secondary events after glomerular or vascular damage. Cytokines and chemokines synthesized by proximal tubular epithelial cells are released into the interstitium, where they contribute to recruit inflammatory cells and lymphocytes causing progressive fibrosis.58

Resident Monocyte and Lymphocyte Activation

The interstitium of normal kidneys contains numerous resident monocytic myelocytes, which express dendritic cell markers and can present antigens.68 Dendritic cells have been described to form an immune sentinel network through the entire kidney, where they probe the environment in search of antigens.69 An inflammatory environment converts the tolerogenic status of resident dendritic cells into an immunogenic one, favoring recruitment of T cells. The importance of kidney dendritic cell activation to kidney injury has been demonstrated by the fact that in transgenic NOH mice (which selectively express the model antigens ovalbumin and hen egg lysozyme in podocytes), dendritic cell depletion resolved established periglomerular mononuclear infiltrates.70 In vitro experiments also have shown that exposure of rat proximal tubular cells to excess autologous albumin, as in the case of proteinuric nephropathies, results in the formation of the N-terminal 24-residue fragment of albumin (ALB1–24).71 This peptide is taken up by dendritic cells, where it is further processed by proteasomes into antigen peptides. These peptides were shown to have the binding motif for major histocompatibility complex (MHC) class I and to be capable of activating CD8+ T cells. Moreover, in vivo, in the rat model of kidney mass ablation, accumulation of dendritic cells in the kidney parenchyma peaked 1 week after surgery and decreased thereafter, concomitant with their appearance in the draining lymph nodes. Dendritic cells from kidney lymph nodes loaded with the albumin peptide ALB1-24 activated syngeneic CD8+ T cells in primary culture.71 Thus, inflammatory stimuli released from damaged tubules after protein overload may represent danger signals that, in the presence of albumin peptides, alert dendritic cells to promote local immune response via CD8+ T cells, which are activated in regional lymph nodes and recruited in the kidney interstitium (Fig. 81.6).

The interstitium infiltrate in most human chronic kidney diseases consists of a number of different effector cells, including macrophages and CD4+ T cells, in addition to CD8+ T cells.72 However, there is substantial functional diversity among CD4+ T cells, so that certain subpopulations, such as CD4+CD25+ T cells (T regulatory [Treg] cells), hinder rather than help the immune response.73 Findings of a study using the green fluorescence protein Foxp3 mouse suggest that Foxp3 expression identifies the regulatory T cell population.74 In the murine model of doxorubicin (Adriamycin) nephropathy, the adoptive transfer of Foxp3-transduced T cells protected against kidney injury. Urinary protein excretion and serum creatinine were reduced, and there were significant decreases in glomerulosclerosis, tubular damage, and interstitial infiltrates.75 These findings highlighted a complex interplay between effector/inflammatory cells and regulatory T cells in the setting of proteinuric chronic kidney diseases.

The modulatory role of Treg cells has also been recently supported by a study in a rat model of kidney ischemia-reperfusion injury (characterized by early proteinuria and increase in serum creatinine levels), after activation of the angiotensin II type 2 receptor (AT2R).76

Treatment with the AT2R receptor agonist Compound 21 (C21) 2 hours before ischemic surgery attenuated postischemic kidney dysfunction and CD3+ and CD4+ T cell infiltration during the acute injury phase (2 hours postreperfusion). During the chronic phase (3–5 days), C21 treatment modulated the kidney microenvironment, as highlighted by increased CD4+ Foxp3 cells and IL-10–secreting T CD4+ cells along with reduced levels of kidney injury molecule-1 and neutrophil gelatinase-associated lipocain.76 These findings pave the way to further explore AT2R-dependent kidney protective effects.

Proteasomal Processing of Albumin by
Renal Dendritic Cells Generates Antigenic Peptides
KIDNEY
Albumin

INFLAMMATION

LYMPH NODES

Dendritic
cell

Fractalkine
NF-κB
activation

CX3CR1
Dendritic
cell

Tubular cell

Proteasome

Acid protease

MHC1

CD8 T cell
8-10 aa
TCR

Alb1-24
Peptide
residues
Alb 1-24
Alb 1-27
Alb 1-30

Alb1-24

Tubular cell

IFN-γ

Proteasome

INTERSTITIAL
INJURY

Fig. 81.6 Proteasomal Processing of Albumin by Kidney Dendritic Cells Generates Antigenic Peptides.
Exposure of proximal tubular cells to excess autologous albumin, as in the case of proteinuric nephropathies, results in the formation of the N-terminal 24-residue fragment of albumin. This peptide is acquired by dendritic cells, where it is further processed by proteasome into antigenic peptides. Then dendritic cells move to regional lymph nodes, where they activate effector CD8 + T cells. These cells are then recruited in the kidney interstitium. Alb1-24, N-terminal 24-residue fragment of albumin; aa, amino

acids; IFN-γ, interferon-γ; MHC, major histocompatibility complex; NF-κB, nuclear factor-κB; TCR, T-cell receptor.

Fibroblast Activation and Extracellular Matrix Deposition

The process of interstitial fibrosis involves the accumulation of myofibroblasts and ECM proteins (Fig. 81.7).77 Resident interstitial fibroblasts and myofibroblasts proliferate in response to macrophagederived profibrogenic cytokines, and their number correlates with the subsequent formation of a scar.77 These cells may derive from transdifferentiated tubular epithelial cells or pericytes of peritubular capillaries, a process promoted by profibrogenic cytokines, including TGF-β, expressed by macrophages.78 Activated kidney fibroblasts may secrete chemokines that in turn may further attract macrophages and perpetuate interstitial injury.79 Moreover, miRNAs are emerging as both downstream effectors of TGF-β–dependent regulation of the fibrogenic process.80 TGF-β upregulates the expression of the profibrotic miR-21 in cultured proximal tubular epithelial cells via Smad3 signaling, both at the transcriptional and posttranscriptional level.81 A functional link between miR-192 and TGF-β–driven kidney fibrosis also has been documented, although the effect of TGF-β on miR-192 expression is not consistent across various studies.80

Eventually, activated fibroblasts produce interstitial matrix components that contribute to interstitial collagen deposition and fibrosis. Increased tubulointerstitial fibrosis is a common feature of kidney injury and results from accumulation of ECM structural proteins. However, it is maintained by continuous remodeling through the proteolytic action of matrix metalloproteinases (MMPs) and the synthesis of new proteins. MMPs are inhibited by tissue inhibitors of TIMPs. Of note, TIMP-3 levels are upregulated in patients with diabetic nephropathy, which anticipates more interstitial fibrosis.82

A recent study suggests that an endoplasmic reticulum resident protein, thioredoxin domain containing 5 (TXNDC5), which was found to be specifically upregulated in collagen-secreting kidney fibroblasts, could be a key mediator in experimental kidney fibrosis.83 Global deletion of txndc5 gene markedly attenuated the extent of kidney fibrosis in three mouse models of chronic kidney disease, that is, unilateral ureteral obstruction, unilateral ischemia-reperfusion injury, and folic acid nephropathy. Mechanistically, TXNDC5 augmented kidney fibrosis by promoting kidney fibroblast activation/proliferation and ECM production through posttranslational stabilization and upregulation of type I TGF-β receptor.83

Accumulating evidence indicates that stimulation of AT2R may exert antifibrotic effects.84 Indeed, AT2R-deficient mice were found to develop a more severe course of nephropathy and kidney fibrosis in models of diabetic kidney disease and 5/6 nephrectomy.85 86

Consistently, in a mouse model of type 1 diabetic nephropathy, treatment with the AT2R agonist C21 significantly reduced the expression of several inflammatory and profibrotic mediators, and upregulated collagen degradation induced by MMP-2 and MMP-9.87

Chronic Hypoxia

One of the most important contributors to the development of tubulointerstitial fibrosis is chronic ischemia.88 The production of

Mechanisms of Interstitial Damage Induced by Proteins
Activated proximal tubular cell

cytokines,
chemokines,
growth factors
Interstitium

Interstitial
fibrosis
EMT Pericyte
Cell
proliferation
ECM protein
synthesis

Myofibroblasts/
fibroblasts

Lymphocyte/macrophage
infiltration
TGF-β
EGF, FGF,
PDGF

Cytokines/
chemokines

ECM
degradation

Fig. 81.7 Mechanisms of Interstitial Damage Induced by Proteins. Cytokines, chemokines, and growth factors are released from the activated tubule into the interstitium, where they contribute to recruit inflammatory cells and lymphocytes, causing progressive fibrosis. ECM, Extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transdifferentiation; FGF, fibroblast growth factor; PDGF, plateletderived growth factor; TGF-β, transforming growth factor-β.

Ang II and the inhibition of the production of nitric oxide underlie chronic vasoconstriction, which may contribute to tissue ischemia and hypoxia.89 In that regard, histologic studies of the human kidney have documented that there is often a loss of peritubular capillaries in areas of tubulointerstitial fibrosis.89 Downregulation of VEGF may be functionally implicated in the progressive attrition of peritubular capillaries and tissue hypoxia. Moreover, given that the size of the interstitial compartment determines the diffusion distance between peritubular capillaries and tubular cells, interstitial fibrosis further impairs tubular oxygen supply. Focal reduction of capillary blood flow leading to the starvation of tubuli may underlie tubular atrophy and loss. Under these conditions the remaining tubules are subject to functional hypermetabolism, with increased oxygen consumption, which in turn creates an even more severely hypoxic environment in the kidney interstitium. Such hypoxia stimulates fibroblast proliferation and ECM production by tubular epithelial cells.90

PRIMARY CHRONIC TUBULOINTERSTITIAL INJURY

Tubulointerstitial disease is common to all chronic progressive kidney diseases, irrespective of the initial trigger or site of injury. Once viewed as an inconsequential corollary to pathologic events that overwhelm glomeruli, tubulointerstitial disease is now recognized as a key and prominent factor in the progression of kidney disease. In addition to the setting of proteinuric nephropathies, inflammation and injury of the kidney interstitium also can occur in nonproteinuric kidney disease, as exemplified by primary chronic tubulointerstitial diseases. In this case the key event is the expression of local nephritogenic antigens. They are derived from kidney cells and tubular basement membranes (TBMs) or exogenous antigens processed by tubular cells. The case of molecules, including drugs, which may become nephritogenic antigens by acting as haptens or through molecular mimicry, is particularly unusual. A humoral response underlies rare cases of interstitial nephritis in which a portion of a drug (e.g., methicillin) may act as a hapten, bind to the TBM, and elicit anti-TBM antibodies.91 Among the numerous causes of primary chronic tubulointerstitial injury, drugs and toxins (see Table 65.1), in addition to genetic cystic diseases, are major players.

Analgesics and Nonsteroidal Antiinflammatory Drugs

Analgesic nephropathy is a specific form of kidney disease characterized by papillary necrosis and chronic interstitial nephritis, caused by prolonged and excessive consumption of analgesic mixtures. It is invariably caused by compound analgesic mixtures containing aspirin or antipyrine in combination with phenacetin, paracetamol, or salicylamide and caffeine or codeine, in popular over-the-counter proprietary mixtures.92 The mechanisms responsible for the kidney injury are incompletely understood. Phenacetin is metabolized to acetaminophen and to reactive intermediates that can injure cells, in part by lipid peroxidation.93 These metabolites tend to accumulate in the medulla along the medullary osmotic gradient (created by the countercurrent system). As a result, the highest concentrations are seen at the papillary tip, the site of the initial vascular lesions.94 The potentiating effect of aspirin, with both phenacetin and acetaminophen, may be related to two factors. (1) Acetaminophen undergoes oxidative metabolism by prostaglandin H synthase to reactive quinonimine, which is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. However, if acetaminophen is ingested with aspirin, the aspirin is converted to salicylate, which becomes highly concentrated and depletes glutathione in both the cortex and papillae of the kidney. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.94 95 (2) Aspirin and other nonsteroidal antiinflammatory drugs suppress prostaglandin production by inhibiting cyclooxygenase enzymes. Kidney blood flow, particularly within the kidney medulla living at the edge of hypoxia, is highly dependent on systemic and local production of vasodilatory prostaglandins. The final injury is therefore due to both the hemodynamic and the cytotoxic effects of these drugs, resulting in papillary necrosis and interstitial fibrosis.

Aristolochic Acid

In 1992 nephrologists in Belgium noted an increasing number of women presenting with kidney failure, often near end stage, after their exposure to a slimming regimen containing Chinese herbs.96 97 The main histologic lesion in human biopsy samples, which is located principally in the cortex, is extensive interstitial fibrosis with atrophy and loss of the tubules. Cellular infiltration of the interstitium is scarce. Important tryptase-positive mast cells were observed in the fibrotic areas in kidney biopsy samples.98 Thickening of the walls of the interlobular and afferent arterioles resulted from endothelial cell swelling. The glomeruli are spared, relatively speaking, and immune deposits are not observed. These findings suggest that the primary lesions may be centered in the vessel walls, thereby leading to ischemia and interstitial fibrosis.99

A plant nephrotoxin, aristolochic acid, has been proposed as the possible etiologic agent (see Chapter 65). Balkan endemic nephropathy, a chronic, familial, noninflammatory tubulointerstitial disease, most commonly seen in southeastern Europe, also has been potentially attributed to chronic exposure to dietary aristolochic acid (see Chapter 65).100

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disorder, accounting for 8% to 10% of patients receiving renal replacement therapy for ESKD worldwide.101 In ADPKD patients, mutations in genes encoding for polycystin 1 or polycystin 2 lead to polycystin complex dysfunction. This results in reduced intracellular calcium concentration, leading to higher activity of adenylyl cyclase enzyme and upregulation of 3 ,5 -cyclic adenosine monophosphate (cAMP) levels.102 In turn, high intracellular cAMP levels lead to aberrant tubular epithelial cell proliferation and chloride-driven fluid secretion, the two key components of the process of cyst formation and growth in ADPKD.103 In addition, activation of the Ser/Thr kinase mammalian target of rapamycin (mTOR) may also contribute to cyst expansion.104 Uncontrolled cyst growth results in crowding of adjacent nephrons, injury of normal kidney parenchyma, interstitial inflammation and fibrosis, and eventually, substantial enlargement of the kidneys and progressive kidney failure.105 106

It is assumed that kidney function starts to decline only after several decades, whereas cyst formation and growth already starts in utero This preservation of GFR in early-stage ADPKD has been posited to be caused by compensatory hyperfiltration of remnant nephrons that have not yet been lost due to disease progression, a phenomenon referred to as glomerular hyperfiltration.107 In the long term, however, this maladaptive response to reduced nephron number may translate into accelerated loss of residual hyperfunctioning nephrons and relentless progression to kidney failure. Indeed, evidence points to glomerular hyperfiltration as a risk factor for ADPKD progression. In particular, in 180 children with ADPKD, glomerular hyperfiltration (defined as creatinine clearance ≥140 mL/min/1.73 m2) was associated with an increased rate of kidney growth and faster GFR decline.108 Similarly, among 91 adult ADPKD patients, glomerular hyperfiltration at baseline (140 mL/min/1.73 m2) was associated with higher GFR loss during the 15-year follow-up.109 Therefore, the combination of cyst growth, tubulointerstitial injury, and maladaptive hyperfiltration of the remaining nephrons eventually results in ADPKD progression.

Insights into the pathophysiology of ADPKD have helped develop novel disease-modifying treatments (see Chapter 46).110 111

CONCLUSIONS

There is now clear evidence that, rather than simply a marker of damage, abnormal ultrafiltration of proteins can be toxic to the kidney and incites complex pathways and mediators that target glomerular, tubular, and interstitial cells, eventually promoting kidney disease progression to ESKD. Moreover, tubulointerstitial injury is also common in nonproteinuric kidney diseases and is critical for their progression to ESKD. More insights in the pathophysiologic mechanisms of progressive proteinuric and nonproteinuric kidney diseases will be instrumental to search for novel biomarkers that allow intervention in the earlier stages of CKD and may open the way to new treatments.

SELF-ASSESSMENT QUESTIONS

1. What is the pathologic podocyte response to protein trafficking throughout the glomerulus?
A. Podocytes start to proliferate.
B. Podocytes are damaged by excessive protein load and uptake of albumin.
C. Podocytes adhere to Bowman’s capsule.
2. What is the main consequence of podocyte loss on endothelial cells during chronic kidney injury?
A. Endothelial cell apoptosis
B. Endothelial cell proliferation
C. Increase of vascularization of the kidney

3. What is the role of resident dendritic cells in the kidney during proteinuric diseases?
A. Dendritic cells proliferate.
B. Dendritic cells generate albumin peptides that activate CD8+ T cells.
C. Dendritic cells undergo apoptosis.
4. How does the progressive enlargement of kidney cysts in autosomal dominant polycystic kidney disease develop?
A. It develops from mesangial cell proliferation.
B. It develops from endothelial cell proliferation.
C. It develops from tubular cell proliferation and fluid transport into the cyst cavity.

REFERENCES

1. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258–1270.
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709–733.
3. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385(9981):1975–1982.
4. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis. 1992;20(1):1–17.
5. Ruggenenti P, Perna A, Mosconi L, et al. Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. The Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Kidney Int Suppl. 1997;63:S54–S57.
6. de Zeeuw D, Remuzzi G, Parving H-H, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int. 2004;65(6):2309–2320.
7. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349(9069):1857–1863.
8. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet. 1998;352(9136):1252–1256.
9. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999;354(9176):359–364.
10. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in nondiabetic proteinuric chronic nephropathies. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Kidney Int. 1998;53(5):1209–1216.
11. Ruggenenti P, Perna A, Remuzzi G. GISEN Group Investigators. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. Kidney Int. 2003;63(6):2254–2261.
12. Hunsicker LG, Atkins RC, Lewis JB, et al. Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial. Kidney Int Suppl. 2004;(92):S99–S101.
13. Ruggenenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal diseases. Lancet. 2001;357(9268):1601–1608.
14. Levidiotis V, Power DA. New insights into the molecular biology of the glomerular filtration barrier and associated disease. Nephrology (Carlton). 2005;10(2):157–166.
15. Haraldsson B, Nyström J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol Rev. 2008;88(2):451–487.
16. Jarad G, Miner JH. Update on the glomerular filtration barrier. Curr Opin Nephrol Hypertens. 2009;18(3):226–232.
17. Hjalmarsson C, Johansson BR, Haraldsson B. Electron microscopic evaluation of the endothelial surface layer of glomerular capillaries. Microvasc Res. 2004;67(1):9–17.
18. Yao Y, Rabodzey A, Dewey CF. Glycocalyx modulates the motility and proliferative response of vascular endothelium to fluid shear stress. Am J Physiol Heart Circ Physiol. 2007;293(2):H1023–H1030.
19. Zoja C, Abbate M, Remuzzi G. Progression of chronic kidney disease: insights from animal models. Curr Opin Nephrol Hypertens. 2006;15(3):250–257.
20. Ibrahim HN, Rosenberg ME, Hostetter TH. Role of the reninangiotensin-aldosterone system in the progression of renal disease: a critical review. Semin Nephrol. 1997;17(5):431–440.
21. Gagliardini E, Conti S, Benigni A, Remuzzi G, Remuzzi A. Imaging of the

porous ultrastructure of the glomerular epithelial filtration slit. J Am Soc Nephrol. 2010;21(12):2081–2089.

22. Durvasula RV, Petermann AT, Hiromura K, et al. Activation of a local tissue angiotensin system in podocytes by mechanical strain. Kidney Int. 2004;65(1):30–39.
23. Benigni A, Gagliardini E, Remuzzi G. Changes in glomerular permselectivity induced by angiotensin II imply podocyte dysfunction and slit diaphragm protein rearrangement. Semin Nephrol. 2004;24(2):131–140.
24. Gagliardini E, Corna D, Zoja C, et al. Unlike each drug alone, lisinopril if combined with avosentan promotes regression of renal lesions in experimental diabetes. Am J Physiol Renal Physiol. 2009;297(5):F1448–F1456.
25. Gagliardini E, Perico N, Rizzo P, et al. Angiotensin II contributes to diabetic renal dysfunction in rodents and humans via Notch1/Snail pathway. Am J Pathol. 2013;183(1):119–130.
26. Qu H, Gong X, Liu X, et al. Deficiency of mitochondrial glycerol 3-phosphate dehydrogenase exacerbates podocyte injury and the progression of diabetic kidney disease. Diabetes. 2021;70(6):1372–1387.
27. Butt L, Unnersjö-Jess D, Höhne M, et al. A molecular mechanism explaining albuminuria in kidney disease. Nat Metab. 2020;2(5):461–474.
28. Benzing T, Salant D. Insights into glomerular filtration and albuminuria. N Engl J Med. 2021;384(15):1437–1446.
29. Neal CR, Muston PR, Njegovan D, et al. Glomerular filtration into the subpodocyte space is highly restricted under physiological perfusion conditions. Am J Physiol Renal Physiol. 2007;293(6):F1787–F1798.
30. Remuzzi A, Remuzzi G. Insights into glomerular filtration and albuminuria. N Engl J Med. 2021;385(5):477.
31. Remuzzi A, Puntorieri S, Mazzoleni A, Remuzzi G. Sex related differences in glomerular ultrafiltration and proteinuria in MunichWistar rats. Kidney Int. 1988;34(4):481–486.
32. Remuzzi A, Conti S, Ene-Iordache B, et al. Role of ultrastructural determinants of glomerular permeability in ultrafiltration function loss. JCI Insight. 2020;5(13):137249.
33. Perico L, Conti S, Benigni A, Remuzzi G. Podocyte-actin dynamics in health and disease. Nat Rev Nephrol. 2016;12(11):692–710.
34. Yamazaki H, Saito A, Ooi H, Kobayashi N, Mundel P, Gejyo F. Differentiation-induced cultured podocytes express endocytically active megalin, a heymann nephritis antigen. Nephron Exp Nephrol. 2004;96(2):e52–e58.
35. Schiffer M, Bitzer M, Roberts IS, et al. Apoptosis in podocytes induced by TGF-beta and Smad7. J Clin Invest. 2001;108(6):807–816.
36. Barton M, Tharaux P-L. Endothelin and the podocyte. Clin Kidney J. 2012;5(1):17–27.
37. Buelli S, Rosanò L, Gagliardini E, et al. β-arrestin-1 drives endothelin1-mediated podocyte activation and sustains renal injury. J Am Soc Nephrol. 2014;25(3):523–533.
38. Boels MGS, Avramut MC, Koudijs A, et al. Atrasentan reduces albuminuria by restoring the glomerular endothelial glycocalyx barrier in diabetic nephropathy. Diabetes. 2016;65(8):2429–2439.
39. Schlöndorff D, Banas B. The mesangial cell revisited: no cell is an island. J Am Soc Nephrol. 2009;20(6):1179–1187.
40. Abbate M, Zoja C, Morigi M, et al. Transforming growth factor-beta1 is up-regulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. Am J Pathol. 2002;161(6):2179–2193.
41. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006;17(11):2974–2984.
42. Barnes JL, Gorin Y. Myofibroblast differentiation during fibrosis: role of NAD(P)H oxidases. Kidney Int. 2011;79(9):944–956.
43. Ballermann BJ. Contribution of the endothelium to the glomerular permselectivity barrier in health and disease. Nephron Physiol. 2007;106(2):p19–p25.
44. Segerer S, Kretzler M, Strutz F, et al. Mechanisms of tissue injury and

repair in renal diseases. In: Schrier R, ed. Diseases of the Kidney and Urinary Tract. Philadelphia: Lippincott Williams & Wilkins; 2007.
45. Collino F, Bussolati B, Gerbaudo E, et al. Preeclamptic sera induce nephrin shedding from podocytes through endothelin-1 release by endothelial glomerular cells. Am J Physiol Renal Physiol. 2008;294(5):F1185–F1194.

References

46. Sangalli F, Carrara F, Gaspari F, et al. Effect of ACE inhibition on glomerular permselectivity and tubular albumin concentration in the renal ablation model. Am J Physiol Renal Physiol. 2011;300(6):F1291–F1300.
47. Peired A, Angelotti ML, Ronconi E, et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. J Am Soc Nephrol. 2013;24(11):1756–1768.
48. Romagnani P. Toward the identification of a “renopoietic system”. Stem Cell. 2009;27(9):2247–2253.
49. Smeets B, Angelotti ML, Rizzo P, et al. Renal progenitor cells contribute to hyperplastic lesions of podocytopathies and crescentic glomerulonephritis. J Am Soc Nephrol. 2009;20(12):2593–2603.
50. Benigni A, Morigi M, Rizzo P, et al. Inhibiting angiotensin-converting enzyme promotes renal repair by limiting progenitor cell proliferation and restoring the glomerular architecture. Am J Pathol. 2011;179(2):628–638.
51. Abbate M, Brown D, Bonventre JV. Expression of NCAM recapitulates tubulogenic development in kidneys recovering from acute ischemia. Am J Physiol. 1999;277(3):F454–F463.
52. Rizzo P, Perico N, Gagliardini E, et al. Nature and mediators of parietal epithelial cell activation in glomerulonephritides of human and rat. Am J Pathol. 2013;183(6):1769–1778.
53. Morigi M, Locatelli M, Rota C, et al. A previously unrecognized role of C3a in proteinuric progressive nephropathy. Sci Rep. 2016;6:28445.
54. Birn H, Christensen EI. Renal albumin absorption in physiology and pathology. Kidney Int. 2006;69(3):440–449.
55. Tejera N, Gómez-Garre D, Lázaro A, et al. Persistent proteinuria up-regulates angiotensin II type 2 receptor and induces apoptosis in proximal tubular cells. Am J Pathol. 2004;164(5):1817–1826.
56. Benigni A, Gagliardini E, Remuzzi A, Corna D, Remuzzi G. Angiotensinconverting enzyme inhibition prevents glomerular-tubule disconnection and atrophy in passive Heymann nephritis, an effect not observed with a calcium antagonist. Am J Pathol. 2001;159(5):1743–1750.
57. Erkan E, Garcia CD, Patterson LT, et al. Induction of renal tubular cell apoptosis in focal segmental glomerulosclerosis: roles of proteinuria and Fas-dependent pathways. J Am Soc Nephrol. 2005;16(2):398–407.
58. Zoja C, Abbate M, Remuzzi G. Progression of renal injury toward interstitial inflammation and glomerular sclerosis is dependent on abnormal protein filtration. Nephrol Dial Transplant. 2015;30(5):706–712.
59. Zanchi C, Macconi D, Trionfini P, et al. MicroRNA-184 is a downstream effector of albuminuria driving renal fibrosis in rats with diabetic nephropathy. Diabetologia. 2017;60(6):1114–1125.
60. Morigi M, Macconi D, Zoja C, et al. Protein overload-induced NFkappaB activation in proximal tubular cells requires H(2)O(2) through a PKC-dependent pathway. J Am Soc Nephrol. 2002;13(5):1179–1189.
61. Motoyoshi Y, Matsusaka T, Saito A, et al. Megalin contributes to the early injury of proximal tubule cells during nonselective proteinuria. Kidney Int. 2008;74(10):1262–1269.
62. Nielsen R, Mollet G, Esquivel EL, et al. Increased lysosomal proteolysis counteracts protein accumulation in the proximal tubule during focal segmental glomerulosclerosis. Kidney Int. 2013;84(5):902–910.
63. Nangaku M. Complement regulatory proteins in glomerular diseases. Kidney Int. 1998;54(5):1419–1428.
64. Abbate M, Zoja C, Rottoli D, et al. Antiproteinuric therapy while preventing the abnormal protein traffic in proximal tubule abrogates protein- and complement-dependent interstitial inflammation in experimental renal disease. J Am Soc Nephrol. 1999;10(4):804–813.
65. Hsu SI-H, Couser WG. Chronic progression of tubulointerstitial damage in proteinuric renal disease is mediated by complement activation: a therapeutic role for complement inhibitors? J Am Soc Nephrol. 2003;14(7

suppl 2):S186–S191.
66. Pratt JR, Basheer SA, Sacks SH. Local synthesis of complement component C3 regulates acute renal transplant rejection. Nat Med. 2002;8(6):582–587.
67. Abbate M, Zoja C, Corna D, et al. Complement-mediated dysfunction of glomerular filtration barrier accelerates progressive renal injury. J Am Soc Nephrol. 2008;19(6):1158–1167.

68. Ferenbach D, Hughes J. Macrophages and dendritic cells: what is the difference? Kidney Int. 2008;74(1):5–7.
69. Soos TJ, Sims TN, Barisoni L, et al. CX3CR1+ interstitial dendritic cells form a contiguous network throughout the entire kidney. Kidney Int. 2006;70(3):591–596.
70. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, et al. Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. J Clin Invest. 2009;119(5):1286–1297.
71. Macconi D, Chiabrando C, Schiarea S, et al. Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. J Am Soc Nephrol. 2009;20(1):123–130.
72. Sean Eardley K, Cockwell P. Macrophages and progressive tubulointerstitial disease. Kidney Int. 2005;68(2):437–455.
73. Thornton AM, Piccirillo CA, Shevach EM. Activation requirements for the induction of CD4+CD25+ T cell suppressor function. Eur J Immunol. 2004;34(2):366–376.
74. Fontenot JD, Rasmussen JP, Williams LM, Dooley JL, Farr AG, Rudensky AY. Regulatory T cell lineage specification by the forkhead transcription factor foxp3. Immunity. 2005;22(3):329–341.
75. Wang YM, Zhang GY, Wang Y, et al. Foxp3-transduced polyclonal regulatory T cells protect against chronic renal injury from adriamycin. J Am Soc Nephrol. 2006;17(3):697–706.
76. Ali R, Patel S, Hussain T. Angiotensin type 2 receptor activation limits kidney injury during the early phase and induces Treg cells during the late phase of renal ischemia. Am J Physiol Renal Physiol. 2021;320(5): F814–F825.
77. Eddy AA. Molecular insights into renal interstitial fibrosis. J Am Soc Nephrol. 1996;7(12):2495–2508.
78. Lan HY. Tubular epithelial-myofibroblast transdifferentiation mechanisms in proximal tubule cells. Curr Opin Nephrol Hypertens. 2003;12(1):25–29.
79. Tampe D, Zeisberg M. Potential approaches to reverse or repair renal fibrosis. Nat Rev Nephrol. 2014;10(4):226–237.
80. Trionfini P, Benigni A, Remuzzi G. MicroRNAs in kidney physiology and disease. Nat Rev Nephrol. 2015;11(1):23–33.
81. Zhong X, Chung ACK, Chen H-Y, Meng X-M, Lan HY. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. J Am Soc Nephrol. 2011;22(9):1668–1681.
82. Kassiri Z, Oudit GY, Kandalam V, et al. Loss of TIMP3 enhances interstitial nephritis and fibrosis. J Am Soc Nephrol. 2009;20(6):1223–1235.
83. Chen Y-T, Jhao P-Y, Hung C-T, et al. Endoplasmic reticulum protein TXNDC5 promotes renal fibrosis by enforcing TGF-β signaling in kidney fibroblasts. J Clin Invest. 2021;131(5):143645.
84. Sumners C, Peluso AA, Haugaard AH, Bertelsen JB, Steckelings UM. Anti-fibrotic mechanisms of angiotensin AT2 -receptor stimulation. Acta Physiol (Oxf). 2019;227(1):e13280.
85. Chang S-Y, Chen Y-W, Chenier I, Tran SLM, Zhang S-L. Angiotensin II type II receptor deficiency accelerates the development of nephropathy in type I diabetes via oxidative stress and ACE2. Exp Diabetes Res. 2011;2011:521076.
86. Benndorf RA, Krebs C, Hirsch-Hoffmann B, et al. Angiotensin II type 2 receptor deficiency aggravates renal injury and reduces survival in chronic kidney disease in mice. Kidney Int. 2009;75(10):1039–1049.
87. Koulis C, Chow BSM, McKelvey M, et al. AT2R agonist, compound 21, is reno-protective against type 1 diabetic nephropathy. Hypertension.

2015;65(5):1073–1081.
88. Nangaku M. Mechanisms of tubulointerstitial injury in the kidney: final common pathways to end-stage renal failure. Intern Med. 2004;43(1):9–17.
89. Nakagawa T, Kang D-H, Ohashi R, et al. Tubulointerstitial disease: role of ischemia and microvascular disease. Curr Opin Nephrol Hypertens. 2003;12(3):233–241.
90. Norman JT, Clark IM, Garcia PL. Hypoxia promotes fibrogenesis in human renal fibroblasts. Kidney Int. 2000;58(6):2351–2366.
91. Markowitz GS, Perazella MA. Drug-induced renal failure: a focus on tubulointerstitial disease. Clin Chim Acta. 2005;351(1–2):31–47.

References

92. Kinkaid-Smith P, Nanra RS. Disease of the kidney. In: Schreirer RW, Gottschalk CW, eds. Disease of the Kidney. Boston: Little Brown; 1993:1099–1129.
93. Bach PH, Hardy TL. Relevance of animal models to analgesic-associated renal papillary necrosis in humans. Kidney Int. 1985;28(4):605–613.
94. Duggin GG. Combination analgesic-induced kidney disease: the Australian experience. Am J Kidney Dis. 1996;28(1 suppl 1):S39–S47.
95. Bennett WM, DeBroe ME. Analgesic nephropathy-a preventable renal disease. N Engl J Med. 1989;320(19):1269–1271.
96. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet. 1993;341(8842):387–391.
97. Jadot I, Declèves A-E, Nortier J, Caron N. An integrated view of aristolochic acid nephropathy: update of the literature. Int J Mol Sci. 2017;18(2):E297.
98. Wu Y, Liu Z, Hu W, Li L. Mast cell infiltration associated with tubulointerstitial fibrosis in chronic Aristolochic Acid Nephropathy. Hum Exp Toxicol. 2005;24(2):41–47.
99. Depierreux M, Van Damme B, Vanden Houte K, Vanherweghem JL. Pathologic aspects of a newly described nephropathy related to the prolonged use of Chinese herbs. Am J Kidney Dis. 1994;24(2):172–180.
100. De Broe ME. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. Kidney Int. 2012;81(6):513–515.
101. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med. 2008;359(14):1477–1485.
102. Bergmann C, Weiskirchen R. It’s not all in the cilium, but on the road to it: genetic interaction network in polycystic kidney and liver diseases and how trafficking and quality control matter. J Hepatol. 2012;56(5):1201–1203.

103. Gerdes JM, Davis EE, Katsanis N. The vertebrate primary cilium in development, homeostasis, and disease. Cell. 2009;137(1):32–45.
104. Shillingford JM, Murcia NS, Larson CH, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. Proc Natl Acad Sci U S A. 2006;103(14):5466–5471.
105. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med. 2011;364(16):1533–1543.
106. Chebib FT, Torres VE. Autosomal dominant polycystic kidney disease: core curriculum 2016. Am J Kidney Dis. 2016;67(5):792–810.
107. Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. Clin J Am Soc Nephrol. 2006;1(1):148–157.
108. Helal I, Reed B, McFann K, et al. Glomerular hyperfiltration and renal progression in children with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2011;6(10):2439–2443.
109. Gentile G, Mastroluca D, Perna A, Remuzzi G, Ruggenenti P. Glomerular Hyperfiltration is a Common Risk Factor for Accelerated GFR Decline in Young Adults with Autosomal Polycystic Kidney Disease (ADPKD). Conference: American Society of Nephrology (ASN) Kidney Week. 2014.
110. Caroli A, Perico N, Perna A, et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. Lancet. 2013;382(9903):1485–1495.
111. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407–2418.

82

Slowing the Progression of Kidney Disease

Aminu K. Bello, Marcello Tonelli

INTRODUCTION

Prior to 2002, there was no standardized definition for chronic kidney disease (CKD). Instead, terms such as chronic renal failure or insufficiency, chronic renal disease, and progressive renal insufficiency were used.[1] In 2002, the US National Kidney Foundation established the Kidney Disease Outcomes Quality Initiative (KDOQI)[2]; an early goal was to define CKD and classify its severity using nomenclature that could be scaled and spread. The KDOQI framework defined CKD as structural or functional abnormalities of the kidney present for at least 3 months, manifested either as kidney damage (most frequently detected as persistent albuminuria) with or without a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2, or as decreased GFR with or without other evidence of kidney damage.[2] In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) updated the framework to enhance its capacity for predicting risk of progression to kidney failure or development of cardiovascular disease (CVD).[3] Central to this revision was to highlight the role of albuminuria as a marker of damage, an early manifestation of CKD, and an important prognostic factor for the progression of kidney disease and development of CVD.[3] Developing a common framework for the presence and severity of CKD was instrumental in accelerating the pace of clinical research that led to better outcomes for people with kidney disease. In this chapter, we review techniques for evaluating and monitoring key indicators of CKD, describe factors associated with the risk of CKD progression, and outline measures to prevent adverse outcomes associated with CKD, such as kidney failure and CVD.

TECHNIQUES FOR EVALUATING AND MONITORING KEY INDICATORS OF CHRONIC KIDNEY DISEASE

Glomerular Filtration Rate

The key index of kidney function is the GFR, which cannot be measured directly but can be estimated from the urinary clearance of an ideal filtration marker. The most common methods used to estimate GFR are serum creatinine (SCr) concentration, creatinine clearance (CrCl), and estimation equations based on serum creatinine such as the Cockcroft-Gault (C-G) equation, and equations used in the Modification of Diet in Renal Disease (MDRD) study and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[4] Details of GFR estimation are presented in Chapters 3

Albuminuria

The preferred method of measuring proteinuria or albuminuria is by calculating urine protein-to-creatinine ratio (PCR) or albumin-tocreatinine ratio (ACR) on a random urine specimen, respectively.[3] Because it is highly accurate and convenient, ACR is preferred to the 24-hour urine collection for quantitative measurement of significant urinary albumin. Random daytime specimens are acceptable if the preferred first morning specimens are not available. The relative merits of the PCR compared with ACR for detection and monitoring kidney damage are unclear.[3] However, because albuminuria is a more sensitive marker than total protein in CKD due to diabetes, hypertension, and glomerular diseases, the ratio in adult spot urine samples should ideally be measured with ACR[3]; if ACR is high, PCR is acceptable. Methods are being developed to estimate ACR directly from PCR.[5]

EPIDEMIOLOGY AND BURDEN OF CHRONIC KIDNEY DISEASE

The number of individuals with kidney failure (end-stage kidney disease) represents less than 2% of those with CKD (stages 1–4). Although most people with CKD will not develop kidney failure, the minority that do pose a significant challenge to the health care system in terms of morbidity and cost, especially in low- and middle-income countries.

Globally, CKD is an important public health problem. According to estimates from the Global Burden of Disease Injuries and Risk Factors study, approximately 1.2 million people died from CKD worldwide in 2017, and the global all-age mortality rate linked to CKD increased over 40% between 1990 and 2017.6 In absolute terms, CKD is estimated to affect approximately 700 million people around the world, with a global prevalence of 9.1% (range, 8.5%–9.8%), and the global all-age prevalence of CKD has increased over 29% over the last 3 decades.6 CKD is associated with high risk of mortality and hospitalization, as well as high health care costs. Like diabetes, CKD has been described as a coronary artery disease “risk equivalent,” reflecting the high risk of vascular disease in this population.7

Susceptibility to CKD is higher in certain families and among members of certain races. This highlights the possibility of genetic predisposition to CKD. For instance, in Canada, the disproportionate burden of CKD among Indigenous populations may reflect the high prevalence of major drivers of CKD such as hypertension and diabetes; patterns are similar for Indigenous populations in Australia and New Zealand.

Among the key risk factors for the initiation of CKD are hypertension, diabetes, hyperlipidemia, obesity, and smoking. In low- and middleincome countries, key risk factors for initiation of CKD may also include communicable diseases such as HIV, hepatitis B and C, malaria, schistosomiasis, and tuberculosis. This double burden of communicable and noncommunicable risk factors has led to a growing burden of CKD across all world regions and population subgroups. Further details on the epidemiology of CKD are presented in Chapter 80

RISK FACTORS FOR PROGRESSION OF CHRONIC KIDNEY DISEASE

The natural history of CKD progresses from susceptibility associated with the presence of risk factors (Table 82.1), to the development of

The Conceptual Model of CKD
Potential antecedents of CKD
Stages of CKD
Consequences of CKD

Increased
risk

Normal
Screening
for CKD
risk factors

Complications

Damage

↓ GFR

Kidney
failure

Death

Diagnosis and
Replacement
Estimate
treatment;
by dialysis and
progression;
treat comorbid
transplantation
treat complications;
conditions;
prepare for
replacement
slow progression

Fig. 82.1 Conceptual model of chronic kidney disease (CKD). GFR, Glomerular filtration rate. (Modified from Levey AS, Stevens LA, Coresh J. Conceptual model of CKD: applications and implications. Am J Kidney Dis. 2009;53[suppl 3]:S4–16.)

CKD risk
reduction;
screening for
CKD

Risk Factors Associated With the Initiation and Progression of Chronic Kidney Disease

TABLE 82.1

Initiation Factors

Progression Factors

Systemic hypertension
Diabetes mellitus
Cardiovascular disease
Dyslipidemia

Smoking
Obesity/metabolic syndrome
Hyperuricemia
Low socioeconomic status
Nephrotoxin exposure: abuse of NSAIDs, analgesics, traditional herbal remedies; exposure to heavy metals, lead

Older age
Sex (male)
Race/ethnicity
Genetic predisposition
Poor BP control
Poor glycemic control
Proteinuria
Cardiovascular disease
Dyslipidemia
Smoking
Obesity/metabolic syndrome
Hyperuricemia
Low socioeconomic status
Nephrotoxins (NSAIDs, contrast agents)
Recurrent AKI events
Metabolic acidosis

AKI, Acute kidney injury; CKD, chronic kidney disease; NSAIDs, nonsteroidal antiinflammatory drugs.

CKD and progression to kidney failure requiring renal replacement therapy, CVD, and/or death (Fig. 82.1).
The risk of progressive CKD is variable and affected by several factors, including demographic characteristics, clinical factors, and access to care (see Table 82.1).[8] Epidemiologic data suggest that the natural history of CKD stages 3 to 4 and development of other adverse health outcomes vary based on patients' baseline risk factor profiles (Fig. 82.2).[8] Many CKD patients with GFR less than 60 mL/min/1.73 m^2 do not reach stage 5 (kidney failure); among those with disease progression, the process is often not linear, with breakpoints in the progression pattern due to a number of factors, including the natural progression of underlying conditions such as infections, dehydration, CKD risk factors (blood pressure [BP], proteinuria), exposure to nephrotoxins (drugs, contrast agents), and acute kidney injury (AKI).

The rate of progression of CKD also varies based on the severity of underlying disease and between individual patients. Historically, the rate of decline in GFR of patients with diabetic nephropathy has been among the fastest, averaging around −10 mL/min/yr. Control of hypertension slows the rate of GFR decline to −5 mL/min/yr, with further improvement (−1 to −2 mL/min/yr) expected in patients with optimally controlled glycemia and hypertension. In nondiabetic nephropathy, patients with chronic glomerulonephritis exhibit a rate of CKD progression that is more than twice as fast as patients with chronic interstitial nephritis and 1.5 times faster than patients with hypertensive nephrosclerosis.
The association of albuminuria and faster progression of CKD has been highlighted in a number of studies. Optimal hydration, relief of obstruction (where indicated), discontinuation of nephrotoxic agents, and control of hypertension often stabilize kidney function in a large percentage of patients. Patients with polycystic kidney disease and impaired kidney function (CKD stage 3b and beyond) may also have a faster rate of progression compared with other nephropathies. More rapid progression of CKD is linked to certain genetic, demographic, and clinical risk factors (see Table 82.1). Recently, the notion of a linear progression to the onset

of kidney failure is being challenged with the proposition that the progression of CKD is strongly influenced by repeated AKI episodes, and that this is most often a hemodynamically driven process.[9]

SLOWING PROGRESSION OF CHRONIC KIDNEY DISEASE

Since the publication of the hyperperfusion-hyperfiltration hypothesis, considerable research has focused on understanding the pathophysiology of CKD,[10] mechanisms of progression, and prevention of kidney failure (Fig. 82.3). Clinical strategies were initially based on manipulation of dietary protein intake and evolved to include inhibition of the renin-angiotensin-aldosterone system (RAAS) and control of glycemia and dyslipidemia (Table 82.2),[11] along with appropriate follow-up based on the level of estimated glomerular filtration rate (eGFR) and severity of albuminuria (Fig. 82.4).

A key goal of clinical follow-up is to recognize reversible causes of acute-on-chronic kidney disease (mimicking progression), such as acute illnesses with volume depletion. Patients with significant comorbidity burden—in particular, chronic heart disease, older age, and use of specific medications (e.g., RAAS inhibitors, sodium-glucose

Associations of CKD Markers With Adverse Health Outcomes
Cardiovascular mortality

All-cause mortality
ACR
<10

ACR
10–29

ACR
30–299

ACR
≥300

eGFR
>105

1.1

1.5

2.2

5.0

eGFR
90–105

Ref

1.4

1.5

eGFR
75–90

1.0

1.3

eGFR
60–75

1.0

eGFR
45–60

ACR
<10

ACR
10–29

ACR
30–299

ACR
≥300

eGFR

>105

0.9

1.3

2.3

2.1

3.1

eGFR
90–105

Ref

1.5

1.7

3.7

1.7

2.3

eGFR
75–90

1.0

1.3

1.6

3.7

1.4

1.8

2.7

eGFR
60–75

1.1

1.4

2.0

4.1

1.3

1.7

2.2

3.6

eGFR

45–60

1.5

2.2

2.8

4.3

eGFR
30–45

1.9

2.3

3.3

4.9

eGFR
30–45

2.2

2.7

3.4

5.2

eGFR
15–30

5.3

3.6

4.7

6.6

eGFR
15–30

14

7.9

4.8

8.1

Acute kidney injury (AKI)

Kidney failure (ESKD)
ACR
<10

ACR
10–29

ACR

30–299

ACR
≥300

eGFR
>105

Ref

Ref

7.8

18

eGFR
90–105

Ref

Ref

11

eGFR
75–90

Ref

Ref

eGFR
60–75

Ref

eGFR
45–60

Progressive CKD

ACR
<10

ACR
10–29

ACR
30–299

ACR
≥300

eGFR
>105

Ref

Ref

2.7

8.4

20

eGFR
90–105

Ref

Ref

2.4

3.8

48

eGFR
75–90

Ref

Ref

Ref

7.4

67

eGFR
60–75

Ref

5.2

22

40

147

eGFR
45–60

eGFR
30–45

56

74

294

763

eGFR
15–30

433

1044

1056

2286

ACR
<10

ACR
10–29

ACR
30–299

ACR
≥300

eGFR
>105

Ref

Ref

0.4

3.0

5.8

eGFR
90–105

Ref

Ref

0.9

3.3

2.5

4.1

eGFR
75–90

Ref

Ref

1.9

5.0

Ref

3.3

6.4

eGFR
60–75

Ref

Ref

3.2

8.1

2.2

4.9

6.4

5.9

eGFR
45–60

3.1

4.0

9.4

57

eGFR
30–45

7.3

10

12

20

eGFR
30–45

3.0

19

15

22

eGFR
15–30

17

17

21

29

eGFR
15–30

4.0

12

21

7.7

Fig. 82.2 Associations of chronic kidney disease (CKD) markers with adverse health outcomes. ACR, Albuminto-creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease. (Modified from Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80[1]:17–28.)

Timeline of Innovations in CKD Evaluation and Management

1970s–1980s

1982

1993–2000

2002

2003–present

Mechanistic
pathways
postulated

Hyperperfusionhyperfiltration
hypothesis paves
the way for
RAAS inhibition

Early trials of RAAS
inhibition published

CKD concept
developed with the
publication of
KDOQI guidelines

Progress and
developments

- Continuous publications of clinical studies targeting key individual risk factors (BP, proteinuria, glycemia, lipids)
- Landmark epidemiology work defining the relationships of CKD to health outcomes
- KDIGO revises the CKD framework
- Newer agents for renoprotection, reduction of CV risk and mortality (SGLT2i)

Fig. 82.3 Timeline of innovations in chronic kidney disease (CKD) evaluation and management. BP, Blood pressure; CV, cardiovascular; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

TABLE 82.2

Evidence-Based Strategies to Slow the Progression of Kidney Disease

Risk Factor
Overweight
Diet

Smoking
Exercise
Proteinuria/albuminuria
Blood pressure
Diabetes

Dyslipidemia
Metabolic acidosis
Other metabolic risk factors
(elevated uric acid)
Multifactorial risk
modification/CV risk
reduction

Guideline Concordant Treatment Goals and
Recommended Agents
Maintain a healthy weight (BMI 20–25 kg/m2)
Lower or maintain salt intake to <90 mmol/day (equivalent to <2 g
sodium/day or <5 g sodium chloride/day)
Low protein intake: 0.8 g/kg/day in adults with diabetes or without
diabetes and CKD (G4–G5), with appropriate education
Smoking cessation
Encourage 30–60 min of aerobic exercise at least 5 times/wk
Monitoring and follow up; treatment with ACE inhibitors/ARBs,
with proteinuria >300 mg/24 h
<130/80 mm Hg (diabetes or proteinuric CKD),a <140/80 mm Hg
(nondiabetic or nonproteinuric CKD)
HbA1c <7% and use of newer agents (i.e., SGLT2 inhibitors may
yield significant benefits for patients with CKD stages 1–4 with
regard to CV and kidney outcomes)
Use of lipid-lowering medicationsb
Bicarbonate supplementation with levels <20 mEq/L
Insufficient evidence to support or refute the use of agents for
hyperuricemia
Multifactorial intervention strategy addressing BP control and CV
risk (with secondary prevention measures, ASA, β-blockers, when
appropriate); use of ACE inhibitors or ARBs, statins, and SGLT2
inhibitors where clinically indicated and appropriate

Certainty of Evidence

Strength of
Recommendation

D
C

1
1

C (diabetes-related CKD); B
(nondiabetic CKD)

Not graded
D
B

2

B

1

A

1

1
1
1

Not graded
Not graded
Not graded

Strength of recommendation: 1, recommended for most patients; 2, suggested for the majority of people, but different choices will be appropriate for some patients; not graded: left to the discretion of care provider, guidance is based on common sense or the given topic does not allow adequate application of evidence.

Certainty of evidence: A, high; B, moderate; C, low; D, very low.

[a] Use of ACE inhibitors/ARBs recommended.

[b] “Fire-and-forget” strategy: a high-dose statin or moderate dose statin combined with ezetimibe recommended for all CKD patients aged >50 years regardless of serum lipid levels. Patients aged 18–50 years should be treated if they have established CV disease, diabetes, or an estimated 10-year risk of coronary death or nonfatal MI >10%.

ASA, Acetylsalicylic acid; BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HbA1c, hemoglobin A1c; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter-2.

cotransporter-2 [SGLT2] inhibitors, diuretics, nonsteroidal antiinflammatory drugs [NSAIDs])—are at increased risk of acute-onchronic kidney disease. Such drugs should be temporarily discontinued during acute intercurrent illnesses, particularly when there is evidence of volume depletion. This advice, termed “sick day rules,” now appears in many CKD management tools (guidelines and pathways).[12]

For decades, BP control and RAAS inhibition have been the cornerstones for preventing progression of CKD. More recently, exciting new evidence has emerged concerning the benefits of SGLT2 inhibitors.[13,14] Two landmark studies have demonstrated the efficacy of these agents on adverse health outcomes (kidney failure, cardiovascular [CV] events, and mortality) among patients with CKD, irrespective of the presence or absence of diabetes. Thus, slowing progression of CKD in the current era will depend on BP control, RAAS inhibition, and use of SGLT2 inhibitors supplemented by nontherapeutic (lifestyle) and other therapeutic strategies, such as lipid-lowering therapy (Fig. 82.5).

Risk Factor Modification: Lifestyle Interventions

Lifestyle modifications such as dietary changes, exercise, weight loss, and smoking cessation are recommended to prevent CVD among CKD patients. These modifications may prevent progression of CKD, reduce risk of attendant complications, and improve patients’ quality of life and survival, although evidence is based on observational studies or small clinical trials.[15]

High salt intake and impaired sodium handling by the kidneys are common in CKD and can lead to high BP. Data on the role of salt intake in the progression of kidney disease and risk of CVD in CKD patients is more limited. No large-scale randomized controlled trials (RCTs) on the influence of dietary sodium restriction have specifically enrolled CKD patients. Dietary salt restriction improves some risk factors associated with CKD progression, such as hypertension and albuminuria, and enhances long-term effects on renal function and reduce CV risk.16 Furthermore, the Dietary Approaches to Stop Hypertension (DASH) study showed the beneficial effects of dietary salt restriction on BP control, which should translate into lower risk of CKD progression.17

Guidelines recommend lowering sodium intake to less than 90 mmol (<2 g) per day (5 g of salt) in adults (see Chapter 36).

Numerous studies have examined the effects of weight loss (dietary or pharmacologic intervention, or bariatric surgery) on BP.18 Nevertheless, there is no solid evidence demonstrating a beneficial effect of weight loss per se (i.e., independent of effects on systemic BP and/or diabetes) on progression of CKD.19

Exercise decreases the risk of incident CV events in numerous patient populations, although not in CKD populations specifically. Exercise can also lower BP, reportedly to a similar extent as a normal dose of an antihypertensive medication. However, adequately powered RCTs reporting the independent effects of exercise on the progression of kidney disease are lacking. One small trial (n = 30) randomized CKD

General Guide to Frequency of Monitoring by GFR and Albuminuria Categories

GFR categories (mL/min/1.73 m2):
Description and range

Persistent albuminuria categories: Description and range
A1

A2

A3

Normal to mildly
increased

Moderately
increased

Severely
increased

<30 mg/g
<30 mg/mmol

30–300 mg/g
3–30 mg/mmol

>300 mg/g
>30 mg/mmol

G1

Normal or high

≥90

1 if CKD

1

2

G2

Mildly decreased

60–89

1 if CKD

1

2

G3a

Mildly to moderately
decreased

45–59

1

2

3

G3b

Moderately to severely
decreased

30–44

2

3

3

G4

Severely decreased

15–29

3

3

4+

G5

Kidney failure

<15

4+

4+

4+

Fig. 82.4 General guide to frequency of monitoring by glomerular filtration rate (GFR) and albuminuria categories. Numbers represent the frequency of visits for kidney care annually. For example, for CKD stage G5 A1, 4+ respresents recommended follow-up visits (as deemed clinically appropriate) at least four times or more per year to receive kidney care. CKD, Chronic kidney disease. (From KDIGO Chronic Kidney Disease Guidelines Working Group. Kidney Int Suppl. 2013; 3:1–150.)

BP Target in Comparison With Other Guidelines
Regular
risk factor
reassessment
(every 3–6
months)

Lifestyle
Healthy diet

First-line drug
therapy

Physical activity

Metformin
(if eGFR ≥30, if T2D)

Smoking cessation

Weight management

RAS inhibitor at maximum
tolerated dose (if HTN*)

SGLT2i
(Initiate if eGFR ≥20; continue
until dialysis or transplant)

Moderate-or
high-intensity statin

Regular reassessment of
glycemia (if T2D), albuminuria,
BP, CVD risk, and lipids

Additional riskbased therapy

GLP-1 RA if needed to
achieve individualized
glycemic target

Other glucose-lowering
drugs if needed to achieve
individualized glycemic target

Nonsteroidal MRA†
if ACR ≥30 mg/g and
normal potassium

Dihydropyridine CCB and/or
diuretic* if needed to achieve
individualized BP target

CKD and T2D

Steroidal MRA if needed for
resistant hypertension if
eGFR ≥45

All CKD

Blood pressure cuff,
blood pressure lowering

Glucometer,
glucose-lowering

Kidney,
kidney protection

Scale,
weight management

Heart,
cardioprotection

Antiplatelet agent for
clinical ASCVD

(Secondary prevention)

Ezetimibe, PCSK9i, or
icosapent ethyl if indicated
based on ASCVD risk and lipids

*Angiotensinconverting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (at maximal tolerated doses) should be first-line therapy for hypertension (HTN) when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker (CCB) or diuretic can also be considered; all 3 classes are often needed to attain BP targets.
†Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist (nsMRA) with proven clinical kidney and cardiovascular benefits.

Abbreviations: ACR, albumin-to-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease;
CVD, cardiovascular disease; CKD, chronic kidney disease; GLP-1 RA, GLP-1 receptor agonist;
Estimated glomerular filtration rate (eGFR), ml/min/1.73 m2;MRA, mineralocorticoid receptor
antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin
system; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

Fig. 82.5 Generic approach to the management of chronic kidney disease, including lifestyle and therapeutic interventions targeted to reduce risk of progression to kidney failure and other adverse health outcomes including cardiovascular events and risk of death. (Modified from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association [ADA] and Kidney Disease: Improving Global Outcomes [KDIGO]. Kidney Int. 2022. Epub ahead of print.)

patients to 30 minutes of daily aerobic exercise or usual care but did not show an effect on the progression of CKD.20 Another observational study showed a 2.8% difference in eGFR decline between physically active people versus those who are sedentary.18

The association between cigarette smoking and more rapid progression of CKD has been repeatedly shown. A large population-based study in Norway (HUNT II) revealed smoking as a significant risk factor for incident kidney failure and showed that smoking cessation ameliorated this risk, at least among men. Although no RCTs have demonstrated that smoking cessation reduces the risk of progressive CKD,21 it is expected that cessation of smoking will improve BP control and lower the risk of adverse kidney and CV outcomes. Thus, smoking cessation should be an integral component of strategies aimed at slowing CKD progression.21

In summary, lifestyle interventions are an important adjunct for preventing CKD progression, and guidelines recommend that people with CKD engage in physical activity at levels compatible with their CV health and tolerance (aiming for at least 30 minutes of aerobic exercise 5 times per week) and stop smoking. Moreover, CKD patients should receive expert dietary advice tailored to the severity of their CKD, and modify their diet (particularly salt intake) accordingly.

Risk Factor Modification: Therapeutic Interventions

Blood Pressure Control: Evaluation, Target, and Treatment

BP can be assessed using in-office manual or multiple in-office automated, home, and ambulatory measurements. In practice, BP is typically monitored via in-office manual measurements. Poorly controlled BP is associated with rapid progression of CKD to kidney failure and high risk for CV morbidity and mortality,22-24 but unfortunately a relatively small proportion of patients with CKD meet the recommended BP targets.25 Because CKD is accompanied by an increased risk of CVD, treatment of hypertension in patients with CKD serves two goals: to decrease the risk of CVD and to halt the progression of CKD. Based on new evidence, BP targets for treatment of hypertension in patients with CKD have been lowered in recent years to less than 130/80 mm Hg for those with albuminuria and/or diabetes and less than 140/90 mm Hg for those without diabetes or albuminuria in most guidelines.26 The risk/benefit ratio of intensive BP reduction in patients with CKD continues to be debated. Details on BP targets can be found in Chapter 37.

Ample evidence reveals that lowering BP reduces the risk of major CV events among patients with and without reduced kidney function,27 and this is irrespective of the type of BP-lowering agent, unlike with renoprotection. A meta-analysis of 18 RCTs shows that compared with less intensive BP reduction, intensive BP lowering is associated with lower mortality among patients with CKD stages 3 to 5.25 In a subgroup analysis of 2646 CKD patients in the Systolic Blood Pressure Intervention Trial (SPRINT), outcomes for an intensive treatment group (target systolic BP <120 mm Hg) were compared with outcomes for a standard treatment group (<140 mm Hg) for a median follow-up period of 3.3 years.28 The intensive treatment group had a lower rate of all-cause mortality and a higher rate of AKI as an adverse clinical event. In the main analysis of 9361 patients in SPRINT, risk factors for AKI were older age, non-White ethnicity, lower baseline eGFR, and presence of CVD at baseline.

In terms of renoprotection, overwhelming evidence accumulated over the last 25 years shows that BP control reduces the progression of CKD and supports the use of antihypertensive therapy, specifically with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients with CKD (Table 82.3 and Fig. 82.6). In 1993 the first large RCT to yield supporting evidence showed that ACE inhibitors (captopril) decreased the likelihood of doubling of serum creatinine or kidney failure by 48% in patients with diabetic nephropathy over a 3-year follow-up period, compared with placebo.29 This study was followed by the Irbesartan Diabetic Nephropathy Trial (IDNT), which showed that ARBs (irbesartan) significantly reduced the rate of CKD progression compared with placebo or amlodipine and also affected all-cause mortality.30 Similar findings were reported in the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial, in which losartan reduced the risks of a composite kidney outcome (doubling of serum creatinine or kidney failure) and mortality among patients with diabetic nephropathy, compared with placebo.31

Studies involving nondiabetic patients also show that lowering BP slows the progression of kidney disease. The first such study was the African American Study of Kidney Disease and Hypertension (AASK) trial that compared intensive and less intensive BP-lowering treatment targets among Black persons with CKD attributed to hypertensive nephrosclerosis.32 Although this study did not find that more intensive BP lowering reduces the risk of death or of progressive CKD, it showed that ACE inhibitors had favorable benefits in slowing eGFR decline compared with β-blockers or calcium channel blockers among the Black population. The Ramipril Efficacy In Nephropathy (REIN) study addressed a similar question in proteinuric, nondiabetic nephropathy33 and again demonstrated that ACE inhibitors decrease progression to kidney failure compared with other antihypertensive therapies, even in the setting of a similar BP control.

In SPRINT, the composite outcome of 50% or greater decrease in eGFR from baseline or kidney failure did not differ between the intensive and less intensive therapy groups. Although more intensive BP control was associated with similar risk of adverse events and similar kidney outcomes compared with standard treatment, the lower risk of CVD associated with more intensive control might suggest that a lower BP target in CKD patients is preferable. These findings have resulted in debate about the optimal BP targets for CKD patients. For example, the American College of Cardiology/American Heart Association has lowered the target to 130/80 mm Hg in their guidelines for the management of hypertension. In contrast, the KDIGO-recommended BP target for CKD patients endorses this goal for albuminuric and diabetic patients but remains less than 140/90 mm Hg for the group of patients without proteinuria and/or diabetes. The KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD was published proposing an SBP target of less than 120 mm Hg in situations where standardized office readings are feasible in the management of CKD.34 This recommendation stemmed from the CV and survival benefits with this level of intensive BP control from the SPRINT trial. The uptake of this new treatment target will be affected by the casual nature of BP measurements in practice and the challenges associated with it.34

In addition to controlling hypertension, RAAS inhibition is essential for preventing CKD progression.31,35 Most guidelines recommend the use of RAAS inhibitors to control hypertension, reduce proteinuria, and slow the progression of CKD. The consensus seems to be that in diabetic and nondiabetic CKD where significant albuminuria is present, RAAS inhibition is the preferred first-line approach, whereas in nonproteinuric disease, the benefit of RAAS inhibition specifically is less well established.3 It is important to recognize and address common situations that may limit the utilization of RAAS inhibition (Fig. 82.7).

RAAS inhibitors are shown to be effective in slowing CKD progression, even in later stages. In post hoc analyses of the REIN33 and RENAAL31 studies, the reduction of kidney failure events with ACE inhibitors and ARBs was independent of baseline GFR. A similar finding was seen in patients with CKD stage 4 treated with benazepril, in which carefully selected patients derived a benefit from ACE inhibitor therapy, even at very low eGFR.36 Taken together, these trials suggest that RAAS inhibition effectively reduces the risk of kidney failure for patients even when CKD is severe.37 This position has been reinforced in guideline recommendations for the management of CKD that in the absence of severe hyperkalemia (potassium >6 mmol/L), AKI, or a decrease in eGFR of more than 30%, these medications should be continued, irrespective of baseline eGFR or stage of CKD. Administration of RAAS inhibitors is associated with lower all-cause mortality and a substantial survival benefit for patients with nondialysis CKD (stages G1–5), even with adjustment for confounders and propensity matching across studies.37 Utilization of ACE inhibitors/ ARBs remains suboptimal, and discontinuation rates remain relatively high in clinical practice, representing an opportunity to further reduce the number of people who experience progressive CKD.

RAAS inhibitors should only be discontinued in situations involving substantial GFR decline (acute-on-chronic kidney disease), and/or severe hyperkalemia that cannot be readily modified or symptomatic hypotension.

Reduction in Albuminuria and Impact on Progressive Kidney Function Loss

Albuminuria is common but not universal in CKD. It is the earliest marker of glomerular diseases, including diabetic glomerulosclerosis, where it generally appears prior to a reduction in kidney function. It is also associated with hypertension/vascular causes in nondiabetic CKD patients, often after a reduction in kidney function.38 Multiple studies show that proteinuria is associated with a faster rate of progression35 and high risk of kidney failure and CVD,39,40 irrespective of the underlying cause of CKD. Conversely, reduction of albuminuria via lifestyle and therapeutic measures is associated with better outcomes; the extent of reduction in albuminuria is often proportional to the benefit accrued by such interventions on CKD progression. The superiority of RAAS inhibition compared with other antihypertensive treatments is due at least in part to its efficacy in reducing albuminuria (see Chapter 81).

Recent studies show that SGLT2 inhibitors reduce the risk of adverse outcomes in patients with CKD (see Table 82.3). In clinical trials involving patients with type 2 diabetes mellitus, these agents

TABLE 82.3

Recommended Medications in the Management of Chronic Kidney Disease

Category	Drug	Dose	Adjustment Based on Level of Kidney Function
ACE inhibitors	Benazepril	10–80 mg once daily	
	Captopril Enalapril Fosinopril Lisinopril	12.5 mg to 50 mg 2–3 times/	

day (up to 450 mg/day)
5 mg once daily
10–80 mg once daily
10–40 mg once daily

eGFR ≥30 mL/min: no dosage adjustment needed
eGFR <30 mL/min: reduce initial dose to 5 mg PO once daily
eGFR 10–50 mL/min: administer 75% of normal dose every 12–18 hours

Perindopril
Quinapril

2–8 mg once daily
10–80 mg once daily

Ramipril
Trandolapril
Azilsartan

2.5–20 mg once daily
1–4 mg once daily
20–80 mg once daily

Candesartan
Irbesartan
Losartan
Olmesartan

8–32 mg once daily
75–300 mg once daily
50–100 mg once daily
20–40 mg once daily

Telmisartan
Valsartan
Canagliflozin

40–80 mg once daily
80–320 mg once daily
100–300 mg once daily

Dapagliflozin

5–10 mg once daily

Empagliflozin

10–25 mg once daily

ARBs

SGLT2
inhibitorsa

aThese

eGFR ≤30 mL/min: in adult patients, reduce initial dose to 2.5 mg PO once daily
No dosage adjustment necessary
eGFR 10–30 mL/min: reduce initial recommended dose by 50% for adults (maximum: 40 mg/
day)
eGFR <10 mL/min: reduce initial dosage to 2.5 mg PO once daily

Not recommended when eGFR <30 mL/min
eGFR 61–89 mL/min: start at 10 mg once daily
eGFR 30–60 mL/min: start at 5 mg once daily
eGFR 10–29 mL/min: start at 2.5 mg once daily
Administer 25% of normal dose when eGFR <40 mL/min
eGFR <30 mL/min: reduce initial dose to 0.5 mg/day
Dose adjustment not required in patients with mild to severe kidney impairment or kidney
failure
Use with caution in patients with eGFR <30 mL/min
No dosage adjustment necessary
No dosage adjustment necessary
No initial dosage adjustment recommended for patients with moderate to significant
reduction in kidney function kidney impairment (eGFR <40 mL/min)
No dosage adjustment necessary
Use with caution in eGFR <30 mL/min
No dose adjustment if eGFR >60 mL/min/1.73 m2
100 mg daily if eGFR 30–59 mL/min/1.73 m2
Avoid initiation with eGFR <30 mL/min/1.73 m2
Discontinue when initiating dialysis
Initiate at 10 mg/day if eGFR ≥20 mL/min/1.73 m2
Avoid initiation with eGFR <25 mL/min/1.73 m2
Discontinue when initiating dialysis
Initiate at 10 mg/day for eGFR ≥20 mL/min/1.73 m2
Avoid initiation with eGFR <20 mL/min/1.73 m2a

recommendations may change with emerging evidence.
ACE, Angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; PO, orally; SGLT2, sodiumglucose cotransporter-2.
Modified from Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO
clinical practice guideline. Ann Intern Med. 2020;10.

Initial Antihypertensive Therapy
Begin with ACE inhibitor or ARB therapy: They are equally protective. ACE inhibitors have more side effects (cough, angioedema), but ARBs may cost more. Aliskiren, the direct renin inhibitor, is not recommended first-line therapy unless the patient is intolerant of both ACE inhibitors and ARBs, which is rare. In CKD, this class of drugs (RAAS blockers) is indicated for kidney and cardiovascular protection even if hypertension is not present. In general, the greater the proteinuria, the greater the benefit of these therapies in slowing CKD progression.

BP goal: Systolic BP in the 120s mm Hg or less if tolerated. Masked hypertension and white coat hypertension are common in CKD. BP status needs to be documented by HBPM.
If HBPM is not feasible, ABPM is recommended to assess whether masked hypertension or white coat hypertension is present. If they are not present, office/clinic BP monitoring may be satisfactory.

If BP not at goal after 2-4 weeks, titrate ACE inhibitor (or ARB) upward to maximally recommended dose Rationale:
High-dose ACE inhibitor (or ARB) may be more cardiovascularly and renally protective than lower dose ACE inhibitor (or ARB).

If BP not at goal after 2-4 weeks, an individualized approach is suggested.

Calcium channel blocker

Note: The kidney and CV protection of the ACE inhibitor + CCB combination was demonstrated in CKD patients with low-level proteinuria.In CKD patients with high-level proteinuria, the advantage of the DHP-CCB may be lost because this class of antihypertensives substantially increases proteinuria. By contrast, NDHP-CCBs tend to lower proteinuria.
So, the ACE inhibitors + NDHP-CCB may be better in CKD with high-level proteinuria.

If BP not at goal after 2-4 weeks, an individualized approach is suggested.

Panel A: Add aldosterone antagonist, especially if one or more of the following are present:
- Pre–diabetes mellitus or diabetic mellitus
- Serum K+ tends to be at the low end of normal
- Arrhythmia/cardiomyopathy concerns
- Start spironolactone 25 mg daily or eplerenone 50 mg daily
- Consider finerenone10 mg daily (if diabetes with CKD and eGFR >25 mL/min)

Panel B: Add diuretic, especially if one or more of the following are present:
- African ancestry
- Habitual high salt intake
- Edema-forming state

If SCr <2.5 mg/dL, start chlorthalidone 12.5 mg every other day.
If SCr >2.5 mg/dL, start furosemide at 20-40 mg/day or torsemide (torasemide) at 10-20 mg/day.
Diuretics are relegated to third-line therapy or less because they cause multiple metabolic dysfunctions and are associated with increased CV and renal risk (see text).

If BP not at goal after 2 to 4 weeks:

- For panel A patients, add diuretic as described in panel B.
- For panel B patients, add aldosterone antagonist as described in panel A.

If BP not at goal after 2 to 4 weeks, reassess the following:

- Is HBPM accurate? If unclear, ABPM is warranted.
- Medication compliance (are prescriptions filled on schedule?)
- Regular use of “over-the-counter drugs” that can raise BP (decongestants, vasoconstrictive nose spray or eye drops, NSAIDs), daily estrogen therapy, or alcohol more than two drinks, cocaine, or licorice
- Excessive salt intake (measure 24-h urine Na (or Na+Cl if the patient is also receiving $NaHCO_3$ and/or KCl)
- Sleep apnea
- New major life stressors

Fig. 82.6 Initial antihypertensive therapy. ABPM, Ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; DHP-CCB, dihydropyridine calcium channel blocker; HBPM, home blood pressure monitoring; NDHP-CCB, nondihydropyridine calcium channel blocker; NSAID, nonsteroidal antiinflammatory drug; RAAS, reninangiotensin-aldosterone system; SCr, serum creatinine; uACR, urinary albumin-to-creatinine ratio; uPCR, urinary protein-to-creatinine ratio.

reduced albuminuria by 30% to 50% and the incidence of composite hard kidney outcomes by 40% to 50%. Furthermore, they appear to interfere with the major mechanism of proteinuric CKD progression (i.e., glomerular hypertension and hyperfiltration). The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study involving 4401 diabetic patients with CKD showed that canagliflozin substantially reduces the risk of progression to kidney failure or mortality associated with kidney or CVD causes.[13] Recently, the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) involving 2510 diabetic patients and 1803 nondiabetic patients with CKD showed a significant reduction in the risk of CKD progression, kidney failure, or mortality from kidney or CVD causes.[14] The benefits of these agents appear to be similar in patients with or without diabetes-related CKD, including patients with chronic glomerulonephritides. It is important to consider the baseline level of kidney function before these agents are initiated (Fig. 82.8).[41,42]

Monitoring of Serum Creatinine and Potassium During ACEi or
ARB Treatment: Dose Adjustment and Monitoring of Side Effects
Initiate ACEi or ARB

Monitor serum creatinine and potassium
(within 2–4 weeks after starting or changing dose)

Normokalemia

Hyperkalemia

>30% increase
in creatinine

<30% increase
in creatinine

Increase dose of ACEi or
ARB or continue on
maximally tolerated dose

• Review concurrent drugs
• Moderate potassium intake
• Consider:
- Diuretics
- Sodium bicarbonate
- GI cation exchangers

• Review for causes of AKI
• Correct volume depletion
• Reassess concomitant medications
(e.g., diuretics, NSAIDs)
• Consider renal artery stenosis

Reduce dose or stop ACEi or ARB as last resort

Fig. 82.7 Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) treatment: dose adjustment and monitoring of side effects. AKI, Acute kidney injury; GI, gastrointestinal; NSAID, nonsteroidal antiinflammatory drug. (Modified from Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO clinical practice guideline. Ann Intern Med. 2021;174[3]:385–394.)

Initiation of SGLT2i in Patients With CKD (With or Without Diabetes)
Stage 3b
(eGFR 30–44 mL/min/1.73 m2)

Stage 4
(eGFR 15–29 mL/min/1.73 m2)

Stage 5
(eGFR <15 mL/min/1.73 m2)

SGLT2 inhibitors*
Canagliflozin

Dapagliflozin

Empagliflozin

Ertugliflozin

Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis

Maximum 100 mg daily

Initiation not recommended with eGFR <25 mL/min/1.73 m 2; may continue if tolerated for kidney and CV benefit until dialysis

10 mg daily†

10 mg daily‡

Initiation not recommended with eGFR <20 mL/min/1.73 m2; may continue if tolerated for kidney and CV benefit until dialysis

Use not recommended with eGFR <45 mL/min/1.73 m 2

Fig. 82.8 Initiation of sodium-glucose cotransporter-2 inhibitor (SGLT2i) in patients with chronic kidney disease (CKD). *Glucose-lowering efficacy is reduced with SGLT2 inhibitor (SGLT2i) as eGFR declines, but kidney and cardiovascular benefits are preserved. †Dapagliflozin is approved for use at 10 mg once daily with an eGFR of 25 to <25 mL/min/1.73 m 2. ‡Initiation not recommended with eGFR <30 mL/min/1.73 m 2 for glycemic control or <20 mL/min/1.73 m 2 for HF. Higher dose can be used but is not effective for glucose lowering and does not offer further clinical benefit in this range of eGFR. CV, Cardiovascular; DPP-4, dipepidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; SGLT2, sodium-glucose cotransporter 2. (Modified from de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association [ADA] and Kidney Disease: Improving Global Outcomes [KDIGO]. Kidney Int. 2022. Epub ahead of print.)

In patients treated with RAAS inhibitors (ACE inhibitors or ARBs), aldosterone breakthrough occurs that ameliorates by using aldosterone antagonists (spironolactone, eplerenone) added to ACE inhibitors or ARBs.43 This strategy reduces proteinuria, risk of CKD progression, and CVD, particularly in patients with diabetes.44 A recent Cochrane Review demonstrated the benefits of aldosterone antagonists in reducing both albuminuria and BP in patients with mild to moderate CKD; however, the use of these agents was linked to increased risk of hyperkalemia, AKI, and gynecomastia (common with the use of spironolactone [Aldactone]), particularly when combined with RAAS inhibition.45

Although earlier guidelines recommended tighter BP control to less than 125/75 mm Hg for patients with albuminuria greater than 1 g/24 h (based on weak evidence from the MDRD trial46), this approach is no longer recommended.

Dyslipidemia

Dyslipidemia is often viewed as a consequence of CKD, but experimental data suggest that lipid abnormalities also could accelerate the progression of CKD.47 Experimental data show that statins may have synergistic effects with RAAS inhibitors in slowing CKD progression.48 Clinical data also show an association between dyslipidemia and a decline in GFR, and that lipid reduction with treatment may preserve kidney function.49 Beyond their effects on cholesterol, statins have additional (“pleiotropic”) effects, including antiinflammatory and antifibrotic influences that could theoretically be of benefit in slowing progression of CKD. Small clinical studies suggested a clinical benefit of statin treatment for progressive kidney function loss, and large meta-analyses of patients with stage 3 CKD and coronary disease found small reductions in the rate of kidney function loss over 5 years. However, these potential benefits were not supported in the most rigorous RCT to date, the Study of Heart and Renal Protection (SHARP), which found that combination treatment with simvastatin and ezetimibe did not reduce the risk of progressive kidney function loss or incident albuminuria.50,51 However, statins have been consistently shown to reduce mortality and major CV events by 20% in people with CKD not requiring dialysis.51 Thus, KDIGO guidelines recommend initiation of treatment with a statin or statin/ezetimibe combination in adults 50 years or older with eGFR less than 60 mL/min/1.73 m2 but not kidney failure,52 irrespective of baseline cholesterol level (a “fire-and-forget” approach). Statin initiation is also recommended for adults with CKD (aged 18–49 years) if they have known coronary artery disease, diabetes mellitus, a history of ischemic stroke, or a greater than 10% estimated 10-year risk of coronary death or nonfatal myocardial infarction. Overall, the indication for statin treatment is prevention of CVD events rather than preventing progressive CKD.

Glycemic Control

Diabetes-related CKD (diabetic nephropathy) is the leading cause of kidney failure worldwide and is considered a microvascular complication of diabetes. Substantial evidence shows that effective management of diabetes ameliorates risk of kidney failure and incident CV events (see Chapter 32). In 2020 KDIGO released clinical practice guidelines for the management of patients with diabetes and CKD, consisting of 12 recommendations and 48 practice points addressing various facets of care, including glycemic monitoring and targets, antihyperglycemic therapies, and educational and integrated care.53

Other Measures

Infection Risk and Prevention

Immunizations against common infections are recommended for patients with CKD, because patients with CKD are at greater risk of infection and related complications. In addition to routine vaccinations, CKD patients should carefully consider the risks and benefits of vaccinations for influenza, pneumococcal, hepatitis B, zoster, and now COVID-19.54 For further details, see Chapters 83 and 87.

Hyperuricemia

Experimental data suggest a link between uric acid concentrations and the progression of hypertensive and toxic nephropathies.55 In humans, a link between hyperuricemia and the development of systemic hypertension, CVD, and kidney disease has been postulated.55-57 Although recently published studies (PERL and CKD-Fix trials) were important contributions, both showed that urate-lowering therapy does not significantly delay CKD progression in the populations studied, suggesting that lowering uric acid is unlikely to yield benefits for patients with CKD. The major critique of both studies was the fact that neither trial restricted inclusion to people with clinical gout and/or hyperuricemia who are presumably at risk for CKD progression. In fact, individuals with history of gout were excluded, despite the fact that gout affects at least one-third of patients with CKD.55

Dietary Interventions

A number of studies investigated the impact of dietary protein restriction on the progression of CKD in the 1970s and 1980s. The MDRD study showed that there was no beneficial effect of dietary protein restriction on progressive kidney function loss.

Avoidance of Nephrotoxins

Chronic lifetime exposure to nephrotoxins such as phenacetin and NSAIDs, heavy metals, and traditional Chinese herbal remedies has been associated with the development of hypertension and CKD progression. For further details, see Chapter 79.

Metabolic Acidosis

A number of studies have linked metabolic acidosis with adverse health consequences in CKD.58 The decrease in serum bicarbonate concentration (HCO3) begins to manifest at lower levels of eGFR (<30 mL/min). This acidosis is linked to progressive kidney function loss and increased mortality risk in CKD.58 A few clinical studies have suggested that bicarbonate supplementation may slow the progression of CKD, but the target HCO3 is unclear, and supplementation is associated with increased pill burden and excess sodium load.59,60 We advise bicarbonate treatment when HCO3 is less than 20 mmol/L, but this is not evidence based.

Multifaceted Strategies

Polypills

Pill burden is high in CKD populations, which may negatively affect quality of life and perhaps reduce the likelihood of adherence. Accordingly, guidelines regarding pharmacologic treatments for patients with CKD recommend combining BP-lowering and lipidlowering medications with glycemia-lowering medications (for those with diabetes)61 in a single pill (polypill). These guidelines are similar to those regarding the management of established CVD.

Multidisciplinary Team–Based Care

Multidisciplinary teams (MDTs) have been established in many settings around the world to provide continuing and comprehensive CKD care, particularly for patients with more advanced disease. These teams typically include not only nephrologists but also nurses, surgeons, general practitioners/family physicians, pharmacists, psychotherapists, social workers, nutritionists, and other specialists (e.g., endocrinologists). Emerging evidence on the benefits of MDTs

Management of Common CKD Complications
Complication

Target

Management

Anemia

Hb 90–110 g/dL

Replace iron deficiency,
erythropoietin, or HIF stabilizer

Mineral bone
disease

Ca: 2.2–2.35 mmol/L
PO4 <1.8 mmol/L

Diet/phosphate binders
active vitamin D

Metabolic acidosis

Serum bicarbonate
>22 mmol/L

Sodium bicarbonate
supplementation

Malnutrition

Adequate calorie and
protein intake

Dietician support

General health
measures:
Vaccinations

—

Immunize for influenza and
pneumococcus, possibly
COVID-19

Fig. 82.9 Management of Common Chronic Kidney Disease (CKD) Complications. Ca, Calcium; Hb, hemoglobin.

BOX 82.1

Referral Criteria

- Acute deterioration of kidney function
- GFR < 30 mL/min/1.73 m2
- Significant and sustained albuminuria (albumin/creatinine ratio ≥ 300 mg/g; equivalent to protein/creatinine ratio ≥ 500 mg/g or proteinuria ≥ 500 mg/24 h)

- CKD progression (sustained decrease in the GFR >5 mL/min/1.73 m2 per year or due to a change of category [from G1 to G2, from G2 to G3a, from G3a to G3b, from G3b to G4, or from G4 to G5] when the latter is accompanied by a GFR loss of ≥ 5 mL/min/1.73 m2)[a]

- Microhematuria not explained by other causes, sediment with >20 RBCs/field, especially in the case of RBC casts
- Resistant high BP (not controlled with a combination of three antihypertensive drugs, including a diuretic)
- Persistent serum potassium abnormalities
- Recurrent nephrolithiasis
- Hereditary kidney disease

Grade of recommendation: 1, recommendation, evidence B.

[a] Small fluctuations in GFR do not necessarily indicate progression. When the above progression criteria are detected, it is necessary to rule out potentially reversible exacerbation factors (progression vs. exacerbation) such as obstructive uropathy, volume depletion, situations of hemodynamic instability or use of NSAIDs, cyclooxygenase-2 inhibitors, nephrotoxic antibiotics, radiocontrast agents, or renin-angiotensin system blockers in certain hemodynamic conditions.

BP, Blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, nonsteroidal antiinflammatory drugs; RBCs, red blood cells.

From KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3.

shows improvements in CKD care, as well as reductions in progressive kidney function loss and hard outcomes such as mortality and CV events.[62]

MDTs may also enhance the management of other CKD-related complications such as anemia, mineral bone disease, metabolic acidosis, and electrolyte imbalance that may accelerate loss of kidney function (or interfere with treatments that could prevent CKD, such as RAAS inhibition; Fig. 82.9). Appropriate referrals should be considered when the recommended criteria are met (Box 82.1); see Chapter 83 for details.

SELF-ASSESSMENT QUESTIONS

1. Which of the following are modifiable risk factors associated with progression of CKD to kidney failure?
A. Age
B. Race
C. Proteinuria
D. Blood pressure
E. C and D

2. Which of the following are adverse health consequences associated with CKD?
A. Heart failure
B. Increased risk of infections
C. Ischemic heart disease and strokes
D. Cognitive dysfunction
E. All of the above

3. A 65-year-old patient with a background history of hypertension, ischemic heart disease, and type 2 diabetes mellitus was referred with a serum creatinine of 175 µmol/L (eGFR of 32 mL/min) and a urine albumin-to-creatinine ratio of 300 mg/g (30 mg/mmol). The eGFR was 39 mL/min about a year ago. A diagnosis of CKD (stage G3b:A2) secondary to diabetes and vascular-related causes was made. The current medications include ramipril 5 mg orally daily, hydrochlorothiazide (HCTZ) 25 mg orally daily, atorvastatin 10 mg daily, and linagliptin 5 mg orally daily. The BP is 118/65 mm Hg, and most recent hemoglobin A1c (HbA1c) was 8.3%. You

SELF-ASSESSMENT QUESTIONS—Cont'd

decided to start the patient on canagliflozin at 100 mg orally daily to optimize the glycemia control and to reduce the risk of cardiovascular and kidney disease progression. The patient asked about the specific effects of this new medication on the risk of kidney failure. Which of the following is correct regarding the effects of canagliflozin on kidney function?

A. Canagliflozin has no effects on kidney function.
B. The rate of progression to kidney failure will be amplified over the coming years.
C. The risks of kidney stones and urinary tract infections are increased with the use of canagliflozin.
D. The risk of proteinuria is increased with the use of canagliflozin.
E. There will be an initial decline in kidney function (eGFR), and this will be accompanied by a slower rate of eGFR decline over time and slowing of progression to incident kidney failure.

4. A 60-year-old patient with a long-term history of hypertension, type 2 diabetes, and CKD (stage G3a:A3) is referred for progressive albuminuria. The patient is a current smoker (>20 pack-year history). Over the past year, the urine albumin-to-creatinine ratio has more than doubled from 500 mg/g (50 mg/mmol) to 1200 mg/g (120 mg/mmol). The physical examination was normal except for a slight overweight with body mass index of 30 kg/m2. Current medications include irbesartan 300 mg daily, chlorthalidone 25 mg daily, and metformin 500 mg twice daily. BP and diabetes are well controlled and currently at 129/72 mm Hg and HbA1c of 7%, respectively.

In addition to continuing the current medications, which one of the following is the most appropriate management of the increased albuminuria?

A. Stop smoking
B. Recommend exercise and weight loss
C. Initiate statin
D. Initiate SGLT2 inhibitor
E. All of the above

5. You received a call from a general practitioner for advice regarding a 70-year-old patient with a known history of type 2 diabetes (metformin 500 mg twice daily and gliclazide 60 mg daily), hypertension (ramipril 10 mg daily and HCTZ 25 mg daily), and dyslipidemia (atorvastatin 10 mg orally daily). The patient was diagnosed with CKD (Stage G3a:A2) about a year ago. The general practitioner recently started the patient on canagliflozin 100 mg daily. The patient is now suffering from acute gastroenteritis following recent travel. The patient cannot maintain adequate fluid intake and is currently hypotensive from volume depletion upon assessment in clinic. Which of the following medications should be stopped until the patient recovers from the acute illness?

A. Angiotensin-converting enzyme inhibitors
B. Diuretics
C. Metformin
D. SGLT2 inhibitors
E. All of the above

REFERENCES

1. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: executive summary and glossary from a Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference. Am J Kidney Dis. 2020;76(2):157–160.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 suppl 1):S1–S266.
3. Stevens PE, Levin A. Kidney disease: improving global outcomes chronic kidney disease guideline development work group members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes. Ann Intern Med. 2013;158(11):825–830.
4. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis. 2014;63(5):820–834.
5. Weaver RG, James MT, Ravani P, et al. Estimating urine albuminto-creatinine ratio from protein-to-creatinine ratio: development of equations using same-day measurements. J Am Soc Nephrol. 2020;31(3):591–601.
6. Collaboration GCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;29(10225):709–733.
7. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012;380(9844):807–814.
8. Levin A, Djurdjev O, Beaulieu M, et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis. 2008;52(4):661–671.
9. Johnson RJ, Rodriguez-Iturbe B. Rethinking progression of CKD as a process of punctuated equilibrium. Nat Rev Nephrol. 2018;14(7):411–412.
10. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med. 1982;307(11):652–659.
11. James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. Lancet. 2010;375(9722):1296–1309.
12. Griffith K, Ashley C, Blakeman T, et al. “Sick day Rules” in Patients at Risk of Acute Kidney Injury: an Interim Position Statement. Think Kidneys Board. https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/07/Think-Kidneys-Sick-Day-Rules-160715.pdf.
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–2306.
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446.
15. Gregg LP, Hedayati SS. Management of traditional cardiovascular risk factors in CKD: what are the data? Am J Kidney Dis. 2018;72(5):728–744.
16. Heerspink L, Holtkamp FA, Parving HH, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. Kidney Int. 2012;82(3):330–337.
17. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344(1):3–10.
18. Robinson-Cohen C, Littman AJ, Duncan GE, et al. Physical activity and change in estimated GFR among persons with CKD. J Am Soc Nephrol. 2014;25(2):399–406.
19. Docherty NG, Canney AL, le Roux CW. Weight loss interventions and progression of diabetic kidney disease. Curr Diab Rep. 2015;15(8):55.
20. Eidemak I, Haaber AB, Feldt-Rasmussen B, et al. Exercise training and the progression of chronic renal failure. Nephron. 1997;75(1):36–40.
21. Hallan SI, Orth SR. Smoking is a risk factor in the progression to kidney failure. Kidney Int. 2011;80(5):516–523.
22. Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in

hypertensive chronic kidney disease. N Engl J Med. 2010;363:918–929.

23. Bansal N, McCulloch CE, Rahman M, et al. Blood pressure and risk of allcause mortality in advanced chronic kidney disease and hemodialysis: the chronic renal insufficiency cohort study. Hypertens. 2015;65(1):93–100.

24. Qureshi S, Lorch R, Navaneethan SD. Blood pressure parameters and their associations with death in patients with chronic kidney disease. Curr Hypertens Rep. 2017;19(11):92.

25. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. JAMA Intern Med. 2017;177(10):1498–1505.

26. Georgianos PI, Agarwal R. Hypertension in Chronic Kidney Disease (CKD): diagnosis, classification and therapeutic targets. Am J Hypertens. 2020;17. hpaa209.

27. Blood Pressure Lowering Treatment Trialists’ Collaboration, Ninomiya VPT, Turnbull F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ. 2013;347:f5680.

28. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol. 2017;28(9):2812–2823.

29. Lewis EJ, Hunsicker G, Bain RP, et al. The effect of angiotensinconverting-enzyme inhibition on diabetic nephropathy: the Collaborative Study Group. N Engl J Med. 1993;329(20):1456–1462.

30. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–860.

31. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–869.

32. Wright Jr JT, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288(19):2421–2431.

33. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet. 1997;349(9069):1857–1863.

34. KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3s):S1–s87.

35. Jafar TH, Stark PC, Schmid CH, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int. 2001;60:1131–1140.

36. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2016;354(2):131–140.

37. HsuT -W., Liu J-S., Hung S-C., et al. Renoprotective effect of reninangiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. JAMA Intern Med. 2014;174(3):347–354.

38. Remuzzi G, Ruggenenti P, Perico N. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. Ann Intern Med. 2002;136:604.

39. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–1305.

40. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303(5):423–429.

41. Sarafidis P, Ortiz A, Ferro CJ, et al. Sodium-glucose co-transporter-2 inhibitors for patients with diabetic and nondiabetic chronic kidney disease: a new era has already begun. J Hypertens. 2021;1(11).

42. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network metaanalysis of randomised controlled trials. BMJ. 2021;372:m4573.

43. Erraez S., López-Mesa M., Gómez-Fernández P.. Mineralcorticoid

receptor blockers in chronic kidney disease. Nefrologia. 2020;S0211–6995(20)30165-X.
44. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–2229.
45. Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2020;27(10). CD007004.

46. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal failure. N Engl J Med. 1994;330:877–884.
47. Moorhead JF, Chan MK, El-Nahas M, et al. Lipid nephrotoxicity in chronic progressive glomerular and tubulointerstitial disease. Lancet. 1982;2:1309–1312.
48. Zoja C, Corna D, Camozzi D, et al. How to fully protect the kidney in a severe model of progressive nephropathy: a multidrug approach. J Am Soc Nephrol. 2002;13:2898–2908.
49. Fried LF, Orchard TJ, Kasiske BL. Effects of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int. 2001;59:260–269.
50. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebocontrolled trial. Lancet. 2011;377(9784):2181–2192.
51. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2014;(5). CD007784.
52. Tonelli M, Wanner C, Kidney Disease. Improving global outcomes lipid guideline development work group members. Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline. Ann Intern Med. 2014;160(3):182.
53. Navaneethan SD, ZoungasS, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO Clinical Practice Guideline. Ann Intern Med. 2020;(11).

54. Chi C, Patel P, Pilishvili T, et al. Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease. Centers for Disease Control and Prevention; 2012. https://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf.
55. Floege J, Johnson RJ. Hyperuricemia and progression of chronic kidney disease: to treat or not to treat? Kidney Int. 2021;99(1):14–16.
56. Doria A, Galecki AT, Spino C, et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382(26):2493–2503.
57. Badve SV, Pascoe EM, Biostat M, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382(26):2504–2513.
58. Madias NE. Metabolic acidosis and CKD progression. Clin J Am Soc Nephrol. 2021;16(2):310–312.
59. Łoniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. Kidney Int. 2014;85(3):529–535.
60. Chen W, Abramowitz MK. Treatment of metabolic acidosis in patients with CKD. Am J Kidney Dis. 2014;63(2):311–317.
61. Coca A, Kreutz R, Manolis AJ, et al. A practical approach to switch from a multiple pill therapeutic strategy to a polypill-based strategy for cardiovascular prevention in patients with hypertension. J Hypertens. 2020;(5):12.
62. Hsu H-T., Chiang Y-C., Lai Y-H., et al. Effectiveness of multidisciplinary care for chronic kidney disease: a systematic review. Worldviews Evid Based Nurs. 2020;(11):28.

83

Clinical Evaluation and Management of Chronic Kidney Disease

David C. Wheeler

Although many patients with chronic kidney disease (CKD) progress to end-stage kidney disease (ESKD) and require kidney replacement therapy (KRT), the majority die of nonrenal causes, particularly premature cardiovascular (CV) events.[1] Early diagnosis of CKD is therefore important because it provides opportunities to delay progression of CKD (see Chapter 82) and prevent CV complications (see Chapters 84 and 85).

DEFINITIONS

CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, with implications for health (Table 83.1).

The relevant Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends classification of CKD based on cause, category of glomerular filtration rate (GFR), and albuminuria (see Fig. 82.2).[2] Because of the impracticalities of using radioisotopes and 24hour urine collections, the KDIGO classification system recommends that kidney function be assessed by estimating GFR (eGFR) from the serum creatinine concentration using an appropriate equation, except in circumstances in which eGFR estimations are known to be less accurate, such as when there is significant muscle wasting. Initially, the Modification of Diet in Renal Disease (MDRD) equation was used, but this has predominantly been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which more accurately categorizes the risk for mortality and progression to ESKD (see Chapter 3).[3] Recently, this formula has been updated in order to eliminate race from the equation (https://www.kidney.org/professionals/kdoqi/gfr_calculator/formula), and although the formula is less precise than the earlier CKD-EPI equation, it is sufficiently accurate for clinical practice. Although staging systems for CKD based on eGFR have limitations, they have proved useful in many clinical settings and are now deeply embedded in KDIGO and other guidelines developed for CKD management and in research.

The evidence base for the management of CKD is evolving. Although every effort has been made to ensure this chapter reflects current recommendations, the reader is advised to check for any new clinical trials and relevant guideline updates.

with an increased prevalence of CKD, which is termed case-finding.

Subgroups of interest include those with diabetes, hypertension, previous acute kidney injury (AKI), CV disease (CVD), structural kidney tract disease, kidney calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g., systemic lupus erythematosus), a family history of category G5 CKD, and hereditary kidney disease, and after opportunistic detection of hematuria or proteinuria.[5]

Evaluation of Chronic Kidney Disease

Establishing Chronicity

When eGFR of less than 60 mL/min/1.73 m^2 is detected, careful attention should be paid to previous blood and urine test results and the clinical history to determine whether this is a result of AKI (i.e., an abrupt decrease in kidney function or CKD that has been present but asymptomatic for some time).

A detailed medical history covering issues, including other medical conditions, family history of kidney disease, prescribed medication, and recreational drug use, may suggest an underlying cause. There may be hints of a history of kidney problems (e.g., hypertension, proteinuria, microhematuria) or symptoms suggestive of prostatic disease.

The findings of a physical examination are not always helpful, although skin pigmentation, scratch marks, left ventricular hypertrophy, and hypertensive fundal changes favor a chronic presentation (Fig. 83.1).

Details of the social and personal circumstances are also crucial, particularly for patients with progressive kidney disease in whom KRT is likely to be required.

Blood tests for other conditions can be helpful because they may indicate evidence of an acute illness that could be the cause of kidney failure, such as systemic vasculitis or multiple myeloma. A normochromic normocytic anemia is usual in CKD but also may be a feature of acute systemic illnesses and therefore is not discriminatory. Low serum calcium and raised phosphate levels also have little discriminatory value, but normal levels of parathyroid hormone (PTH) are more in keeping with AKI. Patients with grossly abnormal biochemical values (e.g., blood urea > 300 mg/dL [>50 mmol/L] and/or serum creatinine > 13.5 mg/dL [>1200 µmol/L]) who appear relatively well and are still passing normal volumes of urine are much more likely to have CKD than AKI.

CLINICAL PRESENTATION

Assessment of Glomerular Filtration Rate

CKD is commonly detected by routine blood testing and is usually asymptomatic until late stage G4 or stage G5. Symptoms of CKD are nonspecific and need to be asked about directly (Box 83.1). There is some evidence that early diagnosis with appropriate management may slow the rate of decline of kidney function and reduce CV risk.[4]

Screening of the general population for CKD is not recommended, but in the UK, the National Institute for Health and Care Excellence (NICE) proposes offering testing to people with conditions associated

For patients in whom the distinction between AKI and CKD is unclear, repeat testing of kidney function should be performed within 2 weeks of the initial finding of eGFR less than 60 mL/min/1.73 m2. However, if previous results confirm that this is a chronic finding, or if repeated blood test results over a 3-month period are consistent, CKD is confirmed. Other tests (such as cystatin C or an isotope-clearance measurement of GFR) can be used to confirm CKD in circumstances in which eGFR based on serum creatinine is known to be less accurate.

TABLE 83.1 Criteria for Definition of Chronic Kidney Disease (CKD)

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. These may include the following:	
Markers of kidney damage	Albuminuria (AER ≥ 30 mg/24 h; uACR ≥ 30 mg/g [≥ 3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities caused by tubular disorders
	Abnormalities detected through histology
	Structural abnormalities detected through imaging
	History of kidney transplantation
Decreased GFR	GFR < 60 mL/min/1.73 m2

AER, Albumin excretion rate; GFR, glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio.

From Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.

BOX 83.1

Symptoms and Signs of Severe Chronic Kidney Disease

- Difficulty sleeping
- Nocturia
- Headache
- Restless leg syndrome
- Metallic taste in the mouth
- Shortness of breath on exertion or at rest, paroxysmal nocturnal dyspnea
- Fatigue, often profound
- Muscle cramps and twitches
- Seizures
- Lack or loss of appetite for food, abdominal pain, nausea, vomiting, and weight loss

Itch, particularly on the trunk and worse at night
Altered respiration including Kussmaul breathing and Cheyne-Stokes respiration
Icteric sclera or “red eye” because of calcium deposition
Muscle weakness
Oral lesions including gingival bleeding or petechiae, xerostomia, periodontitis, and candidiasis
Pericardial and/or pleural rub
Pulmonary and peripheral edema
Skin changes including xerosis (abnormal dryness), scratch marks, pallor, sallow coloration or hyperpigmentation
Uremic flap (asterixis)
Uremic fetor: Ammonia or urine-like odor to the breath
Uremic frost: Crystallized urea deposits that can be found on the skin

Assessment of Proteinuria or Albuminuria

Dipstick testing of the urine and urine culture may reveal microhematuria, which can be a useful pointer toward an underlying diagnosis.[6] Workup of hematuria is discussed in Chapters 4 and 63. Whether or not proteinuria is detected by dipstick, there should be a further measurement of urinary albumin excretion. Albuminuria is an important diagnostic and prognostic marker, and its presence indicates a higher risk for both progression of kidney disease and CV complications.[7] KDIGO guidelines recommend that the preferred method of assessing proteinuria is by measurement of the urinary albumin-to-creatinine ratio (uACR) using an early morning urine sample where practical.[2]

Fig. 83.1 Uremic Pigmentation. Diffuse brown pigmentation as seen here suggests chronic kidney disease rather than acute kidney injury.

The degree of albuminuria is graded by the A1 to A3 category system, replacing previous terms such as microalbuminuria (see Fig. 82.1). However, it is important to be aware that some patients will excrete proteins other than albumin, and a urine protein-to-creatinine ratio (uPCR) may be more useful for certain conditions.[8] Serial uPCR measurements may be particularly useful in glomerular disease because of the higher variability of uACR and the greater cost of determining albumin in urine. Where appropriate, urine tests for Bence Jones protein (immunoglobulin light chains) may be required because this is not detected by standard proteinuria or albuminuria testing.

Kidney Imaging

Imaging of the kidneys with ultrasound is useful for a number of reasons. Small kidneys with reduced cortical thickness, showing increased echogenicity, scarring, or multiple cysts, suggest a chronic process. Structural abnormalities such as those observed in autosomal dominant polycystic kidney disease (ADPKD), hydronephrosis caused by obstruction, or coarse kidney scarring may be detected. NICE guidelines propose that kidney ultrasound scanning is important only in certain circumstances and suggest counseling patients if ADPKD is suspected before imaging.[5] In some situations, imaging with computed tomography (CT), magnetic resonance (MR), or angiography may be useful, taking into account the risks of administering contrast media (see Chapter 6).

Further Investigations

Establishing the cause of CKD is important whenever possible, and further specific testing, as indicated by the history and results of initial investigations, may be required. There may be an underlying treatable condition that requires appropriate management, or there may be a genetic cause such as ADPKD, for which counseling should be offered. Furthermore, some kidney diseases may recur after transplantation (see Chapter 113) and an accurate diagnosis may therefore influence later management. Despite thorough investigation, however, the cause of CKD is often unclear, with an unhelpful medical history, minimal abnormalities on urinalysis, and small kidneys on ultrasound. In such patients, investigation should not be pursued relentlessly because the implications for treatment are often minimal. Attempting to obtain biopsy material from small kidneys is associated with risk, and even if a biopsy is performed, histologic assessment may simply show nonspecific chronic scarring rather than diagnostic features that explain the cause of kidney damage.

PREDICTING PROGNOSIS

With the cause of CKD established if possible, the GFR and the level of albuminuria measured, and other comorbidities categorized, it is possible to estimate the risk for CKD progression and likely future need for KRT. KDIGO recommends consideration of the GFR and the albuminuria categories together according to a heatmap of risk (see Fig. 82.2),2 and there are online tools to assist with risk prediction using this approach (e.g., kidneyfailurerisk.com). Other factors associated with CKD progression may help inform prognosis. These include the cause of CKD, age, sex, ethnicity, dyslipidemia, smoking, obesity, history of CVD, ongoing exposure to nephrotoxic agents, and degree of control of hypertension and hyperglycemia. However, often the best guide to future change in kidney function is the previous pattern of decline, highlighting the importance of considering results of previous blood and urine testing during the initial assessment.

Monitoring and Defining Progression

Once CKD has been identified, arrangements should be made to ensure regular monitoring of kidney function and proteinuria. In patients at low risk for rapid eGFR decline, this can be done annually in either a primary or secondary care setting. However, assessment should be undertaken more regularly if the trajectory of the disease is not clear and in patients at higher risk for progression.

Determining a true change in kidney function over time may be difficult because small fluctuations in eGFR are common and not necessarily indicative of progression. These fluctuations may be caused by reversible factors, such as intravascular depletion or high meat intake, so repeat testing may be required. Both NICE and KDIGO guidelines define accelerated progression as a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months.2 5 In addition, the NICE guidance refers to accelerated progression as a sustained decrease in GFR of 15 mL/min/1.73 m2 or greater per year.5 In patients with accelerated CKD progression, consideration should be given to detection of reversible causes (e.g., kidney tract obstruction) and a specialist referral may be required.

TABLE 83.2

When to Refer to the Nephrologist

Chronic management of patients with early nonprogressive CKD is becoming the responsibility of primary care physicians in many welldeveloped health care systems, with follow-up in secondary care limited to those likely to progress to ESKD and require KRT. However, early assessment by nephrologists is useful for all patients newly diagnosed with CKD in whom a treatable underlying cause is suspected, even in those with advanced disease at presentation, to rule out treatable causes. Timely referral of those with progressive CKD allows preparation for dialysis, kidney transplantation, or initiation of a palliative approach if more appropriate. Substantially similar criteria for referral have been developed by NICE and KDIGO (Table 83.2). Such criteria are not absolute but should provide a guide to the primary care physician as to which patients are likely to benefit from specialist care. For example, many patients with stable category G4 CKD are successfully managed in the community, often after initial assessment by or with virtual advice from secondary care colleagues.

Unfortunately, a substantial proportion of patients with advanced CKD are referred late, often at the time when they need KRT. Late referral is often avoidable, although in some cases, patients may have had a truly silent illness or an acute presentation of a disease with rapid decline in kidney function.9 Over recent years, the introduction of routine reporting of eGFR in some health care systems has facilitated better communication between primary and secondary care providers and has led to a substantial fall in late referrals.10

Late presentation is disadvantageous to the patient because it limits the time to select the mode of dialysis or to be listed for “preemptive” kidney transplantation. There may be increased psychological stress, making it difficult for the patient to come to terms with the illness. Furthermore, because an arteriovenous fistula (AVF) takes several weeks to mature, patients presenting late start hemodialysis (HD) with

Suggested Criteria for Referral of Patients With CKD to a Nephrologist

Advanced CKD

Proteinuria
Hematuria
Progression of CKD

Uncontrolled hypertension
Hereditary kidney disease
Other conditions

NICE 2021

KDIGO 2012

Category G4 and G5 CKD
A 5-year risk of needing kidney replacement therapy of >5%
(measured using the 4-variable Kidney Failure Risk Equation)
High proteinuria: uACR ≥ 70 mg/mmol unless known to be
caused by diabetes and appropriately treated
Proteinuria (uACR ≥ 30 mg/mmol) together with hematuria

Category G4 and G5 CKD

Rapidly declining eGFR:
Sustained decrease in GFR of ≥25% and a change in GFR
category within 12 mo
Sustained decrease in GFR of ≥15 mL/min/1.73 m2 within 12 mo
NEW: 5-year risk of needing kidney replacement therapy of >5%
(measured using the 4-variable Kidney Failure Risk Equation)
Hypertension that remains poorly controlled despite the use of at
least four antihypertensive drugs at therapeutic doses
Known or suspected rare or genetic causes of CKD
Suspected renal artery stenosis

Consistent proteinuria: uACR ≥ 300 mg/g (≥ 30 mg/mmol)
Urinary RBC casts, RBCs > 20/hpf sustained; not readily
explained
Progression of CKD:
Sustained decrease in GFR of ≥25% and a change in GFR
category within 12 mo
Sustained decrease in GFR of ≥5 mL/min/1.73 m2 within 12 mo
CKD and hypertension refractory to treatment with four or
more antihypertensive agents
Hereditary kidney disease
Recurrent or extensive nephrolithiasis
Persistent abnormalities of serum potassium

CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; hpf, high power field; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence; RBC, red blood cell; uACR, urinary albumin-to-creatinine ratio.

Data from Kidney Disease: Improving Global Outcomes [KDIGO] CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150; and National Institute for Health and Care Excellence. Chronic kidney disease assessment and management. 2021. NICE guideline [NG203].

central venous catheters. Catheters are prone to infectious complications and inevitably damage central veins, leading to thromboses and stenoses, which may manifest at a later stage when venous return from one or the other arm is increased by the subsequent construction of an AVF (see Chapter 96).11 Late presentation of CKD also precludes effective treatment of complications such as hypertension and anemia, which may contribute to CVD and ultimately limit life span.12 Most importantly, late referral is associated with greater subsequent costs of medical care and a worse prognosis.13

PREVENTION OF CHRONIC KIDNEY DISEASE PROGRESSION

Management of CKD should be aimed at slowing the rate of decline of kidney function and minimizing the effects of other complications. Except for specific management of the underlying kidney disease where possible, the most effective intervention is control of blood pressure (BP) and introduction of nephroprotective medications including (in patients with albuminuria) angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; see Chapter 82) and sodium glucose cotransporter 2 (SGLT2) inhibitors. Control of glycemia in patients with diabetes and CKD is covered in Chapter 33

Hypertension and Renin Angiotensin Aldosterone System Blockade

Hypertension is very common in patients with CKD, the level of BP being associated with the rate of loss of kidney function,14 and BP control slows the rate of decline (see Chapter 82). BP targets have changed to reflect the available evidence. Although observational studies link low BP to higher mortality,15 interventional trials such as SPRINT have demonstrated the advantages of more intensive BP control in CKD patients.16 Guidelines by both NICE and KDIGO emphasize the importance of considering coexistent CVD, other comorbidities, and side effects when choosing medications and BP targets, particularly for elderly patients.5 17 Lifestyle modifications should be encouraged, including maintenance of a healthy weight, reductions in salt and alcohol intake, and regular exercise (see Chapter 36).

Although current recommendations are based on office BP recordings, these should be standardized if possible (i.e., obtained according to a recommended preparation protocol).18 Home and ambulatory monitoring readings, where available, should be used to complement standardized office recordings. It has been shown that up to 30% of CKD patients who were thought to have hypertension have normal BPs at home, whereas 40% of patients who were thought to be normotensive (or to have adequately treated hypertension) were hypertensive at home.19 Although ambulatory monitoring is not universally recommended, there should be a low threshold for undertaking 24-hour monitoring or asking patients to undertake self-measurements at home if they prefer.

Target BP levels and antihypertensive therapy in CKD patients are discussed in Chapter 82. ACE inhibitors or ARBs are recommended as first-line agents for patients with evidence of proteinuria, both to slow progression of CKD and to reduce CV risk.20 However, multidrug regimens are usually required to obtain good control. Patients with CKD are vulnerable to drug side effects, particularly during intercurrent illness, when they may develop hyperkalemia and AKI. The KDIGO guidelines recommend the temporary discontinuation of certain drugs that may exacerbate AKI or are prone to increased adverse events at low GFR (including ACE inhibitors, ARBs, aldosterone inhibitors, direct renin inhibitors, diuretics, nonsteroidal anti-inflammatory drugs, metformin, lithium, and digoxin) in patients with a GFR of less than 60 mL/min/1.73 m^2 (CKD categories G3a–G5) who have serious intercurrent illness.

Sodium Glucose Cotransporter 2 Inhibitors and Mineralocorticoid Receptor Antagonists

SGLT2 inhibitors enhance urinary excretion of sodium and glucose by blocking their uptake in the proximal tubule. Although originally developed as drugs to improve glycemic control in patients with type 2 diabetes (see Chapter 33), these agents have both kidney and cardioprotective effects that extend to patients with CKD who do not have diabetes.21 A new nonsteroidal mineralocorticoid receptor antagonist (Finerenone) has also recently been demonstrated to have cardiorenal benefits in patients with CKD and type 2 diabetes.22 It seems likely that these newer agents will be used more extensively in the future in the management of CKD in addition to ACE inhibitors and ARBs.

Dietary Advice

Detailed dietary advice and education, along with ongoing support from an appropriately trained professional, are important in the management of patients with CKD. Obesity is associated with a more rapid decline of kidney function, so in early CKD, weight loss may be appropriate. However, in advanced CKD, malnutrition is common (see Chapter 90). The causes are multifactorial but include anorexia, acidosis, insulin resistance, inflammation, oxidative stress, and urinary protein loss. Biochemical indicators may demonstrate a decrease in serum albumin, transferrin, and cholesterol. Weight should be monitored in patients who progress to CKD categories G4 and G5. Serum creatinine concentrations, which, in part, reflect muscle mass, may stop rising despite a progressive loss of kidney function because of compromised nutritional status.

In light of this, recommendations to restrict protein intake are controversial. Although reduced protein intake may slow progression of decline of kidney function, many patients develop protein-calorie malnutrition on a low-protein diet.23 KDIGO has recommended that protein intake should be lowered to 0.8 g/kg/day in adults with CKD and GFR less than 30 mL/min/1.73 m2, whereas high protein intake (>1.3 g/kg/day) should be avoided in adults with CKD at risk for progression. When this recommendation is followed, detailed dietary assessment and supervision are needed to ensure that malnutrition is prevented (see Chapter 90).

One of the earliest effects of CKD is to limit the ability of the kidney to compensate for large changes in sodium and water intake (see Chapter 8). Salt and water retention are major factors contributing to hypertension in CKD patients and, in more advanced stages, to morbidity and mortality through systemic or pulmonary edema. Therefore, sodium intake should ideally be restricted to less than 90 mmol/day (5 g/day of sodium chloride), except in salt-wasting conditions. Advice about optimal fluid intake at each stage of CKD is needed to prevent volume overload. Salt substitutes containing potassium should be avoided because of the risk for hyperkalemia. In stages G4 and G5 CKD, education and advice about restriction of potassium and phosphate may be required.

MANAGEMENT OF COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A detailed discussion of the complications of CKD is provided in Chapters 84 to 92. With the exception of hypertension, there are usually few clinical manifestations associated with CKD stages G1 and G2 (GFR > 60 mL/min/1.73 m2). Other complications (discussed in the following sections) tend to develop progressively as GFR declines to less than 60 and in particular less than 30 mL/min/1.73 m2 (i.e., during CKD stages G4 and G5).

Anemia

Anemia is common in CKD stages G3a to G5 and is caused by a relative deficiency of erythropoietin, although reduced availability of iron and chronic inflammation are frequent contributory factors (see Chapter 86). Anemia may have multiple adverse effects, including worsening cardiac dysfunction by increasing cardiac output and exacerbating left ventricular hypertrophy, thereby accelerating the decline of kidney function. Anemia may also reduce cognition and concentration.

However, clear evidence that reversal of anemia using erythropoiesisstimulating agents (ESAs) is associated with improved clinical outcomes is lacking, and randomized trials have suggested that in some circumstances these agents may cause harm.24 A new approach to the treatment of renal anemia is the use of oral small-molecule stabilizers of hypoxia inducible factor. These agents, which are currently being evaluated in phase 3 studies, could offer a simpler and cheaper therapy compared with ESAs, with potential benefits beyond increases in hemoglobin (Hb) level.25

The relevant KDIGO guideline recommends that all patients identified as having CKD categories G3a and below should have their Hb levels monitored annually, increasing to twice a year for stages G4 and G5.26 Anemia in adults is diagnosed when the Hb concentration is less than 13.0 g/dL in males and less than 12.0 g/dL in females.

NICE recommends that management of anemia should be considered in patients with CKD when the Hb level is up to 11 g/dL.5 In anemic patients, investigations for other causes should be conducted, including measurement of iron stores, serum vitamin B12, and folate levels.

ESAs should not be started until treatment of iron deficiency or other underlying causes have been addressed and then only after considering the balance of benefits (from the reduced requirement for blood transfusions and abrogation of anemia-related symptoms) against the potential harms, which may include an increased risk for stroke and malignancy.

If anemia does not respond to correction of underlying causes, such as iron deficiency, KDIGO recommends that ESAs be commenced when Hb concentrations are less than 10.0 g/dL, if indicated.26 Hb target ranges are discussed in Chapter 86.

Bone and Mineral Metabolism

Hyperphosphatemia, together with a deficiency of 1,25-dihydroxyvitamin D3, can contribute to secondary hyperparathyroidism and ultimately to the development of renal bone disease. These biochemical and endocrine changes, in association with the closely related histologic abnormalities of bone and soft tissue calcification, are collectively termed the CKD–mineral and bone disorder (see Chapter 88).27 Bone disease may already be manifested in CKD category G3b and may be well established in ESKD, even though patients may remain asymptomatic. In addition to the need to prevent bone complications, active management of CKD–mineral and bone disorder may help prevent some of the CV complications of CKD.28

KDIGO recommends measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity in adults with GFR less than 45 mL/min/1.73 m2 (GFR stages G3b–G5). Determining the optimal level of PTH in CKD has been controversial. For patients with levels of intact PTH above the upper normal limit of the assay, efforts should be made to correct hyperphosphatemia, hypocalcemia, and vitamin D deficiency if present. KDIGO guidelines recommend that serum phosphate concentrations be maintained in the normal range according to local laboratory reference values,29 whereas the UK Kidney Association support a level between 0.9 and 1.5 mmol/L for patients with category G4 and G5 CKD.30 Early advice on dietary phosphate management by a specialist dietician or other professional is important in helping patients achieve this. Phosphate-binding drugs may be required, and their choice is discussed in Chapter 88. Prescription of vitamin D supplements or analogs, in the absence of documented deficiency, to suppress elevated PTH concentrations in patients with CKD not on dialysis is not recommended.29 Calcimimetics are a group of drugs that mimic the action of calcium on parathyroid glands by activation of the calcium-sensing receptor and thus reduce the release of PTH. At present, cinacalcet (an oral calcimimetic) and etelcalcetide (which is given intravenously) are generally used in patients receiving dialysis, particularly those that are unfit for surgical parathyroidectomy. Whether these drugs have additional health benefits is not clear (see Chapter 88).

Metabolic Acidosis

The metabolic acidosis associated with CKD is caused by failure of hydrogen ion excretion and may be compounded by the accumulation of organic acids and bicarbonate loss, particularly in interstitial kidney diseases. Clinical symptoms resulting from acidosis are rare until patients reach CKD stage G5, when dyspnea may occur as a result of respiratory compensation. Other causes of dyspnea in advanced CKD, such as anemia and pulmonary edema, should always be considered. Acidosis aggravates hyperkalemia, inhibits protein anabolism, and accelerates calcium loss from bone where the hydrogen ions are buffered.31 Correction of metabolic acidosis may slow progression of kidney disease,32 although larger trials are required to confirm this.

KDIGO recommends that in patients with CKD and serum bicarbonate concentrations less than 22 mmol/L (NICE recommends a threshold of <20 mmol/L), oral bicarbonate supplementation should be given to maintain serum bicarbonate within the normal range, unless contraindicated. However, the associated sodium loading may aggravate hypertension and fluid retention, and severe metabolic acidosis associated with symptoms in a patient with CKD stage G5 may be an indication to start dialysis.2 Novel pipeline drugs include an oral polymer designed to remove acid from the body with high capacity and specificity. This raises the possibility of treatment of acidosis without the problems associated with increased sodium intake.

Cardiovascular Risk

Patients with CKD have an increased prevalence of CVD and are far more likely to die of a CVD-related cause than to progress to ESKD (see Chapter 85). Therefore, appropriate management of existing CVD and minimization of future CV risk is vital for all patients with CKD. Agents used to slow progression of CKD, including ACE/ARBs, SGLT2 inhibitors, and mineralocorticoid receptor antagonists (MRAs), may themselves have cardiovascular benefits in the context of CKD.

Unfortunately, many trials of interventions for CVD have excluded patients with CKD,33 and there is doubt about the relevance of existing standards of care of CVD to patients with CKD.34 Nonetheless, the level of care for coronary heart disease offered to patients with CKD should not be prejudiced by their CKD. NICE suggests that antiplatelet drugs should be offered to patients with CKD for the secondary prevention of CVD, and some experts would extend this recommendation to primary prevention for those at risk for atherosclerotic events.

However, there is an increased risk for minor bleeding, and a recent systematic review of antiplatelet agents for patients with CKD found that although the incidence of myocardial infarction is reduced, major bleeding is increased.35 Thus, the risks may outweigh benefits among individuals with low risk for CV events, including those with early stages of CKD who do not have clinically evident occlusive arterial disease.

For reduction of cardiovascular risk, KDIGO guidelines recommend that statin treatment be routinely offered to patients with

CKD who are aged older than 50 years and to younger patients with additional risk factors, irrespective of baseline lipid values.36 NICE recommends that all people with CKD should be offered atorvastatin 20 mg for the primary or secondary prevention of CVD.37

Risk for Infections

Infection is the second most common cause of death after CVD in patients with ESKD. This is, in part, because of defects in both cellular and humoral immunity, which make CKD a state of chronic immunosuppression (see Chapter 87).38 T-cell responses to de novo antigens are deficient, partly because of impaired antigen presentation by monocytes. Neutrophil activation is defective, and although serum immunoglobulin levels are usually normal, antibody responses to immunization may be poor. Patients with CKD have an increased susceptibility to bacterial infection (particularly staphylococcal), increased risk for reactivation of tuberculosis (typically with a negative tuberculin skin test response), and failure to eliminate hepatitis B and C viruses after infection.

In view of these increased risks, the KDIGO guidelines recommend that all adults with CKD be offered annual vaccination with influenza vaccine unless contraindicated and that all adults with eGFR less than 30 mL/min/1.73 m2 (GFR categories G4–G5) and those at high risk for pneumococcal infection (e.g., patients with nephrotic syndrome, with diabetes, or who are receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated.2 Patients who have received pneumococcal vaccination are offered revaccination within 5 years. In addition, those at high risk for progression of CKD with eGFR less than 30 mL/min/1.73 m2 (GFR categories G4–G5) should be immunized against hepatitis B and the response confirmed by appropriate serologic testing. This should happen as early as possible to maximize the chances of seroconversion.39 Response to COVID-19 vaccination is also attenuated in CKD.40

Gastrointestinal Problems in Chronic Kidney Disease

Gastrointestinal (GI) symptoms and disease are common in patients with CKD (Table 83.3). Anorexia, nausea, and vomiting related to advanced CKD may contribute to malnutrition and wasting, which, in turn, herald an adverse prognosis (see Chapter 90). In addition, uremia-associated reduced taste sensation or abnormal taste can impair dietary intake. Gastroesophageal reflux is also common in patients with CKD and related to GI tract dysmotility or delayed gastric emptying, in particular in diabetes or amyloidosis or patients on peritoneal dialysis, given their increased intra-abdominal pressure. Extensive peptic ulcer disease, gastritis, and duodenitis occur more commonly in CKD than in the general population, with the highest incidence in dialysis patients.41 Peptic ulcers are often multilocular and postbulbar, but pain is less frequent. Helicobacter pylori infection is not increased in CKD. There is a risk for excess calcium and magnesium absorption with some antacids in CKD, and aluminum- or bismuthcontaining preparations should be avoided, given their potential for accumulation in CKD.

In the large bowel, the incidence of diverticular disease is increased in patients with ADPKD (see Chapter 46). Constipation is common in CKD and results from dietary restrictions, restricted fluid intake, electrolyte abnormalities (including hypercalcemia), and commonly prescribed drugs, such as calcium-based phosphate binders, sevelamer, oral iron, opioid analgesics, and calcium resonium. In extreme cases, constipation may result in intestinal pseudo-obstruction, which may also be acutely precipitated by surgery and retroperitoneal hemorrhage. Patients with CKD are at risk for more frequent or severe Clostridium difficile infection, slower treatment response, and more frequent relapse and have a higher risk for death.42

Intestinal ischemia is an important cause of an acute abdomen in older CKD patients. Some cases result from nonocclusive mesenteric

Important Causes of Common
Gastrointestinal Symptoms in Patients With
CKD

TABLE 83.3

Clinical Feature

Causes

Anorexia

Uremic toxicity
Inadequate dialysis clearances
Delayed gastric emptying
Uremic toxicity
Delayed gastric emptying/gastroparesis
Gastritis, duodenitis
Peptic ulcer disease
Drugs
Drugs, including opioid analgesia
GI pseudo-obstruction
Diverticular disease
Diabetic enteropathy
Diverticular disease
Clostridium difficile infection
Dialysis-related amyloidosis (very rare)
Gastritis, duodenitis
Esophagitis
Peptic ulcer disease
Angiodysplasia
Intestinal ischemia
Vasculitis
Dialysis-related amyloidosis (very rare)
Gastritis, duodenitis
Complications of peptic ulcer disease
Acute pancreatitis
Intestinal ischemia
Diverticulitis
GI pseudo-obstruction
Colonic perforation from fecal impaction
Complications of peritoneal dialysis (peritonitis,
dialysis catheter malposition, dialysate
infusion or drain pain)
Complications of autosomal dominant
polycystic kidney disease
Retroperitoneal hemorrhage

Nausea and vomiting

Constipation

Diarrhea

GI hemorrhage

Acute abdominal pain

CKD, Chronic kidney disease; GI, gastrointestinal.

ischemia. Predisposing factors include hypotension, cardiac failure, hypoxia, increased plasma viscosity, and constipation. Abdominal examination can be misleadingly benign at presentation, but often peripheral neutrophil leukocytosis and progressive lactic acidosis are present. GI hemorrhage resulting from peptic ulcers, gastritis, duodenitis, angiodysplasia (Fig. 83.2), or nonulcer, nonvariceal bleeding because of uremic hemostatic defects is also common in CKD and is associated with high mortality. Idiopathic ascites with a high protein content may occur in HD patients, sometimes related to inadequate dialysis dose. The diagnosis is by exclusion of other causes. Management includes optimization of volume and small-solute clearance. The condition may resolve after transplantation or a modality switch to PD.

CARE OF THE PATIENT WITH PROGRESSIVE CHRONIC KIDNEY DISEASE

To optimize the care of patients with progressive CKD, management is provided in a multidisciplinary setting where a range of professionals are able to provide education and information about diet, different

Fig. 83.2 Examples of gastric angiodysplasia (arrows) in a dialysis patient. (Courtesy Drs. R. Winograd and C. Trautwein, Aachen, Germany.)

KRT modalities, transplant options, vascular access surgery, and social care. Psychological comorbidity is common among patients with CKD. Health care professionals working with patients with CKD should take account of the psychological aspects of coping with the condition and offer access to support groups, counseling, or a specialist nurse. The aim is to create an environment in which patients can become informed and proactive in their care.

Chronic Kidney Disease and Risk of Acute Kidney Injury

All patients with CKD are at increased risk for AKI, and AKI is associated with the development and progression of CKD.[43,44] Imaging studies that require iodinated radiocontrast media carry a risk for AKI, and the benefit of a diagnostic scan needs to be balanced against the risks (Chapter 6). If the investigation is needed, the lowest dose of radiocontrast should be used, the patient should be adequately hydrated, and potentially nephrotoxic agents should be withdrawn before and after the procedure; however, the fear of radiocontrastinduced AKI should not prevent or impair a necessary diagnostic workup. The potential risk for nephrogenic systemic fibrosis from gadolinium-based contrast media and measures to reduce it are also discussed in Chapter 6

Many commonly used medications increase the risk for AKI, and the level of GFR should be considered when any drug is prescribed. As discussed earlier, the need for temporary cessation of some medications should be considered during periods of severe intercurrent illness. Other causes of reduction in kidney perfusion can lead to AKI, including volume depletion from excessive diuretics, insufficient fluid intake in hot weather, diarrhea or vomiting, heart failure, myocardial infarction, and tachyarrhythmias. Severe hypercalcemia, resulting from either coadministration of high doses of vitamin D and calciumcontaining phosphate binders or from underlying disease, can also cause AKI.

Clinicians should always consider whether acceleration of loss of kidney function is a result of relapse of the underlying disease or of a superimposed problem such as acute interstitial nephritis (see Chapter 64), obstructive uropathy (see Chapter 61), or renal vein thrombosis.

Timing the Initiation of Kidney Replacement Therapy

Despite all attempts to optimize the management of CKD, many patients will progress to needing KRT. Patients with eGFR less than 20 mL/min/1.73 m^2 and/or who are likely to progress to ESKD within 12 months should receive education and counseling, with the support of a multidisciplinary team, to aid their selection of the most appropriate KRT modality (see Chapter 95). If HD is the preferred option, an AVF should be constructed, remembering that it may take 8 to 12 weeks for veins to become adequately arterialized before needling can be attempted (see Chapter 96). Similar plans need to be made for preemptive insertion of a peritoneal dialysis catheter to allow time for healing and training before any acute need for commencement of dialysis (see Chapter 101).

Early kidney transplantation may be associated with improved long-term outcome,[45] so patients should be assessed for their suitability and, when feasible, activated on the waiting list before dialysis is commenced. This maximizes the chances of the potential recipient remaining in reasonable health. The availability of a living donor should be explored to increase the chances of preemptive transplantation before the patient begins dialysis. The KDIGO guidelines recommend that living donor preemptive kidney transplantation in adults be considered when GFR is less than 20 mL/min/1.73 m2 and there is evidence of progressive and irreversible CKD over the preceding 6 to 12 months.2

Planned early initiation of dialysis is not associated with improvement in outcomes compared with commencement when indicated by signs and symptoms of uremia.46 KDIGO suggests that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or BP; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.2 These problems often but not invariably occur when the GFR is less than 15 mL/min/1.73 m2 (see Chapter 95).

Conservative Management

The potential burden of commencing KRT in terms of high short-term mortality rates, recurrent hospitalizations, time spent traveling, and limited improvement in quality of life for some elderly patients and those with multiple comorbid disease is increasingly recognized. This has led to the practice of offering patients with incipient kidney failure the option of choosing not to start dialysis but to maintain ongoing follow-up and symptomatic support through conservative management.

Although dialysis may offer longer survival, those choosing conservative management may have as many hospital-free days as those who choose HD.47 The symptoms of advanced uremia can be distressing, and it is important to ensure that patients who choose this pathway have access to members of the multidisciplinary team with expertise in palliative care to facilitate a death free of suffering.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is the most common cause of death for people with CKD and eGFR < 60 mL/min/1.73 m2?
A. Failure of dialysis access
B. Sepsis
C. Withdrawal from dialysis
D. Cardiovascular disease
E. Cerebrovascular disease
2. The equation recommended by KDIGO for estimating GFR is:
A. The Modification of Diet in Renal Disease (MDRD) equation
B. The Cockcroft-Gault formula
C. The CKD-EPI formula
D. The Mayo Clinic Quadratic formula
E. The Schwartz formula
3. Which of the following variables is not needed to calculate eGFR from the CKD-EPI formula?
A. Age
B. Weight

C. Race
D. Sex
E. Creatinine
4. Which of the following symptoms is suggestive of CKD, regardless of cause?
A. Pain in the renal angle
B. Nocturia
C. Urinary frequency
D. Tremor
E. Anuria
5. In a well patient, which of the following biochemical or hematologic abnormalities is suggestive of CKD rather than acute kidney injury?
A. Calcium 3.5 mmol/L
B. Potassium 7.5 mmol/L
C. Hemoglobin 10.7 g/dL
D. Creatinine 13.5 mg/dL
E. Sodium 132 mmol/L

REFERENCES

1. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164:659–663.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
3. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307:1941–1951.
4. Richards N, Harris K, Whitfield M, et al. Primary care–based disease management of Chronic Kidney Disease (CKD), based on estimated Glomerular Filtration Rate (eGFR) reporting, improves patient outcomes. Nephrol Dial Transplant. 2008;23:549–555.
5. National Institute for Health and Care Excellence. Chronic Kidney Disease Assessment and Management. NICE guideline; 2021 (NG203).
6. Arm JP, Peile EB, Rainford DJ, et al. Significance of dipstick hematuria. 1. Correlation with microscopy of the urine. Br J Urol. 1986;58:211–217.
7. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–2081.
8. Methven S, Traynor JP, Hair MD, et al. Stratifying risk in chronic kidney disease: an observational study of UK guidelines for measuring total proteinuria and albuminuria. QJM. 2011;104:663–670.
9. Roderick P, Jones C, Drey N, et al. Late referral for end-stage renal disease: a region-wide survey in the south west of England. Nephrol Dial Transplant. 2002;17:1252–1259.
10. Caskey F, Davenport A, Dawnay A, et al. UK renal registry 2013: 16th annual report of the renal association. Nephron Clin Pract. 2013;125:1–4.
11. Roy-Chaudhury P, Kelly BS, Melhem M, et al. Vascular access in hemodialysis: issues, management, and emerging concepts. Cardiol Clin. 2005;23:249–273.
12. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9(suppl 12):S16–S23.
13. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. Am J Med. 2011;124:1073–1080.
14. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334:13–18.
15. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. Nephrol Dial Transplant. 2006;21:1257–1262.
16. Cheung AR, Lóser M, Reboussin DM, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol. 2017;28(9):2812–2823.
17. Kidney Disease: Improving Global Outcomes (KDIGO). Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3S):S1–S87.
18. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;71:e127–e248.
19. Bangash F, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol. 2009;4:656–664.
20. Xie X, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67(5):728–741.
21. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic

and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(1):22.

22. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–2229.
23. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996;7:556–566.
24. Hörl WH. Anaemia management and mortality risk in chronic kidney disease. Nat Rev Nephrol. 2013;9(5):291–301.
25. Maxwell PH, Eckardt KU. HIF prolyl hydroxylase inhibitors for the treatment of renal anaemia and beyond. Nat Rev Nephrol. 2016;12(3):157–168.
26. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
27. Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69:1945–1953.
28. Foley RN. Phosphate levels and cardiovascular disease in the general population. Clin J Am Soc Nephrol. 2009;4:1136–1139.
29. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease–Mineral And Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;76:S1–S130.
30. Renal Association. Clinical Practice Guideline CKD-Mineral and Bone Disorders; 2015. https://renal.org/wp-content/uploads/2017/06/ckdmineral-and-bone-disorders-ckd-mbd204ca231181561659443ff000014d4d8.pdf.
31. Alpern RJ, Sakhaee K. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis. 1997;29:291–302.
32. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20:2075–2084.
33. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. Kidney Int. 2006;70:2021–2030.
34. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80:572–586.
35. Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2013;2:CD008834.
36. Kidney Disease: Improving Global Outcomes (KDIGO) Dyslipidemia Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:263.
37. National Institute of Health and Care Excellence2014Cardiovascular disease. Risk Assessment and Reduction, Including Lipid Modification. Clinical Guideline (CG181); 2014.
38. Descamps-Latscha B, Herbelin A, Nguyen AT, et al. Immune system dysregulation in uraemia. Semin Nephrol. 1994;14:253–260.
39. DaRoza G, Loewen A, Djurdjev O, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. Am J Kidney Dis. 2003;42:1184–1192.
40. Carr EJ, Kronbichler A, Graham-Brown M. Review of early immune response to SARS-CoV-2 vaccination among patients with CKD. Kidney Int Rep. 2021;6:2292–2304.
41. Liang C-C, Muo C-H, Wang I-K, et al. Peptic ulcer disease risk in chronic kidney disease: ten-year incidence, ulcer location, and ulcerogenic effect of medications. PLoS One. 2014;9:e87952.
42. Mullane KM, Cornely OA, Crook DW, et al. Renal impairment and clinical outcomes of clostridium difficile infection in two randomized trials. Am J Nephrol. 2013;38:1–11.

43. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66.
44. Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrol Dial Transplant. 2010;25:2203–2209.

References

45. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725–1730.
46. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010;363:609–619.

47. Carson RC, Juszczak M, Davenport A, Burns A. Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? Clin J Am Soc Nephrol. 2009;4:1611–1619.

84

Pathogenesis and Risk of Cardiovascular Disease in Chronic Kidney Disease

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Diminished estimated glomerular filtration rate (eGFR) and albuminuria are powerful graded, independent predictors of cardiovascular (CV) morbidity and mortality1 and all-cause mortality. Even subtle kidney dysfunction, as suggested by albuminuria, increases CV risk because it may reflect microvasculature health, including endothelial function. Patients with end-stage kidney disease (ESKD) face an extraordinary risk for premature death, largely because of CV complications in the setting of accelerated vascular aging. Patients with eGFR less than 60 mL/min/1.73 m2 are much more likely to die than to develop ESKD, reflecting the burden of cardiovascular disease (CVD) in this population. The most effective strategy for reducing CV morbidity and mortality in this high-risk population would be to target patients with mildly reduced eGFR for prevention and treatment.

Patients with chronic kidney disease (CKD) were often excluded from randomized controlled trials targeting CVD, possibly reducing acceptance of evidence-based therapies (validated in nonrenal patients) and fostering “therapeutic nihilism” in clinicians who treat CKD patients. Thus, novel treatment strategies are urgently needed to reduce the unacceptable high CV event rate.

Like conventional atheromatous occlusive vascular disease, CKD is characterized by generalized vasculopathy, with other characteristics, including left ventricular hypertrophy, vascular calcification, and vascular noncompliance. Numerous CVD risk factors are specific to CKD and operate in addition to conventional risk factors found in the general population.

EPIDEMIOLOGY

Prevalence of Cardiovascular Complications in Chronic Kidney Disease

Interpretation of epidemiologic studies of CVD is problematic because of the difficulty in defining cause of death. Unexpected sudden death most likely results from arrhythmia, but a subarachnoid hemorrhage, massive embolic stroke, or aortic dissection might be indistinguishable from a primary arrhythmic event without an autopsy. Defining “coronary heart disease” (CHD) is also problematic: in the general population, sudden cardiac death is a primary complication of CHD, but this is unlikely to be true for dialysis patients. A history of angina cannot reliably classify a patient as having CHD because angina (resulting from supply-demand mismatch) can occur in patients with left ventricular hypertrophy and angiographically pristine coronary arteries. This probably relates to the increased myocardial fibrosis, diminished relative capillary density, and increased thickening of the intramyocardial vessel walls in uremia. At lower levels of eGFR (especially in dialysis patients), the burden of nonatherosclerotic (vs. atherosclerotic) CVD is relatively increased (Fig. 84.1).2 Although occlusive CHD is common in CKD, acute myocardial infarction (MI) and coronary artery disease account for only 8% of cardiac deaths; 85% of cardiac deaths of hemodialysis (HD) patients in the US Renal Data System (USRDS) database are attributable to arrhythmic mechanisms (www.USRDS.org), continuing a temporal trend of an increasing proportion of deaths attributable to arrhythmic mechanisms. Data from the ERA-EDTA registry are encouraging because the absolute excess mortality for atheromatous CVD decreased between 2007 to 2015.3

Of incident dialysis patients, at least 75% have left ventricular hypertrophy, and 75% to 85% have hypertension. Hypertension, anemia, vascular noncompliance, elevated fibroblastic growth factor 23 (FGF23) levels, and volume overload contribute to left ventricular hypertrophy. Based on echocardiography, 85% to 90% of patients have a left ventricular ejection fraction of 50% or greater despite frequent congestive heart failure (i.e., heart failure with preserved ejection fraction [HFpEF]). Therefore, many volume overload episodes in dialysis patients may be attributable to diastolic dysfunction or circulatory congestion. Fig. 84.2 provides a snapshot of CVD event rates (by modality) in prevalent ESKD patients in 2018.4

Cardiovascular Disease Is Present Long Before the Start of Kidney Replacement Therapy

In elderly patients with stage 2 to 3 CKD, traditional risk factors seem to be the major contributors to CV mortality. Atherosclerosis Risk in Communities (ARIC) data suggest that both traditional and novel risk factors are relevant at CKD stage 4, and novel risk factors are far more prevalent in dialysis patients than in the general population (Fig. 84.3).5 The Framingham predictive instrument does not accurately predict coronary events in CKD. Mild to moderate CKD is associated with increased risk for venous thromboembolism, supporting the concept of hypercoagulability in CKD (see also Chapter 87). Because the incidence of CV events is much higher in the first weeks after HD initiation, concerns have been raised that the dialysis procedure per se may trigger CV events.6

Racial and International Differences in Cardiovascular Disease Prevalence

In the United States, survival is better for African American than for White dialysis patients. However, overall CV mortality among dialysis patients from the United States is significantly greater than is observed in Japan and Europe, even after adjustment for standard risk factors and dialysis dose. Higher mortality rates in US dialysis patients may be related to higher prevalence of sicker or diabetic patients, differences in dialysis practice patterns, cultural habits, differences in diet, or genetic variations.

Reverse Epidemiology

Reverse epidemiology (preferably called confounded epidemiology) refers to the paradoxical observation that the association among hypercholesterolemia, hypertension, obesity, and poor outcomes, including CV

Change in Cardiovascular Risk During CKD Progression

Nonatherosclerotic CVD
LVH
Arrhythmias
Sudden cardiac death
Risk
Arterial calcification
Valve calcification
Hemorrhagic stroke
Others
Atherosclerotic CVD event
CAD
Ischemic stroke
PAD
CKD stages
No CKD

Stage G3

Time
Stage G5D

Risk for fatality after CVD event
Risk

Fig. 84.1 Change in Cardiovascular Risk During Chronic Kidney Disease (CKD) Progression. Cardiovascular disease (CVD) event (upper triangle), contributions of atherosclerotic CVD (tan), nonatherosclerotic CVD (orange), and risk for fatality after CVD event (blue). CAD, coronary artery disease; LVH, left ventricular hypertrophy; PAD, Peripheral artery disease. (From Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet. 2016;388:76–284.)

death, in the general population does not exist and may be reversed in CKD. Patients with wasting and inflammation appear to mostly account for poor survival and confounded epidemiology.

ETIOLOGY AND RISK FACTORS

Traditional Risk Factors

Age, Sex, and Smoking

The US National Health and Nutrition Examination Surveys (NHANES) shows the prevalence of CV factors and CVD prevalence in relation to age and CKD stage. In the United States, the average age in 2018 at kidney replacement therapy (KRT) initiation was 63 years,[4] when CVD is common in the general population. The mean survival for patients who start dialysis in the United States is 3 years. An individuallevel meta-analysis including more than 2 million participants showed that low eGFR and high albuminuria were independently associated with mortality and ESKD regardless of age. Female sex is associated with a 4% independent increased risk for mortality in incident dialysis patients and smoking with a 52% increased risk for death in dialysis patients.

Diabetes Mellitus

Diabetes accounted for 47% of incident US ESKD patients between 2014 and 2018[4] and is a common cause of ESKD in many countries. Diabetic patients starting KRT have numerous cardiovascular risk factors, including dyslipidemia, hypertension, persistent inflammation, gut dysbiosis, increased oxidative stress, and protein-energy wasting. Diabetes at dialysis initiation is a potent independent risk factor for all-cause and CVD-related deaths, including after coronary revascularization or acute MI. Nevertheless, the rate of incident acute MI is even higher for patients with CKD stages 3b-4 without diabetes than for patients with diabetes and CKD stages 1 to 2.

Hypertension

Hypertension predicts mortality in CKD patients before or at dialysis initiation. Isolated systolic hypertension with increased pulse pressure

Overall Prevalence of Common Cardiovascular Diseases in Adult Patients With End-Stage Kidney Disease

100

Percentage

80

60

40

20

0

Any CVD

HF

CAD

AMI

PAD

VHD

Cardiovascular disease

CVA/TIA

AF

SCA

HD

PD

KTx

Fig. 84.2 Unadjusted Prevalence of Common Cardiovascular Diseases in Adult Patients with End-stage Kidney Disease, by Treatment Modality, 2018. AF, Atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HD, hemodialysis; HF, heart failure; KTx, kidney transplant; PAD, peripheral arterial disease; PD, peritoneal dialysis; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient ischemic attack; VHD, valvular heart disease; VTE, venous thromboembolism. (From US Renal Data System. USRDS 2020 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.)

Risk Factors for Cardiovascular Disease in Chronic Kidney Disease

Traditional Risk Factors

- Left ventricular
- Age

hypertrophy

- Male sex
- Hypertension • Diabetes
- Dyslipidemia
- Smoking

O2°

Oxidized

LDL
Leukocyte
activation

Novel and Uremia-Related Risk Factors
Sympathetic activation

Oxidative stress

Subclinical hypothyroidism
Inflammation

Uremic bone disease
Volume overload

Endothelial
dysfunction

Protein-energy wasting
Insulin resistance

Anemia
Erythrocytes

Vascular calcification
Uremic toxins
Fat mass: adipokine imbalance
Genetics/epigenetics
Coagulation disorders
Atherosclerotic plaque

Fig. 84.3 Risk Factors for Cardiovascular Disease in Chronic Kidney Disease. Overview of traditional (i.e., Framingham) risk factors and novel and uremia-related risk factors. LDL, Low-density lipoprotein. (From Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3:505–521.)

VTE/PE

TABLE 84.1 Common Patterns of Hyperlipidemia in Different Stages of Kidney Disease, Compared With the Healthy Population

	CHOLESTEROL			
Stage of Kidney Disease	Total	High-Density Lipoproteins	Low-Density Lipoproteins	Triglycerides
Nephrotic syndrome	↑↑↑	↓	↑↑	↑
Chronic kidney disease	No change	↓	No change[a]	↑↑
Hemodialysis	No change	↓	No change[a]	↑↑
Peritoneal dialysis	↑	↓	↑	↑
Transplantation	↑↑	No change	↑	↑

[a] Composition altered.

is by far the most prevalent blood pressure anomaly in dialysis patients, resulting from arterial medial sclerosis (i.e., arteriosclerosis) with secondary vascular stiffening. Stiff vessels cause increased pulse wave velocity, resulting in increased systolic blood pressure peak pressure by a prematurely reflected pulse wave, progressive left ventricular dysfunction, and finally congestive heart failure. At this stage, mean arterial and diastolic pressure may decrease. The relationship between blood pressure and mortality is U-shaped; isolated systolic hypertension and increased pulse pressure probably indicate high long-term risk in dialysis patients, whereas low mean and diastolic blood pressures predict early mortality. CKD patients are frequently “nondippers” and experience sleep apnea and sympathetic nervous system activation.

Dyslipidemia

The relationship between hypercholesterolemia, CVD, and mortality in CKD is weak because common uremic CV abnormalities, such as cardiomyopathy and arteriosclerosis (i.e., vascular calcification), are less dependent on dyslipidemia than on other factors. Low rather than high serum cholesterol level is associated with poor survival in HD patients, likely related to confounding by protein-energy wasting and inflammation.

Progressive CKD leads to changes in blood lipids typically associated with vascular disease, including decreased apolipoprotein A (apoA)containing lipoproteins and increased apoB-containing lipoproteins (Table 84.1). Serum triglycerides are elevated in most ESKD patients, whereas total serum cholesterol is variable, depending on nutritional status and presence of inflammation. High-density lipoprotein (HDL) cholesterol is typically reduced, and low-density lipoprotein (LDL), intermediate-density lipoprotein, and very low-density lipoprotein cholesterol, as well as lipoprotein(a) levels, tend to be increased. Because of altered molecular composition, the antiinflammatory activity of HDL is lost in the uremic milieu. Compared with long-term HD patients, peritoneal dialysis (PD) patients more often have both hypercholesterolemia and hypertriglyceridemia. Both groups are characterized by low HDL and elevated oxidized LDL cholesterol levels; elevated lipoprotein(a) levels are associated with increased CVD mortality.

Insulin Resistance and Atherosclerosis

In the general population, impaired insulin-stimulated glucose disposal in muscle is often part of a metabolic syndrome that includes dyslipidemia, hypertension, endothelial dysfunction, and sympathetic overactivity. Many of these abnormalities are present in CKD. Although insulin resistance was found to be an independent predictor of CV mortality in dialysis patients, its magnitude of contribution in CKD mortality is uncertain. High urea levels have been linked to insulin resistance.7

Nontraditional and Uremia-Specific Risk Factors

Even mild CKD is an independent risk factor for CVD and similar in magnitude to diabetes and hypertension. The uremic milieu may affect

both quality and quantity of the atherosclerotic plaques. Coronary lesions in uremic patients, compared with nonrenal controls, are characterized by increased media thickness, infiltration and activation of macrophages, and marked media calcification. The mechanism(s) by which a uremic milieu may promote vascular senescence and accelerate vascular aging8 are not well established, but prevalence and magnitude of several nontraditional risk factors, such as oxidative stress, inflammation, gut dysbiosis, and advanced glycation end-products (AGEs), increase as kidney function deteriorates and uremic toxins accumulate. Many uremic retention solutes, such as asymmetric dimethylarginine (ADMA), guanidine, indoxyl sulfate, trimethylamine N-oxide (TMAO), interleukin (IL)-6, and p-cresol, which accumulate in CKD, may have proatherogenic properties.9 Finally, failing kidneys produce fewer substances that may inhibit CVD and atherogenesis (e.g., renalase, a soluble monoamine oxidase that regulates cardiac function and BP).

Oxidative Stress

Oxidative stress may be implicated in the pathogenesis of atherosclerosis, the increased risk for atherosclerotic CV events, protein-energy wasting, and anemia.10 Increased production of reactive oxygen species in the vascular wall characterizes atherosclerosis. Moderate CKD, and in particular ESKD, is a prooxidant state resulting from reduced antioxidant systems (vitamin C and selenium deficiency, reduced intracellular vitamin E levels, reduced activity of the cytoprotective transcription factor Nrf2, reduced glutathione system activity), and

increased prooxidant activity is associated with advanced age, diabetes, chronic inflammation, retained uremic solutes, and dialysis membranes and solutions. Four oxidative stress pathways operate in CKD:
carbonyl stress, nitrosative stress, chlorinated stress, and classic oxidative stress.

Inflammation

Most dialysis patients are in a state of chronic low-grade inflammation, which associate with premature aging processes (i.e., inflammaging).11 Inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), pentraxin 3 (PTX3), fibrinogen, and white blood cell count, are independent predictors of mortality in CKD. It has been argued that repeated CRP measurements will improve dialysis patient care because persistent inflammation (i.e., CRP > 5 mg/L) may be a silent reflection of different pathophysiological alterations that require attention.12 Hypoalbuminemia, strongly associated with systemic inflammation, is another strong outcome predictor in CKD. Whereas both dialysis-related factors and non–dialysis-related factors, infection, gut dysbiosis with a leaky gut, comorbidity, genetic factors, hypogonadism, diet, and kidney function loss may contribute to chronic inflammation, its primary causes are not always evident. The senescence-associated secretory phenotype caused by increased numbers of senescent cells in the uremic milieu13 also may be a

Effect of Altered Cytokine Production in Uremia on Various Target Organs

Unfriendly uremic milieu

Monocyte/macrophage
↑ Proinflammatory cytokines
↓ Antiinflammatory cytokines
↑ Bone remodeling

↑ Insulin resistance

↑ Muscle catabolism

↑ Acute-phase reactants
↓ Fetuin-A
↑

↑ Adipocytokine
production

Appetite
↑ REE

↑ Endothelial dysfunction
↑ Monocyte adhesion
↑ Smooth muscle cell proliferation
↑ LDL oxidation
↑ Vascular calcification

Fig. 84.4 Potential mechanisms by which elevated circulating levels of proinflammatory and antiinflammatory cytokines may promote accelerated atherosclerosis, other uremic complications, and wasting. LDL, Low-density lipoprotein; REE, resting energy expenditure. (From Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3:505–521.)

significant contributor to uremic inflammation. Whether the acutephase response reflects only established atherosclerotic disease or is involved in the initiation and progression of atherosclerosis is unclear. Some inflammatory biomarkers, such as IL-6, PTX3, and tumor necrosis factor, have proatherogenic properties, such as promoting vascular calcification, oxidative stress, and endothelial dysfunction (Fig. 84.4). Evidence suggests associations between inflammation and development of albuminuria. Persistent inflammation may change the risk factor profile for traditional risk factors, such as cholesterol and obesity.14 The link between septicemia and subsequent increased risk for death and CV events, including acute MI, further supports inflammation as a trigger for CV events.

Gut Dysbiosis

The uremic milieu affects the intestinal microbiota and the integrity of the intestinal wall, possibly contributing to inflammation and increased production of uremic toxins, such as proatherogenic indoxyl sulfate, phenylacetic acid, and p-cresol sulfate. The uremic milieu and volume retention may damage the intestinal wall, promoting increased leakiness of endotoxins and translocation of intestinal bacteria. The microbial metabolite and water-soluble uremic toxin TMAO contributes to the development of atherosclerotic heart disease and vascular

calcification, and it is related to adverse CV outcomes in both the general population and in CKD.15

Endothelial Dysfunction

Endothelial dysfunction (as evaluated by impaired endotheliumdependent vasodilation) is common in CKD. Reasons include inflammation, ADMA retention, elevated TMAO, oxidative stress, elevated FGF-23, dyslipidemia, hyperglycemia, and hypertension. Serum ADMA concentrations are associated with endothelial function in uremic resistance vasculature. Surrogate markers of endothelial dysfunction, such as ADMA, PTX3, and adhesion molecules, independently predict death.16 Detached circulating endothelial cells are potential markers of endothelial damage and have prognostic value in HD patients. Normally, in response to an ischemic insult and cytokine stimulation, endothelial progenitor cells are mobilized from the bone marrow to repair endothelial injury, and this seems to be impaired in CKD.

Anemia

Anemia is a major cause of left ventricular hypertrophy and left ventricular dilation in CKD. Although partial correction of anemia with erythropoiesis-stimulating agents (ESAs) results in left ventricular hypertrophy regression, current information suggests no CV outcome benefit of normalized hemoglobin (see Chapter 86).

Secondary Hyperparathyroidism and Mineral Metabolism

Disturbances of calcium and phosphate metabolism might accelerate calcifying atherosclerosis and arteriosclerosis (see also Chapter 88). Chronically elevated FGF-23 levels are associated with high rates of left ventricular hypertrophy, atrial fibrillation, and mortality. In registry data, a strong independent mortality risk is predicted by hyperphosphatemia, an intermediate risk by elevated serum calcium levels, and a weak risk by high or low serum intact parathyroid hormone levels.17 The overall proportion of mortality risk that is potentially attributable to mineral metabolism disorders is estimated to be about 17% in HD patients.

Cardiovascular Calcification

CV calcification may affect the arterial media, atherosclerotic plaques, myocardium, and heart valves. Medial calcification causes arterial stiffness and, consequently, increased pulse pressure.18 The pathophysiologic role of plaque calcification is less clear because soft plaques are assumed to rupture and cause acute MI; atherosclerotic calcification is a potent risk marker for CV events, but its utility as a risk marker for clinical management of CKD patients remains controversial. Valvular calcification mostly affects the aortic and mitral (annulus) valves in dialysis patients and contributes to progressive stenosis and associated morbidity and mortality. In dialysis patients, extensive vascular (especially coronary artery) calcification can occur at young ages. Calciphylaxis (calcific uremic arteriolopathy) is discussed in Chapter 91

Vascular calcification is not derived only from passive calcium and phosphate precipitation. Rather, it involves differentiation of vascular smooth muscle cells toward osteoblasts induced by phosphate, calcium, and other factors, such as calcitriol and proinflammatory cytokines. Uremic bone disease, senescence, vitamin K deficiency, genomic damage, persistent inflammation, somatic mutations, posttranslational protein modification and proteinenergy wasting may be additional risk factors for vascular calcification.19 One mechanism by which chronic inflammation promotes vascular calcification may involve downregulation of fetuin-A, the most potent circulating inhibitor of extraosseous calcification and a component of calciprotein particles. Apart from fetuin-A, other inhibitors, such as magnesium, probably counteract unwanted calcification. Leptin, matrix GLA protein, FGF-23, pyrophosphates, bone morphogenic proteins (e.g., BMP-2 and BMP-7), and osteoprotegerin may be related to accelerated vascular calcification in ESKD. Deficiency of vitamin K and/or treatment with vitamin K antagonists (warfarin) accelerate the vascular calcification process in the uremic milieu.20 Recent studies using dual-energy computed tomography imaging show vascular urate crystalline deposits in the aorta and coronary arteries of a high percentage of subjects with gout, and these urate deposits sometimes colocalize with sites of vascular calcification.21 While studies have not investigated whether this also may occur in CKD, it also raises the possibility that uric acid may also be involved as a nidus for calcification, similar to what occurs in the kidney tract.

Advanced Glycation End-Products

Advanced glycation end-products (AGEs) accumulate in CKD as a result of nonenzymatic glycation, oxidative stress, intestinal food components, and diminished clearance of AGE precursors. These AGEs interact with the receptor for advanced glycation end-products (RAGE); a key molecule in the genesis of CV and arterial thrombosis in CKD.22 Stable AGE residues of long-lived proteins are biomarkers of cumulative metabolic, inflammatory, and oxidative stress; carbonyl stress is speculated to contribute to tissue aging and long-term CKD complications. Whether AGE inhibition may affect CV disease in CKD is unknown.

Dialysis Modality

Reports from dialysis registries are inconsistent regarding whether HD or PD is associated with better outcomes. Valid mortality comparisons between HD and PD modalities are not available because this would require stratification of patients according to underlying ESKD cause, age, and level of baseline comorbidity. Cardiac arrhythmias, such as atrial fibrillation, seem to occur more often on the day of HD compared with PD.23

SELF-ASSESSMENT QUESTIONS

1. Which of the following is not an established risk factor for CV disease in patients with advanced CKD?
A. Inflammation
B. Smoking
C. Dyslipidemia
D. Hyperhomocysteinemia
E. Diabetes
2. What is not true about cardiovascular complications in patients with ESKD?
A. Left ventricular hypertrophy is present in about 75% of the patients.
B. In dialysis patients the incidence of atrial fibrillation is about 15% per year.
C. Low levels of cholesterol predict death.
D. In dialysis patients, extensive vascular, especially coronary artery, calcification can occur even at young ages.

E. The calcific aortic stenosis progression rate is only slightly higher in dialysis patients compared with the general population.
3. What is the most common cause of death in dialysis patients?
A. Congestive heart failure
B. Infection
C. Arrhythmic death
D. Stroke
E. Valvular heart disease
4. Which drug has been shown to reduce mortality in dialysis patients with dilated cardiomyopathy and systolic heart failure?
A. Atorvastatin
B. Digoxin
C. Carvedilol
D. Metoprolol
E. Atenolol

REFERENCES

1. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–1305.
2. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet. 2016;388:76–284.
3. Boenink R, Stel VS, Waldum-Grevbo BE, Collart F, Kerschbaum J, Heaf JG, et al. Data from the ERA-EDTA Registry were examined for trends in excess mortality in European adults on kidney replacement therapy. Kidney Int. 2020;98:999–1008.
4. U.S. Renal Data System. USRDS 2020 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
5. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimburger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3:505–521.
6. Eckardt KU, Gillespie IA, Kronenberg F, Richards S, Stenvinkel P, Anker SD, et al. High cardiovascular event rates occur within the first weeks of starting hemodialysis. Kidney Int. 2015;88:1117–1125.
7. Vanholder R, Gryp T, Glorieux G. Urea and chronic kidney disease: the comeback of the century? (in uraemia research). Nephrol Dial Transplant. 2018;33:4–12.
8. Kooman JP, Kotanko P, Schols AM, Shiels PG, Stenvinkel P. Chronic kidney disease and premature ageing. Nat Rev Nephrol. 2014;10:732–742.
9. Rapp N, Evenepoel P, Stenvinkel P, Schurgers L. Uremic toxins and vascular calcification-missing the forest for all the trees. Toxins (Basel). 2020;12:624.
10. Himmelfarb J, Stenvinkel P, Ikizler T, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62:1524–1538.
11. Kooman JP, Dekker MJ, Usvyat LA, Kotanko P, van der Sande FM, Schalkwijk CG, et al. Inflammation and premature aging in advanced chronic kidney disease. Am J Physiol Renal Physiol. 2017;313:F938–F50.

12. Cobo G, Quershi AR, Lindholm B, Stenvinkel P. C-Reactive protein: repeated measurements will improve dialysis patient care. Semin Dial. 2016;29:7–14.
13. Sturmlechner I, Durik M, Sieben CJ, Baker DJ, van Deursen JM. Cellular senescence in renal ageing and disease. Nat Rev Nephrol. 2017;13:77–89.
14. Stenvinkel P, Gillespie IA, Tunks J, al e. Inflammation modifies the paradoxical association between body mass index and mortality in hemodialysis patients. J Am Soc Nephrol. 2016;27:1479–1486.
15. Tang WH, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest. 2014;124:4204–4211.
16. Stenvinkel P, Carrero JJ, Axelsson J, al e. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3:505–521.
17. Memmos E, Papagianni A. New insights into the role of FGF-23 and Klotho in cardiovascular disease in chronic kidney disease patients. Curr Vasc Pharmacol. 2021;19(1):55–62.
18. Nelson AJ, Raggi P, Wolf M, Gold AM, Chertow GM, Roe M. Targeting vascular calcification in chronic kidney disease. JACC Basic Transl Sci. 2020;5:398–412.
19. Dai L, Schurgers LJ, Shiels PG, Stenvinkel P. Early vascular ageing in chronic kidney disease: impact of inflammation, vitamin K, senescence and genomic damage. Nephrol Dial Transplant. 2020;35(suppl 2): ii31–ii7.
20. Cozzolino M, Fusaro M, Ciceri P, Gasperoni L, Cianciolo G. The role of vitamin K in vascular calcification. Adv Chronic Kidney Dis. 2019;26:437–444.
21. Klauser AS, Halpern EJ, Strobl S, Gruber J, Feuchtner G, Bellmann-Weiler R, et al. Dual-energy computed tomography detection of cardiovascular

monosodium urate deposits in patients with gout. JAMA Cardiol. 2019;10:1019–1028.

22. Ortillon J, Hézard N, Belmokhtar K, Kawecki C, Terryn C, Fritz G, et al. Receptor for advanced glycation end products is involved in platelet hyperactivation and arterial thrombosis during chronic kidney disease. Thromb Haemost. 2020;120:130–1312.

23. Chang CH, Fan PC, Lin YS, Chen SW, Lin MS, Wu M, et al. Atrial fibrillation and associated outcomes in patients with peritoneal dialysis and hemodialysis: a 14-year nationwide population-based study. J Nephrol. 2020.

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Practical Management of Cardiovascular Disease in Chronic Kidney Disease

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PREVENTION AND CARDIOVASCULAR RISK REDUCTION

Control of traditional risk factors and other factors contributing to cardiovascular risk in chronic kidney disease (CKD) is critical to reducing morbidity and mortality burden in this high-risk population.

Lifestyle Factors and Smoking

Because physical inactivity is associated with albuminuria and cardiovascular mortality, CKD patients should be advised to be as physically active as possible and to avoid smoking.

Weight and Diet

Lifestyle changes, including balanced diets with regard to saturated fat and carbohydrates (in diabetic patients), probably reduce cardiovascular morbidity and should be encouraged. However, in all CKD stages, protein-energy wasting must be avoided (see Chapter 90). Especially in dialysis patients, increased body mass index is associated with better outcomes, possibly reflecting worse outcomes among underweight or normal weight patients who also have inflammation. Alternatively, obesity may act as a physiologic reserve against acute illness.

Hypertension

Blood pressure (BP) targets for CKD patients, in particular those with diabetes or proteinuria greater than 1 g/day, are discussed in Chapter 82. Key goals of therapy include volume control (see Chapter 82) and prevention of sodium overload, particularly through dietary sodium restriction. Longer or more frequent hemodialysis (HD) sessions may be beneficial in controlling hypertension. Because of their cardioprotective effects, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the first-line drugs to treat hypertension in patients with CKD or end-stage kidney disease (ESKD). Diuretics, calcium channel blockers, and most other antihypertensive drugs, including centrally acting sympathetic inhibitors, are useful in combination with first-line agents, especially given that combination therapy is usually required to achieve recommended BP targets in CKD. Pure vasodilators (e.g., minoxidil) should be avoided because they may increase volume overload or occasionally cause pericardial effusion. Because sleep-disordered breathing occurs in about 50% of patients in CKD stages 4 to 5 and is associated with hypertension, sleep apnea should be considered in therapy-resistant hypertension.

Diabetes Mellitus

Optimal control of BP and glycemia (see Chapter 32) and treatment of dyslipidemia are crucial in managing diabetic CKD patients. Cardiovascular disease (CVD) should be treated aggressively in this high-risk group. Because the harm associated with severe hypoglycemia might counterbalance the potential benefit of intensive

glucose-lowering treatment, treating to a hemoglobin A1c (HbA1c) level less than 7.0% (53 mmol/mol) is not recommended in CKD stages 3 to 5.[1] Sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists reduce cardiovascular events in patients with type 2 diabetes at high cardiovascular risk. Thus, various guidelines recommend these agents in CKD and nonCKD patients with CVD and/or multiple cardiovascular risk factors.[2-4]

Mineralocorticoid Receptor Antagonism

Mineralocorticoid receptor antagonists reduce the aldosteronemediated proinflammatory effects that are involved in the fibrotic remodeling processes. The new selective nonsteroidal mineralocorticoid receptor antagonist finerenone also blocks the damaging effects of the overactivated aldosterone system. In contrast to the mineralocorticoid receptor antagonists spironolactone and eplerenone, finerenone is equally distributed in myocardial and kidney tissue. Finerenone binds to the same ligand domain but to different amino acids, leading to a different expression pattern of cardiac genes compared with spironolactone and eplerenone. Finerenone also reduced cardiac fibrosis and inflammation more than eplerenone in animal experiments at a comparable dose. In a large cardiovascular outcome trial (FIDELIO-DKD [Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease]) in type 2 diabetic patients with CKD, finerenone compared with placebo reduced the risk of kidney failure, cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for congestive heart failure (CHF) with a low incidence of hyperkalemia.[5] Based on the inclusion criteria of the trial, patients with diabetes and moderately increased albuminuria and impaired estimated glomerular filtration rate (eGFR) or severely increased albuminuria and eGFR should be treated with finerenone.

SGLT2 Inhibitor Treatment

SGLT2 inhibitors cause glucosuria and osmotic diuresis along with weight loss and natriuresis (see Chapter 32). In patients with diabetes, SGLT2 inhibitors significantly reduced cardiovascular morbidity and mortality. CREDENCE (Canagliflozin and renal outcomes in diabetic nephropathy) was the first study with an SGLT2 inhibitor in type 2 diabetic patients with CKD (eGFR ≥30 to <90 mL/min/1.73 m^2) with a combined primary kidney endpoint[6]: within 2.5 years, canagliflozin reduced the risk of kidney replacement therapy, doubling of serum creatinine and death due to kidney insufficiency by 33% versus placebo in addition to reductions of major cardiovascular events and hospitalization for CHF. The DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease) trial showed that in patients with nondiabetic CKD (eGFR 25–75 mL/min/1.73 m^2), dapagliflozin reduced not only the primary endpoint of sustained decline in eGFR of 50% or more, ESKD, and kidney or cardiovascular death but also the secondary endpoint of heart failure hospitalization and cardiovascular death.7

Dyslipidemia

Because CKD, like diabetes, is considered a cardiovascular risk equivalent, CKD patients should be treated to achieve the guideline goal for secondary prevention for low-density lipoprotein (LDL) cholesterol (<55 mg/dL) if eGFR is less than 30 mL/min/1.73 m2 or less than 70 mg/dL in patients with CKD stage 3.4 Post hoc subgroup analyses in the Heart Protection Study, Cholesterol and Recurring Events (CARE) study and the Treating to New Targets (TNT) study support the use of statins in improving outcomes in CKD stages 1 to 2. The Study of Heart and Renal Protection (SHARP) showed that reducing LDL cholesterol with simvastatin 20 mg/day plus ezetimibe 10 mg/day safely reduced the incidence of major atherosclerotic events in patients with advanced CKD.8 However, the negative results from the 4D study and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) do not support initiation of statins (with or without ezetimibe) in dialysis patients. Overall, the beneficial effect of lipid-lowering therapies is attenuated in subjects with low glomerular filtration rate (GFR) and very limited in ESKD patients on HD (Table 81.1).

Anemia

Partial correction of severe anemia with erythropoiesis-stimulating agents (ESAs) results in regression of left ventricular hypertrophy (LVH), and treatment of severe anemia is also associated with fewer ischemic symptoms in coronary heart disease patients. However, randomized controlled trials in HD and CKD patients have shown no benefit of ESA treatment on mortality (see Chapter 86). Thus, anemia correction in patients with advanced CKD to a hemoglobin level of 10 to 12 g/dL is recommended (www.kdigo.org).

Inflammation

A careful search for infectious processes, such as periodontal disease, is recommended in dialysis patients with inflammation. Restriction of central venous catheter use is also important; short daily dialysis with better fluid status was associated with decreasing C-reactive protein (CRP) levels compared with conventional HD. Volume status should be carefully monitored to avoid inflammation. Altered intestinal microbial flora as a potential risk factor for systemic uremic inflammation merits further study. Medium cutoff dialysis membranes reduce uremic inflammation,9 but larger trials with longer treatment periods are encouraged. Interestingly, the CANTOS trial (Canakinumab Antiinflammatory Thrombosis Outcome Study) demonstrated that inhibiting proinflammatory effector molecule interleukin-1β (IL-1β) with canakinumab reduced the risk of cardiovascular events, and that the benefit appeared larger in patients with eGFR less than 60 mL/min/1.73 m2 than in those with eGFR greater than or equal to 60 mL/min/1.73 m2 10

Chronic Kidney Disease–Mineral Bone Disorder

Recent meta-analyses and the updated Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease–mineral bone disorder (CKD-MBD) guidelines (www.kdigo.org) suggest that avoiding calcium-containing phosphate binders may reduce cardiovascular events, calcification progress, and mortality; however, there is a low level of evidence and multiple studies have not confirmed this (see Chapter 88). We suggest that these agents should be avoided in CKD patients with significant life expectancy, particularly in patients on the transplant waiting list, independent of the presence or absence of calcifications. The potential detrimental effects of sevelamer (and other commonly used drugs) on gut microflora require further studies.11

Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) call into question the survival advantage for HD patients taking vitamin D. In the Paricalcitol Capsules Benefits Renal Failure Induced Cardiac Morbidity in Subjects with CKD Stage 3/4 (PRIMO) study, 48 weeks of paricalcitol therapy did not alter cardiac mass index or improve measures of diastolic dysfunction.12 Thus, the use of native vitamin D or vitamin D receptor agonists in CKD patients should primarily be governed by CKD-MBD parameters (see Chapter 88).

The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) study13 showed that cinacalcet only reduced the risk for death or major cardiovascular events in dialysis patients with moderate to severe secondary hyperparathyroidism after adjustment for age—a nominally significant finding. In a second trial in similar dialysis patients, cinacalcet plus low-dose vitamin D sterols tended to attenuate vascular and cardiac valve calcification compared with an exclusively vitamin D sterol–based approach.14

FGF-23, a bone hormone, is cardiotoxic and induces LVH but does not induce vascular calcification. In a post hoc analysis of EVOLVE data, treatment of secondary hyperparathyroidism with cinacalcet was associated with reduced FGF-23 levels, and patients with a 30% or 50% drop in FGF-23 levels experienced significantly fewer cardiovascular events.15 In patients with advanced secondary hyperparathyroidism, treatment with a calcimimetic alone may therefore be preferred to combined therapy with a vitamin D agonist.

CORONARY ARTERY DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

With respect to the diagnosis of coronary artery disease (CAD), noninvasive stress testing shows reduced accuracy in patients with CKD and in particular in those on HD. Both medical and interventional therapy of acute or chronic coronary syndromes are not different between patients with or without CKD, and patients with CKD should receive a similarly stringent treatment with drugs/procedures that have been shown to provide a prognostic benefit.

Chronic Coronary Syndrome

Diagnosis

CAD in patients with CKD differs from nonrenal controls by exhibiting more and larger plaques and more signs of inflammation.16

Dialysis patients also exhibited more calcified plaques in coronary arteries, whereas plaques of nonrenal patients were mostly fibroatheromatous.17 In addition, a lower eGFR was associated with increased numbers of newly formed intramural blood vessels and intraplaque hemorrhages,17,18 suggesting a more vulnerable plaque phenotype.

In CKD patients with suspected obstructive CAD, special attention should be paid to the fact that symptomatic angina is less common, whereas silent ischemia is more common.19 The diagnostic approach to CAD in CKD patients is similar compared with non-CKD patients,4 except that accuracy of noninvasive testing is lower, particularly in dialysis patients.20 The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for CVD in dialysis patients recommend an electrocardiogram at dialysis initiation and then annually.21

In addition, KDOQI guidelines recommend echocardiography in all dialysis patients after they achieve “dry weight” targets, preferably 1 to 3 months after dialysis initiation on an interdialytic day for HD patients and at 3-year intervals thereafter.22 The rationale is that diminished left ventricular (LV) systolic function, an important independent risk factor for CVD and mortality,23 is not accurately diagnosed

Accuracy of DSE vs MPS for Diagnosing CAD in Kidney Transplant Recipients
1.0

Posttest probability

0.8

0.6

0.4

MPS (positive)
DSE (positive)
MPS (negative)

0.2

DSE (negative)
0.0
0.0

0.2

0.4
0.6
Pretest probability

0.8

1.0

Posttest Probability
Pretest probability (%)
of coronary artery disease

Test

Dobutamine stress
echocardiography (DSE)

Myocardial perfusion
scintigraphy (MPS)

Posttest probability (%)
after positive result

Posttest probability (%)
after negative result

Low risk (10-29)

42-72

3-10

Intermediate risk (30-59)

73-90

10-27

High risk (60-90)

91-98

28-70

Low risk (10-29)

24-54

5-15

Intermediate risk (30-59)

55-81

16-38

High risk (60-90)

81-96

39-79

Fig. 85.1 Pre test and post test probabilities of coronary artery disease (CAD) associated with positive and negative results of dobutamine stress echocardiography (DSE) versus myocardial perfusion scintigraphy (MPS) in renal kidney transplant candidates. (From Shroff GR, Herzog CA. Coronary revascularization in patients with CKD stage 5D: pragmatic considerations. J Am Soc Nephrol. 2016;27:3521–3529.)

by history, physical examination, or chest radiography. Detection of unsuspected cardiomyopathy is also important, given that carvedilol therapy in such patients improved LV systolic function, decreased hospitalization, and reduced mortality. As in the general population, CKD patients with left ventricular ejection fraction (LVEF) below 40% should be evaluated for coronary heart disease (exceptions are pediatric or young adult patients with nondiabetic CKD and other patients known to be at low risk for CAD).

Overall, noninvasive stress testing shows reduced accuracy (vs. invasive coronary angiography) in patients with advanced CKD[24] compared with patients with normal kidney function. The accuracy of both pharmacologic stress echocardiography and single-photon emission computed tomographic nuclear imaging is lowest in ESKD patients even under the most optimal circumstances (i.e., in clinics with a high level of expertise). Reviews cite overall sensitivity percentages in the mid-70s and specificity in the mid-80s for stress echocardiography and sensitivity and specificity in the mid-70s for SPECT myocardial perfusion imaging. Based on Medicare data, 87% of cardiac stress testing in US patients with CKD employs nuclear scintigraphy.[25]

ESKD patients are poorly suited for conventional exercise stress electrocardiography because of limited exercise tolerance and frequent resting electrocardiographic abnormalities. As noted earlier, even under optimal circumstances, the most widely used stress imaging techniques (compared with invasive coronary angiography) are at best imperfect, and in real-world clinical practice they may even be worse. For this reason, local institutional expertise with imaging of ESKD patients will dictate clinical practice irrespective of the published “theoretical” accuracy. Moreover, prediction of the likelihood of future events may differ considerably from predictions based on coronary anatomy. Noninvasive stress testing is probably better at predicting mortality than coronary anatomy—something that continues to vex clinicians, as typically in an individual patient we don’t want to miss “significant” obstructive CAD (i.e., angiographic definition), yet from the broader perspective of population epidemiology, the focus is on events like MI or death (not angiographic stenoses). A meta-analysis concluded that presence of inducible myocardial ischemia by any stress-imaging test is independently predictive of increased acute MI risk and cardiac death, whereas a fixed or resting defect or abnormality is predictive of cardiac death but not acute MI.[26]

In kidney transplant candidates the sensitivities and specificities of stress nuclear and echocardiographic imaging for detection of coronary heart disease have been reported to range from 44% to 90%—not terribly helpful to the nephrologist or even cardiologist dealing with an individual patient. Consistent with others,[25] a meta-analysis (Fig. 85.1) concluded that dobutamine stress echocardiography is probably more accurate than myocardial stress nuclear scintigraphy for noninvasive

Management of Coronary Artery Disease in Renal Transplant Candidates
Low-risk
patients

Evaluation before
transplant

High-risk
patients

Two-dimensional
echocardiography

Atypical chest pain,
asymptomatic diabetes,
previous MI, multiple
risk factors

Dobutamine
echocardiography
Transplant

Symptomatic CAD

Positive

Coronary
angiography

Ambiguous/flow-limiting
lesions?

Negative

Post PCI
<75% stenosis

Fractional flow
reserve
or
Dobutamine
echocardiography

≥75% stenosis

Positive

Negative
Low-risk
patients

High-risk
patients
No intervention

Intervention
CABG or PCI

No intervention

Consider further
intervention

Transplant
No transplant
(severe diffuse disease)
Dobutamine
echocardiography

Fig. 85.2 Algorithm for management of coronary heart disease in kidney transplant candidates. CABG, Coronary artery bypass graft surgery; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention. (Modified from Herzog CA. Acute MI in dialysis patients: how can we improve the outlook? J Crit Illn. 1999;14[11]:613–621.)

detection of coronary heart disease in kidney transplant candidates.27 However, a recent analysis concluded “there are no compelling reasons to routinely select one particular stress imaging modality in preference to others, although there may specific circumstances that favor a particular test.”25

The major problem with searching for CAD in asymptomatic kidney transplant candidates (or dialysis patients) is that the evidence for prophylactic revascularization is weak.21 The best observational data supporting preemptive coronary revascularization showed a 3-year cardiac event–free survival of 90% for transplant wait-listed revascularized patients.28 Optimal medical therapy (which should constitute the treatment strategy for all patients) may potentially attenuate the putative benefit of prophylactic coronary revascularization. One algorithm for screening and management of CAD in kidney transplant candidates is presented in Fig. 85.2. However, challenging the rationale for this or any other algorithm employing prophylactic coronary revascularization, in the ISCHEMIA-CKD trial (see later) an invasive strategy of optimal medical therapy and coronary angiography (with revascularization) did not improve outcomes compared with optimal medical therapy alone.29

Biomarkers

Plasma brain natriuretic peptides (BNP and NT-proBNP), cardiac troponins (cTnT, cTnI), and high-sensitivity CRP (hsCRP) are prognostic risk markers in the evaluation of heart disease in ESKD.30 BNP reflects cardiac filling pressures (not limited to the left heart), troponins reflect myocardial cell death (but not necessarily ischemia), and hsCRP reflects inflammation. Elevation of cTnT occurs even in pediatric CKD patients and is associated with cardiac dysfunction. Elevated levels of serum troponin in ESKD patients should not be uncritically attributed to myocardial ischemia caused by obstructive CAD as they also reflect the presence and severity of HD-induced myocardial stunning.31 The cardiac biomarker–based diagnosis of acute coronary syndrome requires a time-appropriate rise and fall of the biomarker.

Fig. 85.3 graphically displays the relationship of cTnT and cTnI levels in asymptomatic dialysis patients and long-term survival. On the basis of these data, the US Food and Drug Administration approved the measurement of cTnT in dialysis patients for risk stratification (mortality prediction).

High-sensitivity cardiac troponin (hs-cTn) assays are highly precise and serve two complementary roles: the diagnosis of acute MI coronary angiography in CKD patients to diagnose clinically unsuspected valvular disease or cardiomyopathy, to gauge preprocedure volume status, and to assess LV function (to avoid excessive exposure to radiocontrast media through unwarranted ventriculography). Noninvasive coronary CT angiography may be problematic in dialysis patients because of medial calcification interfering with angiographic interpretation.34 Coronary CT angiography is noninvasive and has similar accuracy to invasive coronary angiography but is associated with a lower risk of significant AKI in kidney transplant candidates. Noninvasive gadolinium-based magnetic resonance angiographic imaging in patients with severe CKD remains problematic because of residual concerns about nephrogenic fibrosing dermopathy (see Chapter 91).

Survival by Baseline Troponin Values

Cumulative survival (%)

100
90
80
70
60
cTnT <0.01 μg/L
cTnT ≥0.01 to <0.04 μg/L
cTnT ≥0.04 to <0.10 μg/L
cTnT ≥0.10 μg/L

50
40
30

0

0.5
1.0
1.5
2.0
2.5
Time since blood draw (years)

3.0

Number of
cTnT <0.01 μg/L
cTnT ≥0.01 to <0.04 μg/L
cTnT ≥0.04 to <0.10 μg/L
cTnT ≥0.10 μg/L

132
214
239
148

106
166
180
93

25
41

63
20

Revascularization

Cumulative survival (%)

90
80
cTnl <0.01 μg/L

70
60
50

cTnl ≥0.10 μg/L

40
0

0.5
1.0
1.5
2.0
2.5
Time since blood draw (years)

3.0

Number of
cTnl <0.01 μg/L
cTnl ≥0.10 μg/L

Drug Therapy in Chronic Coronary Syndrome Patients With Chronic Kidney Disease

According to current guidelines, drug therapy in chronic coronary syndrome (CCS) patients with CKD should not differ from therapy in non-CKD patients, but renally excreted drugs used in CCS should be dose adjusted for kidney function.

12
15
18
8

100

30

977

688
45

514
31

120
6

51
2

Fig. 85.3 Kaplan-Meier survival curves by baseline troponin values.

cTnI, Cardiac troponin I; cTnT, cardiac troponin T. (From Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation. 2002;106:2941–2945.)

and risk stratification based on detection of hs-cTn in asymptomatic patients (e.g., perhaps a marker for apoptosis). Similar to elevated troponin serum levels discussed earlier, hs-cTn–based risk stratification should also employ changes in values over time, rather than simple thresholds.[32]

Coronary Angiography

Coronary angiography should be considered in stable ESKD patients with evidence for inducible myocardial ischemia, unstable patients with acute coronary syndrome (performed urgently for ST-segment elevation MI [STEMI]), and patients with LVEF less than 40%. In CKD and dialysis patients with residual kidney function, fear of contrast nephropathy may restrain use of coronary angiography (see Chapter 74 for preventive measures). However, one retrospective study of 76 nondialysis patients with mean eGFR of 12.5 mL/min/1.73 m^2 found no significant postangiographic deterioration in kidney function. Although acute kidney injury (AKI) after coronary angiography increases the risk of mortality, ESKD, and hospitalization,[33] fear of AKI should not deter clinically mandated coronary angiography. Echocardiography should be performed before any nonemergent

CKD is a strong risk factor for death after coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[35,36] Coronary revascularization complicated by AKI is associated with excess mortality; operative mortality for nonCKD patients who require acute dialysis after cardiac surgery is 44%. Observational studies suggest lower mortality in CKD (including dialysis) patients undergoing coronary revascularization compared with no revascularization. A post hoc analysis of CKD patients in the Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trial indicated a superior outcome with an early invasive strategy in ACS compared with conservative management. However, the optimal coronary revascularization method in CKD remains controversial. A post hoc analysis of CKD patients enrolled in the Arterial Revascularization Therapies Study (ARTS) found similar outcomes for CABG or multivessel PCI with non–drug-eluting stents for death, MI, or stroke. In elderly non–dialysis-dependent CKD patients, the incidence of ESKD was lower after PCI (5.4% at 3 years vs. 6.8% for CABG), but long-term risk for death (3year mortality with PCI 33% vs. 28% with CABG) or the combined event of death or ESKD was lower after CABG. The relative survival advantage of CABG versus PCI occurs only more than 6 months after revascularization.[37] Dialysis patient survival after CABG is better than after PCI with non–drug-eluting stents[38] and drug-eluting stents,[39] but 2-year mortality remains high at 44% versus 52% for PCI.[38] In the absence of data from dedicated cardiovascular outcome trials in patients with ESKD or on HD, recommendations are based on large observational studies. Current guidelines recommend that the revascularization strategy (PCI vs. CABG) should be chosen based on the general condition, preferences, and life expectancy of the patient, the least invasive approach being more appropriate in the most fragile and compromised patients.[40]

The ISCHEMIA-CKD trial compared an invasive or conservative care approach in CKD patients (eGFR <30 mL/min/1.73 m^2 or dialysis) with stable CAD. Patients with moderate or severe ischemia on stress testing were randomly assigned to an initial invasive strategy consisting of coronary angiography and revascularization (if appropriate) added to medical therapy or an initial conservative strategy consisting of medical therapy alone and angiography reserved for those in whom medical therapy failed. After a median follow-up of 2.2 years, there was no difference for the primary composite endpoint of death or nonfatal MI between groups. Compared with the conservative strategy, the invasive strategy was associated with a significantly

Estimated Mortality of Dialysis Patients
After Acute Myocardial Infarction
100

Overall mortality

Mortality (%)

80
Mortality from
cardiac causes

60

40

20

0

0

2

4

6

8

10

Years
No. at risk 34,189 6753
2284
834
304
105

Fig. 85.4 Estimated mortality of dialysis patients after acute myocardial infarction. (From Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339:799–805.)

higher incidence of stroke and a higher incidence of death or initiation of dialysis.29 In addition, both groups did not differ with respect to angina-related health status during follow-up.41

Acute Coronary Syndrome

Acute MI in dialysis patients is associated with poor long-term survival. Unadjusted 2-year mortality has not improved over time (71% in 1977–1984 and 72% in 200842) despite dramatic improvements in acute MI outcomes in the general population (Fig. 85.4). Significant improvement has occurred only in dialysis patients with STEMI, specifically related to inhospital mortality. Rates of non-STEMI (NSTEMI) mortality or postdischarge mortality have not improved.42 In-hospital mortality increases with decreasing GFR, which has been attributed to underrecognition resulting from atypical presentations, underuse of appropriate diagnostic investigations, and undertreatment (therapeutic nihilism).43 A US registry of dialysis patients hospitalized for acute MI found the following43:

✓•✓ With respect to acute coronary syndrome, 45% of dialysis patients were diagnosed incorrectly versus 21% of nondialysis patients.

✓•✓ ST-segment elevation was found in 19% of dialysis patients versus 36% of nondialysis patients.

✓•✓ After other clinical exclusions, 10% of dialysis patients and 25% of nondialysis patients were eligible for acute coronary reperfusion.

✓•✓ Of those who were eligible, 47% of dialysis patients and 75% of nondialysis patients actually received reperfusion.

Similar findings occur across the CKD spectrum; the likelihood of increased mortality and lower prevalence of both STEMI and chest pain are correlated with severity of non–dialysis-dependent CKD in patients with acute MI.[44,45] Compared with those with normal eGFR, patients with eGFR less than 45 mL/min/1.73 m^2 are three times as likely to present with acute MI as the initial manifestation of coronary heart disease, rather than stable angina.

Given the poor prognosis of patients with acute MI and the fact that CKD patients are less likely to receive appropriate therapy, current guidelines recommend that acute coronary syndrome patients with CKD should be treated as aggressively as in patients without CKD.

HEART FAILURE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Patients with CKD show an increased risk to develop heart failure, and the presence of this comorbidity tremendously impairs the prognosis of CKD patients. Some therapeutic approaches in heart failure in patients have not been tested in patients with advanced CKD. However, SGLT2 inhibitors have shown benefit in both patients with heart failure and CKD and should be used in CKD patients not on HD (see Chapter 82).

Heart failure in patients with CKD, in particular those on HD, is possibly related to maladaptive ventricular hypertrophy and fibrosis.[46] LVH occurs early in progressive CKD, probably because of high hypertension prevalence, including frequent nocturnal hypertension.

Pressure overload, caused by hypertension and arterial stiffness, results in concentric hypertrophy. Volume overload manifests as eccentric hypertrophy. Left ventricular dilation strongly predicts poor outcome.

It may be an end result of severe LVH, diffuse ischemic damage, or recurrent volume overload; a high-output arteriovenous fistula may contribute. Diastolic dysfunction is strongly associated with LVH and risk for intradialytic hypotension.

Hemodialysis can produce repetitive myocardial injury, leading to global and segmental reduction in left ventricular systolic function; HD-induced myocardial stunning is associated with increased 1-year mortality. Even pediatric HD patients can experience HD-induced myocardial stunning, indicating that large-vessel obstructive CAD is not a prerequisite for this pathologic finding. Biofeedback dialysis or reduced dialysate temperature can help reduce intradialytic hypotension and severity of HD-induced myocardial stunning.

With respect to HF diagnosis, NT-proBNP and BNP are equivalent predictors of decompensated heart failure in CKD, but NT-proBNP is a better predictor of survival.

Congestive Heart Failure Treatment in Patients With Chronic Kidney Disease

No treatments convincingly reduce morbidity and mortality in CKD patients with CHF and preserved ejection fraction (HFpEF; LVEF ≥50%) or moderately impaired left ventricular function (HFmrEF; LVEF 40%–49%).

Therapy of Heart Failure and Reduced Ejection Fraction in Chronic Kidney Disease

Treatment of CHF in the general population is based on data from large cardiovascular outcome trials that have led to the development of certain treatment algorithms.[47] However, patients with severe CKD were excluded from the landmark trials, and therefore recommendations for this group are largely based on data from the general population (Fig. 85.5).[48]

ACE Inhibitors/Angiotensin 2 Receptor Blockers

ACE-inhibitors reduce morbidity and mortality in patients with heart failure, and reduced ejection fraction (HFrEF) and solid data exist for the use of ACE-inhibitors in patients with CKD stage I–III plus HFrEF, but no data exist for those with CKD stages 4 to 5. In patients with ACE-inhibitor intolerance it is recommended to treat with an angiotensin receptor blocker (ARB).

β-Blockers

First-line therapy in patients with HFrEF also includes treatment with β-blockers. A meta-analysis of six studies analyzing the effect of β blocker therapy in CHF and CKD stages 3 to 5 show that patients with advanced CKD benefited from β-blocker therapy.49

Evidence for improvement in outcome in patients with HF

HF Therapies According to LVEF and Kidney Filtration Function
Strong
ilol

Carved

B
er B
ACEi (CKD G5D)

Oth

Moderate

ARB (CKD G5D)

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CR

Digoxin

RA

M

Absent
CKD GFR
category

Risk:benefit ratio likely to
be similar for eGFR > 60

Potential harm with
digoxin in CKD G5D

0

10
CKD G5
Dialysis indicated

20

30

eGFR (mL/min per 1.73 m2)

CKD G4

CRT (i) = QRS > 120 ms, LBBB QRS morphology, EF ≤ 35%;
or QRS > 130 ms, EF ≤ 30%
CRT (ii) = QRS > 150 ms

40

50

60

CKD G3a-G3b
Loop diuretics (p.o./i.v.) (furosemide, bumetanide, torsemide)
and thiazide diuretics (metolazone [p.o.], chlorothiazide [i.v.])
= benefit uncertain

Fig. 85.5 Positioning of heart failure (HF) therapies according to left ventricular ejection fraction (LVEF) and glomerular filtration rate. ACEi, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; CKD G5D, chronic kidney disease glomerular filtration rate category 5 patient on dialysis; CKD G5 ND, chronic kidney disease glomerular filtration rate category 5 patient not on dialysis; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; H-ISDN, hydralazine and isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist. (From House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95:1304–1317.)

Mineralocorticoid Receptor Antagonists

If patients with HFrEF and a medication of ACE inhibitors and β blockers are still symptomatic, and if LV ejection fraction is 35% or less, they should be treated with a mineralocorticoid receptor antagonist with attention in particular to the development of hyperkalemia.

These agents are effective in patients with CHF and CKD stages 1 to 350 but are contraindicated in CKD stages 4 to 5.

Diuretics

Treatment with diuretics is indicated in patients with venous congestion and New York Heart Association (NYHA) II, as well as in patients with CHF stage NYHA III and IV. Patients can be treated with loop diuretics or thiazides, but patients with CKD stages 4 to 5 should receive either loop diuretics alone or thiazides in combination with loop diuretics. In particular, the latter should be monitored for hypokalemia. After cardiac decompensation, at least a low-dose diuretic therapy should be continued.

Angiotensin Receptor Neprilysin Inhibitor

If patients treated with a combination of ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists are still symptomatic, and if ACE inhibitors have been well tolerated, it is recommended to change from ACE inhibitors or ARBs to angiotensin receptor neprilysin inhibitor (ARNI)

treatment provided that kidney function permits. For LCZ696 (sacubitril + valsartan), a reduction of mortality, cardiovascular mortality, and CHF hospitalization has been shown in comparison to enalapril, and this benefit has also been found in patients with eGFR of 30 to 60 mL/min/1.73 m2 51 Therefore, ARNIs are effective in patients with heart failure and CKD stages 1 to 3; in patients with CKD stages 4 to 5, no data are available.

SGLT2 Inhibitors

Two large cardiovascular outcome trials conducted in patients with HFrEF with or without diabetes have shown that dapagliflozin or empagliflozin significantly reduce the combined endpoint of cardiovascular death and CHF hospitalization compared with placebo. In addition, these agents reduce kidney endpoints and worsening of nephropathy. Given that these studies included patients with eGFR as low as 30 mL/min/1.73 m2 (DAPA-HF)52 or 20 mL/min/1.73 m2 (EMPERORReduced),53 these agents seem to be effective in patients with CKD stages 3 to 4. Based on these data, one of the SGLT2-inhibitors, dapagliflozin, has recently been approved for use in patients with HFrEF and eGFR as low as 30 mL/min/1.73 m2 independent of the presence of diabetes.

Extracellular Volume Overload

Extracellular volume overload resulting from loss of sodium excretory capacity is the major cause of hypertension in dialysis patients.

Whether prevention of recurrent hypervolemia reduces cardiovascular morbidity and mortality remains unproven. If adjustments are made for comorbidity and advanced age, a strong, incremental risk for all-cause and cardiovascular mortality is associated with interdialytic weight gains. Recurrent hypervolemia may result in LVH and dilation, peripheral or pulmonary edema, jugular venous distension, or a third heart sound, or it may be largely asymptomatic. Tolerance of large ultrafiltration volumes intradialytic or increase in blood pressure may indicate that the dry weight target (see Chapter 99) has not been reached. Reaching the optimal dry weight does not necessarily lead to normotension; a lag phase of some weeks can precede improvement.

ARRHYTHMIAS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in advanced CKD, and its incidence is increasing in older patients initiating dialysis in the United States.54 Incident AF is an independent risk factor for development of ESKD in CKD.55 The historically reported prevalence among dialysis patients is 15% to 20%, but small series employing implantable loop recorders suggest that the true prevalence may be as high as 27% to 40%, if episodes of paroxysmal AF are included.56

No trials have examined the clinical benefits and risks of anticoagulation in CKD populations specifically. In observational studies, adjusted-dose warfarin was associated with a 76% reduction in the relative risk for ischemic stroke or systemic embolism among AF patients with CKD stage 3.57 Irrespective of CKD severity, in nondialysis acute MI patients with AF, warfarin treatment was associated with a lower 1-year risk for the composite outcome of death, MI, and ischemic stroke without a higher risk for bleeding. In contrast, the usefulness of warfarin for primary prevention of stroke in dialysis patients with AF is controversial; some observational studies suggest harm, and a consensus statement from KDIGO did not advise routine warfarin therapy for primary prevention of stroke in AF patients with CKD stage 5D (however, warfarin for secondary prevention of stroke was suggested based on expert opinion).58 59 Warfarin use in dialysis patients is also challenging given the difficulty of maintaining the optimal anticoagulation range and the potential for accelerated vascular calcification with vitamin K antagonists. Post hoc analyses from randomized controlled trials suggest beneficial effects of direct oral anticoagulants compared with warfarin in moderate CKD (Fig. 85.6); however, in dialysis patients, treatment with apixaban was not associated with a lower incidence of new stroke, transient ischemic attack, or systemic thromboembolism but was associated with a higher incidence of fatal or intracranial bleeding.60

No data support the sole use of aspirin for prevention of stroke in CKD patients with AF.

Sudden Cardiac Death

In the US Renal Data System database, 85% of all cardiac deaths and 34% of all-cause mortality in HD patients were attributable to arrhythmias; although overall cardiovascular and all-cause mortality have improved over time, deaths attributable to arrhythmic mechanisms have not, leading to a larger proportion of mortality attributable to arrhythmia (Fig. 85.7).61 The reported rate of cardiac arrest in HD centers is 3.8 to 7.1 events per 100,000 dialysis sessions. Strong predictors of sudden cardiac death are a history of coronary heart disease, peripheral arterial disease, diabetes, elevated inflammatory biomarkers, and reduced LVEF. Even a modest reduction in LVEF to 40% to 50% is prognostically important in both HD and peritoneal dialysis (PD) patients. Factors probably contributing to the special vulnerability of ESKD patients to sudden cardiac arrest include LVH, rapid electrolyte

Efficacy and Safety of NOACs vs Warfarin
Intervention

Hazard ratio (95% Cl)

Dabigatran 150 mg (n = 1232)
Stroke or
systemic embolism

Dabigatran 110 mg (n = 1196)
Rivaroxaban 15 mg (n = 1474)
Apixaban 5 mg (n = 1508)
Edoxaban 30 mg (n = 1302)

Dabigatran 150 mg (n = 1232)
Major bleeding

Dabigatran 110 mg (n = 1196)
Rivaroxaban 15 mg (n = 1474)
Apixaban 5 mg (n = 1508)
Edoxaban 30 mg (n = 1302)

0.5
1.0
2.0
Favors NOAC
Favors warfarin

Fig. 85.6 Efficacy and safety of novel oral anticoagulants (NOACs) versus warfarin in the subgroup of patients with moderate chronic kidney disease from randomized, clinical trials in atrial fibrillation. CI, confidence interval. (From Qamar A, Bhatt DL. Stroke prevention in atrial fibrillation in patients with chronic kidney disease. Circulation 2016;133[15]:1512–1515.)

0.2

Mechanisms of Death in Chronic Kidney Disease
Sudden
(noncardiac) deaths
Stroke
Ruptured aneurysm
Pulmonary embolism
Trauma

Sudden
cardiac deaths
Tachyarrhythmia
and
bradyarrhythmia

Sudden
deaths

Terminal
arrhythmia
Asystole

Noncardiac
deaths

Ventricular tachycardia

Cardiac
deaths

Ventricular fibrillation

Noncardiac,
nonsudden deaths
Dialysis withdrawal
Infection
Malignancy

Cardiac,
nonsudden deaths
MI
Heart failure

Nonsudden
deaths

Fig. 85.7 Mechanisms of death in chronic kidney disease patients. MI, Myocardial infarction. (From Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J. 2018;39:2314–2325.)

VALVULAR DISEASE

The progression of calcific aortic valve stenosis is approximately three times faster in dialysis patients than in the general population (Fig. 85.8).65 Annual echocardiography is recommended for asymptomatic dialysis patients with an aortic valve orifice area of less than 1.0

Prevalence of Valvular Calcification in the

General Population and CKD
100

80
Proportion of patients

shifts and hyperkalemia in HD, autonomic dysfunction and sympathetic overactivity, including sleep apnea, and abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis, decreased perfusion reserve, and diminished ischemia tolerance.62 Low-potassium dialysate (<2 mmol/L) doubles the risk for cardiac arrest.63 The rate of cardiac arrest is 50% higher for HD than for PD patients at 3 months after dialysis initiation but is higher for PD patients at 3 years. The highest rate of sudden cardiac death occurs in the first 2 months after HD initiation.

On-site defibrillation capability in HD centers (preferably with automatic external defibrillators) was recommended in a US practice guideline in 2005. The role that implantable cardioverterdefibrillators (ICDs) may play in reducing mortality in CKD patients is controversial, particularly regarding primary prevention. CKD may attenuate the survival advantage of ICDs, but older age and medical comorbidity should not routinely exclude patients from receiving ICDs. Despite the small number of dialysis patients in clinical studies, guidelines also recommend primary prophylactic ICD implantation if the ejection fraction is 35% or less. A small randomized controlled trial for prevention of sudden cardiac death in dialysis patients with LVEF greater than 35%, the ICD-2 trial, was terminated for futility.64

60

54%
45%

40
25%

23%

20
11%

6%

2%
0

GP

DM

CKD

HD

GP

11%

DM

CKD

HD

Aortic valve calcification

Mitral valve calcification

Fig. 85.8 Prevalence of valvular calcification in the general population and in patients with kidney disease. CKD, Chronic kidney disease; DM, diabetes mellitus; GP, general population; HD, hemodialysis. (From Marwick TH, Amann K, Bangalore S, et al. Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes [KDIGO] Controversies Conference. Kidney Int. 2019;96:836–849.)

cm2 who are suitable candidates for valve replacement. A meta-analysis of dialysis patients undergoing valve replacement surgery found no difference in survival for patients receiving tissue versus mechanical valves and fewer valve-related complications with tissue valves. The overall mortality is high, with in-hospital mortality about 20% (four times higher than in non-CKD patients) and a 2-year survival of 40%.66 In kidney transplant recipients, in-hospital mortality was 11% for tissue and 15% for mechanical valve patients, and 2-year mortality rates were 62%

and 60%, respectively. In the entire cohort of kidney transplant patients, the rate of endocarditis after valve surgery was 5% per year.23 Transcatheter aortic valve replacement may be appropriate in dialysis patients with symptomatic aortic stenosis who are not good candidates for surgery. Still, the prognosis of dialysis patients following transcatheter aortic valve replacement is worse compared with nondialysis patients.67

SELF-ASSESSMENT QUESTIONS

1. SGLT2 inhibitors have not been shown to reduce the risk of:
A. hospitalization for heart failure.
B. cardiovascular death.
C. progression of kidney failure.
D. myocardial infarction.
E. progression to ESKD.

2. Strong predictors of sudden cardiac death in hemodialysis patients do not include:
A. a history of CHD.
B. a history of peripheral arterial disease.
C. diabetes.
D. reduced ejection fraction.
E. a history of atrial fibrillation.

3. CKD patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m2 should be treated to achieve the guideline goal for secondary prevention for low-density lipoprotein cholesterol of:
A. less than 100 mg/dL.
B. less than 70 mg/dL.
C. less than 55 mg/dL.
D. less than 40 mg/dL.
E. less than 25 mg/dL.

4. Coronary artery disease in patients with CKD differs from nonCKD controls by exhibiting:
A. more and larger plaques.
B. fewer signs of inflammation.
C. less calcification.
D. fewer macrophages.
E. fewer T-lymphocytes.

REFERENCES

1. Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364:818–828.
2. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98:S1–S115.
3. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43:487–493.
4. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41:255–323.
5. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219–2229.
6. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–2306.
7. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436–1446.
8. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebocontrolled trial. Lancet. 2011;377:2181–2192.
9. Zickler D, Schindler R, Willy K, et al. Medium Cut-Off (MCO) membranes reduce inflammation in chronic dialysis patients-A randomized controlled clinical trial. PLoS One. 2017;12:e0169024.
10. Ridker PM, MacFadyen JG, Glynn RJ, et al. Inhibition of interleukin-1beta by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. J Am Coll Cardiol. 2018;71:2405–2414.
11. Dai L, Meijers BK, Bammens B, et al. Sevelamer Use in End-Stage Kidney Disease (ESKD) patients associates with poor vitamin K status and high levels of gut-derived uremic toxins: a drug-bug interaction? Toxins (Basel). 2020;12.
12. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012;307:674–684.
13. Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367:2482–2494.
14. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant. 2011;26:1327–1339.
15. Moe SM, Chertow GM, Parfrey PS, et al. Cinacalcet, Fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the evaluation of cinacalcet HCl therapy to lower cardiovascular events (EVOLVE) trial. Circulation. 2015;132:27–39.
16. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care. 2003;26:688–696.
17. Yoshida H, Yokoyama K, Yaginuma T, et al. Difference in coronary artery intima and media calcification in autopsied patients with chronic kidney disease. Clin Nephrol. 2011;75:1–7.
18. Nakano T, Ninomiya T, Sumiyoshi S, et al. Chronic kidney disease is associated with neovascularization and intraplaque hemorrhage in coronary atherosclerosis in elders: results from the Hisayama Study. Kidney Int. 2013;84:373–380.
19. Schmidt A, Stefenelli T, Schuster E, Mayer G. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. Am J Kidney Dis. 2001;37:56–63.
20. Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC State-of-the-Art review. J Am Coll Cardiol. 2019;74:1823–1838.

21. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American heart association and the

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American College of Cardiology Foundation: endorsed by the American Society of transplant Surgeons, American Society of transplantation, and National kidney Foundation. Circulation. 2012;126:617–663.
K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45:S1–S153.
Sharma A, Gilbertson DT, Herzog CA. Survival of kidney transplantation patients in the United States after cardiac valve replacement. Circulation. 2010;121:2733–2739.
Bangalore S. Stress testing in patients with chronic kidney disease: the need for ancillary markers for effective risk stratification and prognosis. J Nucl Cardiol. 2016;23:570–574.
Dilsizian V, Gewirtz H, Marwick TH, et al. Cardiac imaging for coronary heart disease risk stratification in chronic kidney disease. JACC Cardiovasc Imaging. 2021;14:669–682.
Rabbat CG, Treleaven DJ, Russell JD, Ludwin D, Cook DJ. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a metaanalysis. J Am Soc Nephrol. 2003;14:431–439.
Wang LW, Fahim MA, Hayen A, et al. Cardiac testing for coronary artery disease in potential kidney transplant recipients. Cochrane Database Syst Rev. 2011;2011:Cd008691.
Kumar N, Baker CS, Chan K, et al. Cardiac survival after pre-emptive coronary angiography in transplant patients and those awaiting

transplantation. Clin J Am Soc Nephrol. 2011;6:1912–1919.

Bangalore S, Maron DJ, O’Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. N Engl J Med. 2020;382:1608–1618.

Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation. 2002;106:2941–2945.

Breidthardt T, Burton JO, Odudu A, Eldehni MT, Jefferies HJ, McIntyre CW. Troponin T for the detection of dialysis-induced myocardial stunning in hemodialysis patients. Clin J Am Soc Nephrol. 2012;7:1285–1292.

Sandoval Y, Herzog CA, Love SA, et al. Prognostic value of serial changes in high-sensitivity cardiac troponin I and T over 3 Months using reference change values in hemodialysis patients. Clin Chem. 2016;62:631–638.

James MT, Ghali WA, Knudtson ML, et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation. 2011;123:409–416.

Winther S, Svensson M, Jørgensen HS, et al. Diagnostic performance of coronary CT angiography and myocardial perfusion imaging in kidney transplantation candidates. JACC Cardiovasc Imaging. 2015;8: 553–562.

Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2002;39:1113–1119.

Cooper WA, O’Brien SM, Thourani VH, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. Circulation. 2006;113:1063–1070.

Charytan DM, Li S, Liu J, Herzog CA. Risks of death and end-stage renal disease after surgical compared with percutaneous coronary revascularization in elderly patients with chronic kidney disease. Circulation. 2012;126:S164–S169.

Shroff GR, Solid CA, Herzog CA. Long-term survival and repeat coronary revascularization in dialysis patients after surgical and percutaneous coronary revascularization with drug-eluting and bare metal stents in the United States. Circulation. 2013;127:1861–1869.

Chang TI, Shilane D, Kazi DS, Montez-Rath ME, Hlatky MA, Winkelmayer WC. Multivessel coronary artery bypass grafting versus percutaneous coronary intervention in ESRD. J Am Soc Nephrol. 2012;23:2042–2049.

Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)]. G Ital Cardiol (Rome). 2019;20:1s–61s.

References

41. Spertus JA, Jones PG, Maron DJ, et al. Health status after invasive or conservative care in coronary and advanced kidney disease. N Engl J Med. 2020;382:1619–1628.
42. Shroff GR, Li S, Herzog CA. Trends in mortality following acute myocardial infarction among dialysis patients in the United States over 15 years. J Am Heart Assoc. 2015;4:e002460.
43. Herzog CA, Littrell K, Arko C, Frederick PD, Blaney M. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation. 2007;116:1465–1472.
44. Shroff GR, Frederick PD, Herzog CA. Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. Am Heart J. 2012;163:399–406.
45. Szummer K, Lundman P, Jacobson SH, et al. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. J Intern Med. 2010;268:40–49.
46. House AA. Management of heart failure in advancing CKD: Core Curriculum 2018. Am J Kidney Dis. 2018;72:284–295.
47. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18:891–975.
48. House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95:1304–1317.
49. Badve SV, Roberts MA, Hawley CM, et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:1152–1161.
50. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11–21.
51. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
52. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995–2008.
53. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020.
54. Goldstein BA, Arce CM, Hlatky MA, Turakhia M, Setoguchi S, Winkelmayer WC. Trends in the incidence of atrial fibrillation in

55.

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57.

58.

59.

60.

61.

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66.

67.

older patients initiating dialysis in the United States. Circulation. 2012;126:2293–2301.

Bansal N, Fan D, Hsu CY, Ordonez JD, Go AS. Incident atrial fibrillation and risk of death in adults with chronic kidney disease. J Am Heart Assoc. 2014;3:e001303.

Königsbrügge O, Posch F, Antlanger M, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: crosssectional results of the Vienna InVestigation of AtriaL Fibrillation and Thromboembolism in Patients on HemoDIalysis (VIVALDI). PLoS One. 2017;12:e0169400.

Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2599–2604.

Hart RG, Eikelboom JW, Ingram AJ, Herzog CA. Anticoagulants in atrial fibrillation patients with chronic kidney disease. Nat Rev Nephrol. 2012;8:569–578.

Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80:572–586.

Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clin J Am Soc Nephrol. 2020;15:1146–1154.

Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J. 2018;39:2314–2325.

Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med. 2011;365:1099–1107.

Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int. 2011;79:218–227.

Jukema JW, Timal RJ, Rotmans JI, et al. Prophylactic Use of implantable cardioverter-defibrillators in the prevention of sudden cardiac death in dialysis patients. Circulation. 2019;139:2628–2638.

Marwick TH, Amann K, Bangalore S, et al. Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;96:836–849.

Chan V, Chen L, Mesana L, Mesana TG, Ruel M. Heart valve prosthesis selection in patients with end-stage renal disease requiring dialysis: a systematic review and meta-analysis. Heart. 2011;97:2033–2037.

Allende R, Webb JG, Munoz-Garcia AJ, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J. 2014;35:2685–2696.

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Anemia in Chronic Kidney Disease

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Anemia is an almost universal complication of chronic kidney disease (CKD). It contributes considerably to reduced quality of life (QOL) for patients with CKD and has been associated with a number of adverse clinical outcomes. Before the availability of recombinant human erythropoietin (EPO; epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, viral hepatitis, and human leukocyte antigen (HLA) sensitization, which reduced the chances of successful transplantation. The advent of erythropoiesis-stimulating agents (ESAs) in the late 1980s changed this situation completely. The ability to correct anemia has not only reduced fatigue and increased physical capacity but also improved a broad spectrum of physiologic functions. Thus, there is a strong rationale for managing anemia in CKD patients, and yet the optimal treatment strategies are still incompletely defined. Apart from therapy with ESAs, iron replacement is essential for anemia management, and thresholds for iron parameters in patients treated with maintenance dialysis must be more liberal than in those with normal kidney function to ensure optimal rates of red blood cell (RBC) production. The costs of anemia management have fallen but are still significant, and because full anemia correction may cause harm, careful consideration of the risks and benefits is mandatory.

PATHOGENESIS

The anemia associated with CKD is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia.

Both RBC life span and the rate of RBC production are reduced, but the latter is more important. The normal bone marrow has sufficient capacity to compensate for the reduction in erythrocyte life observed in association with CKD, but this capacity is impaired in CKD. Serum EPO levels remain within the normal range and fail to show the inverse exponential relationship with blood oxygen content characteristic of other types of anemia. EPO is normally produced by interstitial fibroblasts in the kidney cortex, in close proximity to tubular epithelial cells and peritubular capillaries.1 2 In addition, hepatocytes and perisinusoidal Ito cells in the liver can produce EPO (Fig. 86.1). Hepatic EPO production dominates during fetal and early postnatal life but does not compensate for the loss of kidney production in adult organisms. Subtle changes in blood oxygen content induced by anemia, reduced environmental oxygen concentrations, and high altitude stimulate the secretion of EPO through a widespread system of oxygen-dependent gene expression.2–4 Central to this process is a family of hypoxiainducible transcription factors (HIFs), composed of different oxygenregulated α subunits and a constitutive β subunit. The production of HIF-α is largely independent of oxygen, but its degradation is related to cellular oxygen concentrations. Hydroxylation of specific prolyl and asparagyl residues of HIF-α, for which molecular oxygen is required as a substrate, determines proteasomal destruction of HIF and inhibits its transcriptional activity. Apart from EPO, several hundred HIF target genes have been identified. HIF-2, rather than HIF-1, is the transcription factor primarily responsible for the regulation of EPO production.5 6 The discovery of the HIF pathway and the underlying mechanisms of oxygen sensing was awarded the Nobel Prize in Physiology or Medicine in 2019.7

The role of renal EPO production in the pathogenesis of the anemia associated with CKD is supported by the particularly severe anemia in anephric individuals. However, the mechanisms impairing EPO production in diseased kidneys remain poorly understood. The production capacity for EPO remains significant, even in kidney failure. Thus, patients with anemia and CKD can respond with a significant increase in EPO production to an additional hypoxic stimulus.1 The main problem therefore appears to be a failure of EPO production to increase in response to chronically reduced hemoglobin (Hb) concentrations. In line with this view, endogenous EPO production can be induced in CKD patients by pharmacologic inhibition of HIF degradation (see later).

EPO is a glycoprotein hormone consisting of a 165–amino acid protein backbone and four complex, heavily sialylated carbohydrate chains.1 The latter are essential for the biologic activity of EPO in vivo because partially or completely deglycosylated EPO is rapidly cleared from the circulation. This is why recombinant EPO must be manufactured in mammalian cells; bacteria lack the capacity to glycosylate recombinant proteins.

EPO stimulates RBC production by binding to homodimeric EPO receptors, which are primarily located on early erythroid progenitor cells, the burst-forming units erythroid (BFU-e) and the colonyforming units erythroid (CFU-e). Binding of EPO to its receptors salvages these progenitor cells and the subsequent earliest erythroblast generation from apoptosis, thereby permitting cell division and maturation into RBCs.8 Inhibition of RBC production by yet unknown uremic inhibitors of erythropoiesis may contribute to the pathogenesis of anemia associated with CKD, and dialysis per se can improve the anemia and the efficacy of ESAs. Moreover, the interindividual dose requirements for ESAs vary considerably among CKD patients, and the average weekly dose is much higher than estimated production rates of endogenous EPO in healthy individuals. An alternative view to the accumulation of inhibitors of erythropoiesis in CKD is that in many patients there is overlap between renal anemia and the anemia of chronic disease, which is characterized by inhibition of EPO production and EPO efficacy, as well as by reduced iron availability, mediated through inflammatory cytokines.9 The hepatic release of hepcidin, the key regulator of iron metabolism, is upregulated in inflammatory states. Hepcidin simultaneously blocks iron absorption from the gut and promotes iron sequestration in macrophages.10

Relationship Between
Hemoglobin and eGFR

Feedback Control of Erythropoiesis

Males

Arterial oxygen
saturation

17
Hemoglobin (g/dL)

Hemoglobin
concentration

Blood oxygen
content

15
13
11
95th percentile
Median
5th percentile

9
7

Tissue perfusion

0
Erythropoiesis

Tissue
oxygenation

A

30

60

90

Hemoglobin (g/dL)

EPO/other HIF target genes
→ increases in oxygen
supply or hypoxia tolerance

Fig. 86.1 Feedback control of erythropoiesis. EPO, Erythropoietin.

Females

EPIDEMIOLOGY AND NATURAL HISTORY

The incidence and severity of anemia progressively increases at lower glomerular filtration rate (GFR). The reported prevalence of anemia by CKD stage varies significantly and depends to a large extent on the definition of anemia and whether study participants are selected from the general population, are at high risk for CKD, have diabetes, or are already under the care of a nephrologist. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the distribution of Hb levels starts to fall at estimated GFR (eGFR) less than 75 mL/min/1.73 m2 in males and less than 45 mL/min/1.73 m2 in females (Fig. 86.2).11 The prevalence of Hb values less than 13 g/dL increases at eGFR less than 60 mL/min/1.73 m2 in males and less than 45 mL/min/1.73 m2 in females in the general population. Among patients under regular care for CKD, the prevalence of anemia was found to be much greater, with mean Hb values of 12.8 (CKD stages 1 and 2), 12.4 (CKD stage 3), 12.0 (CKD stage 4), and 10.9 g/dL (CKD stage 5).12 Although anemia develops largely independently of the cause of kidney disease, there are two important exceptions. Patients with diabetes develop anemia more frequently, at earlier stages of CKD, and more severely at a given level of kidney impairment.13 14 Conversely, in patients with polycystic kidney disease, Hb is on average higher than in other patients with similar severity of CKD, and polycythemia may occasionally develop.

With the advent of ESAs, Hb values in patients with CKD have changed. In particular, in patients on dialysis, average Hb values have steadily increased for many years and then declined again in view of later evidence recommending lower target levels.13 The average Hb value still varies considerably among countries, reflecting variability in practice patterns (Table 86.1).14 Moreover, Hb values vary considerably among patients in the same treatment setting and within patients

15
13
11
95th percentile
Median
5th percentile

9
7
0

B

150

Estimated GFR (mL/min per 1.73 m)
2

17
Hypoxia-inducible
factors (HIF-1, HIF-2)

120

30

60

90

120

150

Estimated GFR (mL/min per 1.73 m2)

Fig. 86.2 Relationship Between Hemoglobin Concentration and Estimated Glomerular Filtration Rate (eGFR). Data are from a crosssectional survey of individuals randomly selected from the general U.S.

population (Third National Health and Nutrition Examination Survey [NHANES III]). Results and 95% confidence interval are shown for males (A) and females (B) at each estimated GFR interval. (From McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004;20:501–510.)

over time, mainly reflecting persistent and time-dependent changes in responsiveness.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

It is best to diagnose anemia and assess its severity by measuring the Hb concentration rather than the hematocrit (Hct). Hb is a stable analyte that is measured directly in a standardized fashion, whereas the Hct is relatively unstable, indirectly derived by automatic analyzers, and lacks standardization. Within-run and between-run coefficients of variation in automated analyzer measurements of Hb are half and onethird those for Hct, respectively.13

There is considerable variability in the Hb threshold used to define anemia. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, anemia should be diagnosed at Hb concentrations of less than 13.0 g/dL in males and less than 12.0 g/dL in females,15 consistent with the World Health Organization (WHO) definition. In children, age-dependent differences in the normal values must be considered. Normal Hb values are increased in high-altitude residents. It is important to note that thresholds for the diagnosis of anemia and evaluation of the causes should not be interpreted as being thresholds for the treatment of the anemia.15

TABLE 86.1

Hemoglobin Levels in Patients on Dialysis

	AMONG PATIENTS ON DIALYSIS FOR >180 DAYS			AMONG PATIENTS AT START OF DIALYSIS		
Country	N	Mean Hb (g/dL)	Hb < 11 g/dL (% of patients)	N	Mean Hb (g/dL)	Hb < 11 g/dL (% of patients)
Sweden	456	12.0				
United States	1690	11.7				
Spain	513	11.7				
Belgium	442	11.6				
Canada	479	11.6				
Australia and New Zealand	423	11.5				
Germany	459	11.4				
Italy	447	11.3				
United Kingdom	436	11.2				
France	341	11.1				
Japan	1210					

10.1

23
27
31
29
29
36
35
38
40
45
77

168
458
170
213
150
108
142
167
93
86
131

10.7
10.4
10.6
10.3
10.1
10.1
10.5
10.2
10.2
10.1
8.3

55
65
61
66
70
70
61
68
67
65
95

Mean hemoglobin (Hb) levels and percentage of patients with Hb levels less than 11 g/dL who have been on dialysis therapy for more than 180 days and at the time of starting dialysis, by country. Data are from the Dialysis Outcomes and Practice Patterns Study, Phase II (DOPPS 2) and are derived from 308 randomly selected, representative dialysis facilities. Note that there are marked differences among countries, but at least one-fourth and up to three-fourths of dialysis patients, and, in most countries, more than two-thirds of patients starting chronic dialysis have Hb values less than the recommended lower target of 11 g/dL.
Modified from Pisoni RL, Bragg-Gresham JL, Young EW, et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study [DOPPS]. Am J Kidney Dis. 2004;44:94–111.

In addition to the Hb value, the evaluation of anemia in CKD patients should include a complete blood count (CBC) with RBC indices (mean corpuscular Hb concentration [MCHC], mean corpuscular volume [MCV]), white blood cell (WBC) count (including differential), and platelet count. Although the anemia associated with CKD is typically normochromic and normocytic, deficiency of vitamin B12 or folate may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (such as thalassemia) may produce microcytosis. Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins, nutritional deficit, or myelodysplasia. Hypochromia probably reflects iron-deficient erythropoiesis. The absolute reticulocyte count is a useful marker of erythropoietic activity (normal 40,000–50,000 cells/µL of blood).

Iron status tests should be performed to assess the level of iron in tissue stores or the adequacy of iron supply for erythropoiesis. Although serum ferritin is the only available marker of storage iron, several tests reflect the adequacy of iron for erythropoiesis, including transferrin saturation (TSAT), the percentage of hypochromic red blood cells (PHRC), the reticulocyte Hb content (CHr), the MCV, and the MCHC. Storage time of the blood sample may elevate PHRC, and MCV and MCHC are less than the normal range only after longstanding iron deficiency; in clinical practice, TSAT remains the most frequently used parameter.

Anemia in CKD patients may signify nutritional deficits, systemic illness, or other conditions that warrant attention. Moreover, even at modest degrees, anemia reflects an independent risk factor for hospitalizations, cardiovascular (CV) disease (CVD), and mortality.[13]

The diagnosis of anemia caused by CKD requires careful judgment of the severity of anemia in relation to the level of GFR and exclusion of other or additional causes. Because there is significant variability in the degree of anemia in relation to the impairment in kidney function, no simple diagnostic criteria can be applied. Causes of anemia other than EPO deficiency should be considered when (1) the severity of anemia is disproportionate to the reduction in GFR, (2) there is evidence of iron deficiency, or (3) there is evidence of leukopenia or thrombocytopenia. Concomitant conditions such as sickle cell disease may exacerbate the anemia, as can drug therapy. For example, inhibitors of the renin-angiotensin system may reduce Hb levels through (1) the direct effects of angiotensin II (Ang II) on erythroid progenitor cells,[16] (2) accumulation of N-acetyl-seryl-lysyl-proline (Ac-SDKP), an endogenous inhibitor of erythropoiesis in patients treated with angiotensin-converting enzyme (ACE) inhibitors,[17] and (3) reduction of endogenous EPO production, possibly because of the hemodynamic effects of Ang II inhibition. Myelosuppressive effects of immunosuppressants may further contribute to anemia.[18] The measurement of serum EPO concentrations is usually not helpful in the diagnosis of anemia associated with CKD because there is relative rather than absolute deficiency, with a wide range of EPO concentrations for a given Hb concentration.

CLINICAL MANIFESTATIONS

In the early clinical trials of recombinant EPO performed in the late 1980s, the mean baseline Hb concentration was about 6 or 7 g/dL, and this progressively increased to about 11 or 12 g/dL under treatment. Patients subjectively felt much better, with reduced fatigue, increased energy levels, and enhanced physical capacity, and there were also objective improvements in cardiorespiratory function.[19] Thus, many of the symptoms previously attributed to the “uremic syndrome” may have been caused by severe anemia associated with CKD (Boxes 86.1 and 86.2). Although the avoidance of blood transfusions and improvement in QOL are obvious early changes, there are also possible effects on the CV system (see Box 86.1). The physiologic consequences of long-standing anemia are an increase in cardiac output and a reduction in peripheral vascular resistance. Anemia is associated with the development of left ventricular (LV) hypertrophy in CKD patients and is thought to exacerbate LV dilation. Sustained correction of severe anemia in CKD patients tends to reverse most of these CV abnormalities, with the notable exception of LV dilation (although anemia

Cardiovascular Effects Resulting From Anemia Correction

BOX 86.1

Reduction in high cardiac output
Reduced stroke volume
Reduced heart rate
Increase in peripheral vascular resistance
Reduction in anginal episodes
Reduction in myocardial ischemia
Regression of left ventricular hypertrophy
Stabilization of left ventricular dilation
Increase in whole blood viscosity

BOX 86.2

Correction

Other Effects of Anemia

Beneficial
Reduced blood transfusions
Increased quality of life
Increased exercise capacity
Improved cognitive function
Improved sleep patterns
Improved immune function
Improved muscle function
Improved depression
Improved nutrition
Improved platelet function
Adverse
Hypertension
Vascular access thrombosis
Increased risk for stroke

correction may prevent further dilation in some patients[20]). Other effects of anemia correction reported in clinical trials include improvements in QOL, cognitive function, sleep patterns, nutrition, sexual function, menstrual regularity, immune responsiveness, and platelet function. The majority of these trials were not placebo controlled, so the spectrum and extent of possible benefits remain uncertain.

There has been considerable debate about the optimal target range of Hb in CKD patients. A presumed improvement in QOL and expectations of positive effects on CV function and kidney disease progression with increasing Hb concentrations led to a suggested level of greater than 10 to 11 g/dL in all CKD patients.[13,14] However, studies targeting Hb concentrations in the near-normal range found no survival benefit and showed various risks, including increased rates of thromboembolic events, strokes, and possibly death.[21–24] Thus, there is a possible tradeoff among improved QOL, reduced transfusion requirements, and risk for harm (see discussion later), and a target Hb level of greater than 13 g/dL should be avoided.[13,15]

TREATMENT

Erythropoiesis-Stimulating Agents and HypoxiaInducible Factor Stabilizers

Epoetin Therapy

Manufacture of recombinant human EPO (epoetin) is achieved by gene transfer into a suitable mammalian cell line such as Chinese hamster ovary

(CHO) cells. The early clinical trials were conducted with both epoetin

alfa and epoetin beta, both produced in CHO cells. Like the endogenous hormone, both epoetins consist of a 165–amino acid backbone with one O-linked and three N-linked glycosylation chains. Invariably, however, there are some differences in the glycosylation pattern among different recombinant preparations and the endogenous hormone. “Biosimilar” or “copy” epoetins have been approved in many countries of the world after demonstration of their efficacy and safety in clinical trials.25
Before 1998, epoetin alfa in Europe was formulated with human serum albumin, but the latter was replaced with polysorbate 80.
Epoetin beta is formulated with polysorbate 20, along with urea, calcium chloride, and five amino acids as excipients. The importance of the formulation of epoetins was highlighted in 2002 when an upsurge in cases of antibody-mediated pure red cell aplasia (PRCA) was associated with the subcutaneous use of epoetin alfa after its change of formulation. Patients affected by this complication develop neutralizing antibodies against both recombinant and endogenous hormone, which result in severe anemia and transfusion dependence.26 27 The development of neutralizing anti-EPO antibodies was also observed during a clinical trial with an epoetin alfa biosimilar,28 and a low rate of PRCA also occurs with epoetin beta and darbepoetin alfa. Peginesatide was used to treat patients with EPO-antibody induced PRCA (see below), but since it is no longer available RBC transfusions and immunosuppressive therapy remain the only options.
The epoetins are administered either intravenously or subcutaneously.
The earliest clinical trials of the epoetins used intravenous (IV) injections two or three times per week. This was partly because of the short half-life of IV epoetin (6–8 hours)29 and partly because of the convenience for the patient on dialysis. With use of this regimen, more than 90% of patients show a significant increase in Hb concentration. Good iron management is pivotal for the success of epoetin therapy (see later discussion).
Although the bioavailability of subcutaneous epoetin is 20% to 30%, the prolonged half-life after subcutaneous (SQ) administration compared with IV administration allows less frequent injections. Furthermore, the dose required to achieve the same Hb response is about 30% lower with SQ than with IV administration.29 There appears to be little difference in efficacy among the thigh, arm, or abdomen as injection sites.

Darbepoetin Alfa

Darbepoetin alfa is a second-generation ESA that is a supersialylated analog of epoetin, possessing two extra N-linked glycosylation chains. This property confers a lower clearance rate in vivo, and the elimination half-life of this compound in humans after a single IV administration is 25.3 hours versus 8.5 hours for epoetin alfa. Thus, this agent can generally be given less frequently than the standard epoetins, with administration intervals of once weekly and once every 2 weeks with similar dose requirements.30
In contrast to the epoetins, dosage requirements for darbepoetin alfa in CKD patients are the same for IV and SQ administration. The conversion factor for switching patients from epoetin alfa or beta to darbepoetin alfa is usually quoted as 200to 1, but this may vary considerably depending on the population, the dose, and the route of administration.

Methoxy Polyethylene Glycol–Epoetin Beta

Alternative bioengineering techniques to prolong the half-life of EPO further resulted in the development of methoxy polyethylene glycol–epoetin beta (CERA), a pegylated derivative of epoetin beta with an elimination half-life of around 130 hours when administered either via IV or SQ. Many patients can be treated with once-monthly administration of CERA, which has greater efficacy than once-monthly dosing of darbepoetin alfa when administered via IV to hemodialysis (HD) patients.31 Once-monthly CERA was also noninferior to shorter-acting ESAs with respect to rates of major adverse CV events or all-cause mortality.32

Adverse Effects of the Erythropoiesis-Stimulating Agents

Adverse effects of ESAs include a moderate increase in blood pressure and an increased rate of thromboembolic events, including vascular access thrombosis. Although these effects probably depend to a large degree on the increase in Hb concentration, ESAs may enhance thrombogenicity and tumor growth in patients with malignancy or exacerbate vascular events in CKD independently of Hb concentration. Thus, the lowest possible doses of ESA should be used to avoid the presumed pleiotropic effects of this class of drugs. Similarly, because no "safe" upper dose level has been determined, it is advisable to avoid repeated dose escalation.[15] In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), patients with a history of malignancy had an increased rate of cancer-related deaths when treated with darbepoetin.[24] Although no study has investigated anemia management in patients with CKD and active cancer, ESAs should be used only with great caution in such patients, in particular when cure from cancer is the anticipated outcome.[15] Similarly, in patients with a history of stroke or recent venous thromboembolic event, the benefit-to-risk ratio of ESA therapy should be carefully considered (see later discussion).

Peginesatide

Peginesatide (previously called Hematide) was an EPO-mimetic peptide that shared the same functional and biologic properties as epoetin and was shown to be an effective treatment for anti-EPO antibody–mediated pure RBC aplasia because of a lack of cross-reactivity with anti-EPO antibodies.[33] Approximately a year after its introduction, peginesatide was withdrawn from the market because of severe hypersensitivity reactions, including fatal anaphylactic events.

Management of Anemia in CKD

Anemia of CKD

Exclude causes other than EPO deficiency
(e.g., iron, B12, folate deficiency)

If ferritin <100 μg/L, consider trial
of IV iron alone, 200–500 mg

If ferritin .100 μg/L or no response
to IV iron, start EPO, 4000–6000 IU/wk
or darbepoetin alfa 20–30 mg/wk

Adjust ESA dose by 25%–50% monthly
until Hb in target range of 10–12 g/dL

Hypoxia-Inducible Transcription Factor Stabilizers

The HIF stabilizers are competitive inhibitors of HIF prolyl hydroxylases[2,3,34] and asparagyl hydroxylase enzymes involved in the metabolism of HIF and its transcriptional activity. The HIF stabilizers, also referred to as prolyl-hydroxylase domain protein inhibitors (PHD inhibitors) cause an increase in endogenous EPO production from both the liver and the diseased, nonfunctioning kidneys.[34,35] Such compounds are orally active, and several of these drugs (e.g., roxadustat, daprodustat, vadadustat, and molidustat) are currently undergoing clinical development.[34,36] The results of phase II trials have shown efficacy in terms of increasing or maintaining the Hb level in both dialysis-dependent and non–dialysis-dependent CKD patients and revealed no evidence of acute adverse effects.[36] Levels of endogenous EPO induced by PHD inhibitors are lower than those observed under IV treatment with ESAs, potentially avoiding dose-dependent toxicity of ESAs. On the other hand, PHD inhibitors are likely to have a range of consequences additional to increasing levels of EPO through activation of other HIF-target genes or interference with other cellular pathways.2 3 34 Such pleiotropic effects could be beneficial, for example, by improving iron availability or reducing lipid levels.36 However, given the widespread biologic role of HIF, including its effects on neoangiogenesis and vascular function, the long-term benefit-to-risk relationship is difficult to predict and can be assessed only through rigorous long-term observation. Phase III trials comparing vadadustat with darbepoetin alfa showed noninferiority with respect to CV safety in dialysis-dependent CKD patients37 but inferiority in non–dialysis-dependent CKD patients.38 Several trials of a global phase III program comparing roxadustat to epoetin alfa or placebo in dialysis-dependent and non–dialysis-dependent patients have also been published.39–43 Roxadustat is licensed for use in China, Japan, Chile, and South Korea, but its risk-benefit profile is still debated, and a Food and Drug Administration (FDA) Advisory Committee voted against approval in the United States in July 2021.44 Daprodustat has shown noninferiority to comparator ESAs in both dialysis and nondialysis

Maintain iron status according to levels
in Table 86.3 giving IV iron as required

Fig. 86.3 Management of anemia in patients with chronic kidney disease (CKD). EPO, Erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous.

patients for both Hb and major adverse CV events (MACE) and a significant improvement in the physical component of a QOL measurement in nondialysis patients compared with placebo.45 46 However, an FDA Advisory Committee recommended approval of daprodustat only in dialysis patients.47

Initiation of and Maintenance Therapy With Erythropoiesis-Stimulating Agents

Before ESA therapy is considered in CKD patients, it is essential to exclude and to correct causes of anemia other than EPO deficiency, such as iron and vitamin deficiencies (Fig. 86.3). If the serum ferritin concentration is less than 100 μg/L, the first therapeutic approach in anemic patients should be iron supplementation. Iron is best given by IV administration, although oral iron can be considered in patients not yet on dialysis.48 Some patients may respond to IV iron alone (see later discussion). If the ferritin level is greater than 100 μg/L (in the absence of systemic inflammation) or there is a suboptimal response to iron, ESA therapy is an option. However, the Hb level at which ESAs should be initiated remains controversial, mainly because the topic has not been rigorously studied. In TREAT, the largest ESA trial so far, darbepoetin therapy (with a target Hb level of 13 g/dL) was compared with placebo, with a rescue protocol for Hb less than 9 g/dL.24 In the darbepoetin arm, the number of patients transfused was lower and there was an increase in QOL, but the stroke rate was twice as high, so that the benefit-to-risk relationship was clearly negative. Although these data argue strongly against the initiation of ESA therapy in patients with mild anemia, there is only one, much smaller randomized controlled trial (RCT) in HD patients that tested two different target ranges of 9.5 to 11.0 g/dL and 11.5 to 13.0 g/dL against placebo in patients with severe anemia.49 Patients in both epoetin treatment arms experienced improved QOL and exercise capacity, but there was no difference between the arms. Based on these findings, the KDIGO guidelines recommend use of ESAs to prevent the Hb level from falling below 9 g/dL.15 However, individualization is possible, acknowledging the fact that some patients have improved symptoms at higher Hb levels and are prepared to take increased risks. A commonly used target Hb range is between 10 and 12 g/dL. The Hb level should not be intentionally increased to 13 g/dL or more.

The usual IV or SQ starting doses are: for epoetin, about 25 to 50 international units (IU)/kg (e.g., 2000 IU two or three times weekly); for darbepoetin alfa, 20 to 30 µg once weekly; and for CERA, 30 to 60 µg once every 2 weeks. Within 3 to 4 days after treatment initiation, the reticulocyte count typically increases, and within 1 to 2 weeks, there is a significant rise in the Hb concentration, usually of the order of 0.25 to 0.5 g/dL/wk. Thus, over the course of 1 month, a significant increase of 1 to 2 g/dL in Hb concentration is usually achieved. If a patient fails to respond satisfactorily to ESAs, the dose is increased in stepwise upward titrations of 25% to 50%, and if there is still an inadequate response, causes of resistance to ESA therapy should be investigated (see later discussion).

Hyporesponsiveness to Erythropoiesis-Stimulating Agents

According to KDIGO guidelines, hyporesponsiveness to ESA therapy is identified when the Hb concentration does not increase from baseline after the first month of ESA treatment on appropriate weightbased dosages or if, after treatment with stable doses, patients require two increases in ESA doses up to 50% beyond the dose at which their condition had previously been stable.15 Patients who are hyporesponsive have a worse prognosis than those who do respond.50 The causes of resistance to ESA therapy are listed in Box 86.3, and it is important to correct them when possible. The major causes include iron deficiency (see later discussion), infection or inflammation, and underdialysis.13 15 If the patient is self-administering (e.g., for PD patients), poor compliance with therapy must be excluded. If there is any doubt about the possibility of iron deficiency, a trial of IV iron may be useful. Vitamin B12, folate, and thyroxine deficiency can be excluded easily by appropriate laboratory tests, as can severe hyperparathyroidism. Depending on the ethnic origin of the patient, a hemoglobinopathy should be excluded by performing Hb electrophoresis. Some patients taking ACE inhibitors or angiotensin receptor blockers may require higher doses of ESA therapy, although it is rarely necessary to stop these drugs. The possibility of a primary bone marrow disorder, such as myelodysplastic syndrome, should be investigated by a bone marrow examination if all other causes have been excluded. A bone marrow test also may be necessary in the diagnosis of antibody-mediated PRCA, although measurement of the reticulocyte count and anti-EPO antibodies may provide an earlier clue.26 If a patient receiving ESA therapy has a high reticulocyte count, the bone marrow is generating more than adequate quantities of new RBCs and bleeding or hemolysis should be investigated by means of endoscopy or hemolysis screen (Coombs test, serum bilirubin, lactate dehydrogenase, and haptoglobin levels). There is no defined upper dose limit of ESAs, and doses of 60,000 IU of EPO per week are not uncommon in the United States, but there is concern that high doses of ESAs may increase side effects

Causes of a Poor Response to Erythropoiesis-Stimulating Agent Therapy

BOX 86.3

Frequent
- Iron deficiency
- Infection, Inflammation
- Underdialysis

Less Common
- Poor compliance to ESA therapy
- Blood loss
- Hyperparathyroidism
- Aluminum toxicity (now rare)
- Vitamin B12 or folate deficiency
- Hemolysis
- Primary bone marrow disorders (e.g., myelodysplastic syndrome)
- Hemoglobinopathies (e.g., sickle cell disease)
- ACE inhibitors, angiotensin receptor blockers
- Carnitine deficiency
- Anti-EPO antibodies causing pure red cell aplasia

ACE, Angiotensin-converting enzyme; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent.

independently of Hb concentrations, as described earlier. In patients with acute illness requiring hospitalization, Hb frequently falls despite continued ESA therapy, indicating increased blood loss and temporary hyporesponsiveness. The optimal management of anemia under these conditions remains unclear. Although cost considerations may speak for withholding of ESA therapy until responsiveness is reestablished, it has been proposed that doses should be increased in an attempt to overcome hyporesponsiveness. Anecdotally, very high doses can be effective even in critically ill patients in intensive care units, but an RCT failed to demonstrate a reduction in transfusion requirements and observed an increase in deep vein thrombosis.51 From a practical point of view, and pending evidence to the contrary, it seems sensible to continue the same dose of ESA during acute illness.

Iron Management

Iron is an essential ingredient for heme synthesis, and adequate amounts of this mineral are required for the manufacture of new RBCs. Thus, under enhanced erythropoietic stimulation, greater amounts of iron are used, and many CKD patients (particularly those on HD) have inadequate amounts of available iron to satisfy the increased demands of the bone marrow.52 Even before the introduction of ESA therapy, many CKD patients were in negative iron balance as a result of poor dietary intake, poor appetite, and increased iron losses from occult and overt blood losses (see Chapter 83). Iron losses in HD patients are up to 5 or 6 mg/day compared with 1 mg in healthy individuals, which may easily exceed the absorption capacity of the gastrointestinal (GI) tract, particularly when there is any underlying inflammation. Iron absorption capacity in patients with CKD is considerably lower than in nonuremic individuals, particularly in the presence of systemic inflammation, and this is mediated by hepcidin upregulation.10 For this reason also, traditional oral iron therapy (e.g., with ferrous sulfate) is ineffective in many CKD patients, and parenteral iron administration is required, particularly in those receiving HD.51 However, a newer preparation of oral iron (ferric citrate) that shows greater absorption of iron from the gut is now available in the United States and Japan, and this agent can be used to concomitantly lower phosphate and increase iron levels in CKD patients.

TABLE 86.2 Recommended Iron Status Levels in Chronic Kidney Disease (CKD)

Test	Recommended Range
Serum ferritin	CKD: 100–500µg/L Hemodialysis: 200–500 µg/L
Transferrin saturation	20%–40%
Hypochromic red cells	<10%
Reticulocyte hemoglobin content	>29 pg/cell
Serum transferrin receptor	Not established
Erythrocyte zinc protoporphyrin	Not established

An inadequate supply of iron to the bone marrow may be caused by an absolute or a functional iron deficiency.[51] Absolute iron deficiency occurs when there are low whole-body iron stores, as indicated by a serum ferritin level less than 30 µg/L. Functional iron deficiency occurs when there is ample or even increased storage iron, but the iron stores fail to release iron rapidly enough to satisfy the demands of the bone marrow. Several markers of iron status are available, but none of them is ideal (Table 86.2). Serum ferritin is a marker of storage iron but is spuriously raised in inflammatory conditions and liver disease. TSAT is a function of the circulating serum iron in relation to the total iron-binding capacity and is often regarded as a better measure of available iron; however, levels can be highly fluctuant because of significant diurnal variation in the measurement of serum iron.[52] The percentage of hypochromic RBCs and the CHr are RBC and reticulocyte parameters, respectively, that are indirect measures of how much iron is being incorporated into the newly developing or mature RBCs. No one measure of iron status is usually adequate to exclude iron deficiency, and the recommended levels for these measures are based on limited scientific evidence. Functional iron deficiency is usually diagnosed when there is a normal or increased ferritin level and a reduced TSAT (<20%) or increased hypochromic RBCs (>10%). The KDIGO guideline suggests a trial of iron in CKD patients with anemia who are not on iron and ESA therapy and in whom an increase in Hb concentration is desired and in patients on ESA therapy in whom an increase in Hb concentration or a decrease in ESA dose is intended when TSAT is up to 30% and ferritin level is up to 500 µg/L[15] (see Table 86.2). Levels of ferritin above this threshold usually do not confer any clinical advantage and may exacerbate iron toxicity. The optimal TSAT is greater than 20% to 30% to ensure a readily available supply of iron to the bone marrow. No upper limits of ferritin or TSAT were specified in the KDIGO anemia guideline, largely because there is no robust evidence to determine a threshold beyond which harm or loss of efficacy supervenes. However, until more information become available,

the treating nephrologist should exercise caution in administering IV iron to patients with ferritin levels greater than 800 µg/L or TSAT greater than 30%. Several studies support maintaining the percentage of hypochromic RBCs at less than 6% and the CHr at greater than 29 pg/cell.

Oral iron is generally poorly absorbed in people with severe CKD, and there is a high incidence of GI side effects. Thus, IV administration of iron has become the standard of care for many CKD patients, particularly those receiving HD.52 Several IV iron preparations are available worldwide, including iron dextran, iron sucrose, iron gluconate, and the newer iron preparations ferric carboxymaltose, ferumoxytol, and iron isomaltoside 1000. The last three iron preparations allow higher doses of IV iron to be administered more rapidly, without the need for a test dose. All of the iron preparations contain elemental iron surrounded by a carbohydrate shell, which allows them to be injected intravenously.

An RCT comparing proactive high-dose administration of IV iron sucrose (400 mg iron per month up to a ferritin of 700 µg/L) with reactive low-dose iron sucrose (0–400 mg iron per month) in 2141 incident hemodialysis patients (PIVOTAL)53 showed lower ESA dose and transfusion requirements, as well as improved mortality and CV events with the high-dose regimen. Follow-up in the study was for a median of 2.1 years (maximum 4.4 years), and thus the longer-term safety of IV iron remains unknown.

All IV iron preparations also carry a risk for immediate hypersensitivity reactions, which may be characterized by hypotension, dizziness, and nausea. These reactions are usually short-lived and caused by too large a dose given in too short a time. Iron dextran also carries the risk for acute anaphylactic reactions because of preformed dextran antibodies, although this was largely a problem with the high-molecularweight IV iron dextran preparations, which have now been withdrawn from the market.

In nondialysis patients, both oral and IV iron may be used and there are advantages and disadvantages for each route of administration, which have been compared in two RCTs. The FIND-CKD study showed that both routes of administration were effective in this patient population, although higher-dose IV iron resulted in a faster and greater rise in Hb, with no safety concerns.48 However, the REVOKE study suggested that the rate of CV- and infection-related serious adverse events was greater in the IV iron treatment group compared with the oral iron group.54 The reasons for these discrepant findings remain unknown. Thus, the physician has to balance the low costs and convenience of oral iron treatment with known poor adherence to treatment, GI side effects, and reduced efficacy; IV iron, on the other hand, requires special facilities and set-up for administration and carries a very small risk for hypersensitivity reactions and potential additional risks.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is false regarding the characteristics of renal anemia?
A. The RBCs produced are usually normochromic and normocytic.
B. There is usually no associated leukopenia or thrombocytopenia.
C. The reticulocyte count is usually around 40,000 to 50,000/μL of blood.
D. Serum erythropoietin levels are usually within the normal range.
E. The RBC life span is usually normal.

2. Which of the following statements is false?
A. Dose requirements of epoetin are generally 20% to 30% less when the agent is administered subcutaneously compared with intravenously.
B. ESA therapy should be used with caution in patients with previous or current malignancy.
C. Patients who are hyporesponsive to ESA therapy have a worse prognosis than those who do respond.
D. The defined upper dose limit of epoetin is 60,000 IU/wk because it is known that CV toxicity occurs above this dose level.
E. ACE inhibitors may confer resistance to ESA therapy in some patients.

3. Which of the following statements is false regarding the TREAT study?
A. Patients receiving darbepoetin alfa were randomized to either a target hemoglobin (Hb) of 13 or a target Hb of 9 g/dL.

B. Patients randomized to a target Hb of 13 g/dL had a small increase in quality of life compared with the control arm.
C. There was a significant reduction in the use of RBC transfusions in patients randomized to a target Hb of 13 g/dL.
D. There was a doubling of the rate of stroke in patients randomized to a target Hb of 13 g/dL.
E. There was a significant increase in cancer-related mortality in the subset of patients with a history of malignancy who were randomized to a target Hb of 13 g/dL.

4. Which of the following statements is true regarding IV iron supplementation?
A. All IV iron preparations require a test dose before their first administration, as per their product label.
B. All the newer IV iron preparations (ferumoxytol, ferric carboxymaltose, and iron isomaltoside 1000) have the advantage that up to 1 g may be administered as a single dose.
C. IV iron preparations vary in their lability and speed of iron release from the carbohydrate shell, with iron gluconate being the most stable and iron dextran the least stable compound.
D. IV iron may improve the anemia of chronic kidney disease in up to 30% of patients not receiving ESA therapy who have a low ferritin level.
E. Hypersensitivity reactions are more common with lowmolecular-weight iron dextrans than with high-molecularweight iron dextran compounds.

REFERENCES

1. Jelkmann W. Molecular biology of erythropoietin. Intern Med. 2004;43:649–659.
2. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015;11:349–410.
3. Schödel J, Ratcliffe PJ. Mechanisms of hypoxia signaling: new implications for nephrology. Nat Rev Nephrol. 2019;10:641–659.
4. Semenza GL. Oxygen-sensing hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol. 2014;9:47–71.
5. Warnecke C, Zaborowska Z, Kurreck J, et al. Differentiating the functional role of hypoxia-inducible factor (HIF)-1α and HIF-2α (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2α target gene in Hep3B and Kelly cells. FASEB J. 2004;18:462–464.
6. Scortegagna M, Morris MA, Oktay Y, et al. The HIF family member EPAS1/HIF-2alpha is required for normal hematopoiesis in mice. Blood. 2003;102:634–640.
7. Eckardt KU. The noblesse of kidney physiology. Kidney Int. 2019;96:1250–1253.
8. Chen C, Sytkowski AJ. The erythropoietin receptor and its signalling cascade. In: Jelkmann WFP, ed. Erythropoietin: Molecular Biology and Clinical Use. Johnson City, TN: Graham Publishing; 2003:165–194.
9. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133:40–50.
10. Drakesmith H, Prentice HM. Hepcidin and the iron-infection axis. Science. 2012;338:768–772.
11. Astor BC, Muntner P, Levin A, et al. Association of kidney function with anemia: the third National Health and nutrition examination survey, 1988-1994. Arch Intern Med. 2002;162:1401–1408.
12. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004;20:501–510.
13. K/DOQI. Anemia guidelines in CKD patients. Am J Kidney Dis. 2006;47(suppl 3):S1–S146.
14. Pisoni RL, Bragg-Gresham JL, Young EW, et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44:94–111.
15. KDIGO Anemia Guideline Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
16. Cole J, Ertoy D, Lin H, et al. Lack of angiotensin II–facilitated erythropoiesis causes anemia in angiotensin-converting enzyme–deficient mice. J Clin Invest. 2000;106:391–398.
17. Le Meur Y, Lorgeot V, Comte L, et al. Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: relationship with erythropoietin requirements. Am J Kidney Dis. 2001;38:10–17.
18. Winkelmayer WC, Kewalramani R, Rutstein M, et al. Pharmacoepidemiology of anemia in kidney transplant recipients. J Am Soc Nephrol. 2004;15:347–352.
19. Macdougall IC, Lewis NP, Saunders MJ, et al. Long-term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. Lancet. 1990;335:489–493.
20. Parfrey PS, Foley RN, Wittreich BH, et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2005;16:2180–2189.
21. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584–590.
22. Drüeke TB, Locelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071–2084.
23. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085–2098.
24. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019–

2031.
25. Macdougall IC. New anemia therapies: translating novel strategies from bench to bedside. Am J Kidney Dis. 2012;59:444–451.

26. Macdougall IC, Roger SD, de Francisco A, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesisstimulating agents: new insights. Kidney Int. 2012;81:727–732.
27. Boven K, Stryker S, Knight J, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int. 2005;67:346–353.
28. Haag-Weber M, Eckardt KU, Hörl WH, et al. Safety, immunogenicity and efficacy of subcutaneous biosimilar epoetin-α(HX575) in non-dialysis patients with renal anemia: a multi-center, randomized, double-blind study. Clin Nephrol. 2012;77:8–17.
29. Kaufman JS, Reda DJ, Fye CL, et al. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative study group on erythropoietin in hemodialysis patients. N Engl J Med. 1998;339:578–583.
30. Vanrenterghem Y, Barany P, Mann JF, et al. For the European/Australian NESP 970200 Study Group. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int. 2002;62:2167–2175.
31. Carrera F, Lok CE, de Francisco A, et al. Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycolepoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial. Nephrol Dial Transplant. 2010;25:4009–4017.
32. Locatelli F, Hannedouche T, Fishbane S, Morgan Z, Oguey D, White WB. Cardiovascular safety and all-cause mortality of methoxy polytheylene glycol – epoetin beta and other erythropoiesis-stimulating agents in anemia of CKD: a randomized noninferiority trial. Clin J Am Soc Nephrol. 2019;14:1701–1710.
33. Macdougall IC, Rossert J, Casadevall N, et al. A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. N Engl J Med. 2009;361:1848–1855.
34. Maxwell PH, Eckardt KU. HIF prolyl hydroxylase inhibitors for the treatment of renal anaemia and beyond. Nat Rev Nephrol. 2016;12:157–168.
35. Bernhardt W, Wiesener MS, Scigalla P, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. J Am Soc Nephrol. 2010;21:2151–2156.
36. Wish JB, Eckardt KU, Kovesdy CP, Fishbane S, Spinowitz BS, Berns JS. Hypoxia-inducible factor stabilization as an emerging therapy for CKD-related anemia: report from a scientific workshop sponsored by the National Kidney Foundation. Am J Kidney Dis. 2021. (accepted for publication).
37. Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. N Engl J Med. 2021;384:1601–1612.
38. Chertow G, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. N Engl J Med. 2021;384:1589–1600.
39. Provenzano R, Fishbane S, Szczech L, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. Kid Int Rep. 2020;6:613–623.
40. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. Kid Int Rep. 2020;6:624–635.
41. Shutov E, Sułowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, double-blind, placebo-controlled study (ALPS). Nephrol Dial Transplant. 2021;gfab057.
42. Provenzano R, Shutov E, Eremeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant. 2021;gfab051.
43. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized

phase 3 study. J Am Soc Nephrol. 2021;32:737–755.

44. FibroGen. Fibrogen announces outcome of FDA Advisory Committee review of roxadustat for treatment of anemia of chronic kidney disease. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogenannounces-outcome-fda-advisory-committee-review.

45. Johansen K, Cizman B, Cobitz AR, et al. ASN 2021: effects of daprodustat on hemoglobin and quality of life in patients with CKD: results of the ASCENT-NHQ randomized, placebo-controlled trial. J Am Soc Nephrol. 2021;32:36.

References

46. Singh AK. Daprodustat for the treatment of anemia in patients undergoing dialysis. N Engl J Med. 2021;25:2325–2335.
47. GSK reports outcome from US FDA Advisory Committee meeting on daprodustat for anaemia of CKD. https://www.gsk.com/en-gb/media/press-releases/gsk-reports-outcome-from-us-fda-advisory-committeemeeting-on-daprodustat-for-anaemia-of-ckd/.
48. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant. 2014;29:2075–2084.
49. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ. 1990;300:573–578.

50. Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363:1146–1155.
51. Corwin HL, Gettinger A, Fabian TC, et al. EPO Critical Care Trials Group. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med. 2007;357:965–976.
52. Macdougall IC, et al. Iron management in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int. 2016;89:28–39.
53. Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med. 2019;380:447–458.
54. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015;88:905–914.

87

Other Blood and Immune Disorders in Chronic Kidney Disease

Matthias Girndt, Gunnar H. Heine

IMMUNE DYSFUNCTION

Patients with chronic kidney disease (CKD) have a high morbidity and mortality from infection. This is partially due to immune dysfunction, although multiple other factors are involved.

Bacterial Infections

Infections are a major cause of hospitalization in patients with CKD; infection-related hospitalization rates are at least three to four times (nondialysis CKD) or eight times (dialysis) higher than in individuals with normal kidney function.1 The number of days spent in hospital for infections has slightly decreased over the last decade. Nevertheless, they are still higher than those for cardiovascular (CV) disease (4 vs. 2.2 days per patient year).1 Infection is also an important cause of mortality, accounting for 8% of deaths in dialysis patients. The risks of pulmonary infections and infections of the genitourinary system both increase with decreasing kidney function. For example, patients with stage 4 CKD have a 15-fold higher risk for severe pulmonary infections compared with those with an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m2. Furthermore, mortality from pneumonia is markedly enhanced by concurrent CKD,2 which was reflected in the extremely high mortality among patients undergoing hemodialysis (HD) during the COVID-19 pandemic3 (see Chapter 59).

In HD patients, bloodstream infections are another major cause of infection-related hospitalization, particularly in patients with central venous catheters.4 Catheter-based HD is among the major risk factors for the development of bacterial endocarditis. More than 50% of cases of bacteremia are caused by Staphylococcus aureus. Nevertheless, there is also a relevant rate of gram-negative bacteremia in dialysis patients, indicating that contamination or infection of the dialysis access is not the only cause of bloodstream infection.

The high incidence of bacterial infection in CKD patients may be one clinical consequence of immune dysfunction; another is atypical clinical presentations of infections, such as the lack of fever in 20% to 40% of kidney patients with bacteremia. When bacteremia is suspected, blood cultures should be obtained frequently. Another aspect of immune dysfunction is the high rate of false-negative tuberculin (Mantoux) skin tests with anergic skin reactions in the presence of positive interferon-γ release assays, indicating impaired T-lymphocyte function.5

Other factors besides immune dysfunction predispose to infection in persons with CKD. Thirty-nine percent of patients with end-stage kidney disease reported by the US Renal Data System are age 65 years or older,1 and in other countries the percentage exceeds 50%. Besides advanced age, many CKD patients have underlying kidney or extrarenal autoimmune disease that requires therapeutic immunosuppression and other comorbidities that facilitate infection such as diabetes or heart failure. Dialysis patients and patients with cardiorenal syndrome often have excess pulmonary fluid, which may impair alveolar bacterial clearance and contribute to the risk for pneumonia. Repeated breaks in the skin barrier by cannulation provide opportunity for bacterial invasion. Finally, dialysis patients frequently receive intravenous iron preparations, and iron overload is a risk factor for bacterial infection as a result of inhibition of monocyte and macrophage function.

Viral Infections

Viral hepatitis has been a scourge of dialysis ever since kidney replacement therapy became a routine treatment. Only rigorous infection control practices and active vaccination against hepatitis B virus

(HBV) made large-scale HD safe. However, impaired immune defense was only one among other causes for the high prevalence of viral hepatitis in this patient group. The viruses can be easily transmitted nosocomially in HD patients without proper precautions. Nevertheless, the early outbreaks of HBV infection showed an abnormal clinical course related to the immune defect in CKD.6 The acute infection could sometimes only be detected by measurement of transaminases; the typical clinical syndrome of icterus, subfebrile temperatures, and malaise was often absent. Most affected dialysis patients developed chronic persistent infection, which occurs in only 10% of patients with normal kidney function.

The clinical manifestations of hepatitis C virus infection are not significantly influenced by the immune deficiency of kidney failure. The infection usually runs a subclinical course and becomes chronic even in the absence of CKD.

Vaccinations in Chronic Kidney Disease

Immune deficiency leads to a high rate of nonresponse to hepatitis B vaccination. Dialysis patients should always receive a double-dose vaccination and extended vaccination protocols (Fig. 87.1), but even with the most recent vaccines, some 20% of patients do not develop protective antibody levels.7 This impaired response led to the development of specifically adjuvanted vaccines or intracutaneous application protocols8 with improved efficiency in former nonresponders.

Other vaccinations are also affected by the immune defect in CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline9 recommends annual influenza vaccinations. Studies comparing vaccination efficiency in patients with CKD and healthy individuals have methodological limitations; therefore the extent to which immune dysfunction compromises these vaccination results is unclear. Most likely, the efficacy is lower in patients receiving dialysis. A recent systematic review on the protective effects with regard to hard endpoints such as mortality or hospitalization pointed out that the universal recommendation to vaccinate—albeit very plausible—has a weak evidence base.10 In contrast to the experience in the general population, enhanced-dose influenza vaccine does not seem to be superior to standard vaccines.11

Hepatitis B Vaccination Scheme for Patients With Chronic Kidney Disease
Serologic testing
(HBsAg, anti-HBs, anti-HBc)

At least 1
marker positive

No vaccination

All negative

3–4x double dose vaccination*
intramuscularly

Serologic testing
(anti-HBs)
4 weeks after inj.

Anti-HBs > 100 IE/L

Anti-HBs < 10 IE/L

Anti-HBs 10–100 IE/L

3–4x double dose vaccination*
intramuscularly
or 8x5 μg intradermally

Serologic testing
(anti-HBs)
annually

Anti-HBs < 100 IE/L

Anti-HBs
≥ 10 IE/L

Serologic testing
(anti-HBs)
4 weeks after inj.

Anti-HBs < 10 IE/L

Single booster dose
40 μg intramuscularly

No further vaccination attempts
HBsAg monitoring annually

Fig. 87.1 Hepatitis B vaccination scheme for patients with chronic kidney disease (CKD). *The schedule varies with different vaccine preparations. HBsAg, Hepatitis B surface antigen.

Vaccines against herpes zoster have proven to be most effective in preventing zoster manifestations in the elderly. It seems to be justified to extend the general recommendation to vaccinate individuals older than 60 years to patients with CKD. The newer recombinant vaccine has not been studied in this patient group; however, the earlier attenuated vaccine led to excellent seroresponses in dialysis patients.12
Several studies have been published on SARS-CoV-2 vaccination in

patients with CKD and on dialysis; this vaccination is highly desirable in these vulnerable populations (see Chapter 59).

In contrast to antiviral vaccinations, the efficacy of those against bacteria appear to be mildly reduced by CKD. Vaccination against pneumococcal infections is recommended[9] for all adults with eGFR less than 30 mL/min/1.73 m^2. Evidence of efficacy in terms of antibody titers comes from very old studies or series with small patient numbers. Likely, maximum antibody titers are lower and protection lasts shorter in CKD patients,[13] but data on hospitalization or mortality can be derived only from observational studies.[14] Because multiple vaccine preparations are available, the congruence of local epidemiology and the vaccine coverage should be considered (Fig. 87.2). Newer conjugate vaccines have a rather narrow spectrum of serotype coverage while being highly effective in inducing seroprotection; thus there is an argument to vaccinate CKD patients sequentially with conjugate vaccine first, followed in 6 to 12 months by the broad polysaccharide vaccine. Revaccination with the polysaccharide vaccine is recommended after 6 years.

Further recommendations for vaccination in CKD are given in Table 87.1

INFLAMMATION

Chronic inflammation is typical for patients with stage 4 or 5 CKD or on kidney replacement therapy, and C-reactive protein (CRP) and plasma cytokines increase steadily with every stage of CKD. The majority of HD and peritoneal dialysis patients periodically or permanently have CRP values above the normal limit despite the absence of clinical infection.[15]

Causes of Inflammation

Although early research in this field focused on dialysis membrane bioincompatibility, contamination of dialysis fluids, or vascular access as causes of inflammation, chronic inflammation also occurs in patients with stages 3 and 4 CKD. One important reason may be the renal

Europe

Number of cases

1500

Conj-10
Conj-13
PS-23

1000

500

0
19F

4

14 7F 1
3 19A 12F 8
Str. pneumonia serotype

22F

USA

Number of cases

400

Conj-10
Conj-13

300

PS-23

200
100
0

clearance of circulating proinflammatory cytokines.16 Impaired kidney function leads to prolonged cytokine serum half-life, thus enhancing and prolonging inflammatory episodes that usually would have abated quickly.

At least 30% of patients with advanced CKD have diabetes mellitus, a comorbidity that promotes inflammation both by itself and through diabetic complications such as ulcers. In addition, many patients with CKD have poor dental health, and periodontitis is associated with systemic inflammation.17

Whether inflammation is also related to classic uremic toxicity remains a matter of debate. Typical toxins with increased plasma levels are indoxyl sulfate, paracresyl sulfate, and trimethylamine N-oxide (TMAO). Across stages of CKD, plasma levels of TMAO show a positive correlation with inflammatory markers, and both decrease after kidney transplantation.18 Several studies show that serum levels of indoxyl sulfate or paracresyl sulfate increase with kidney dysfunction in parallel with inflammatory markers; however, a causal relationship remains to be proven.

The extent of inflammation is at least in part controlled by the genetic predisposition of the individual. This may be clinically relevant in patients with CKD because inherited single-nucleotide polymorphisms in the gene of the antiinflammatory cytokine interleukin (IL)-10 influence the quantity of its production in response to inflammatory stimuli and thus the way a patient can contain and limit inflammation.19

18 1
C
23
F
4
6B
19
F
7F
6A
19 3
A
12
F
9N
15
B
A
22
15 F
B

5
9V
14

Consequences of Inflammation

Str. pneumonia serotype

Fig. 87.2 Streptococcus pneumoniae serotypes in clinical isolates (as of 2010) from Europe (European Center of Disease Control) and United States (Centers for Disease Control and Prevention) in relation to vaccine serotype coverage. Conj-10, 10-valent conjugate vaccine; Conj-13, 13-valent conjugate vaccine; PS-23, 23-valent polysaccharide vaccine. Low isolate numbers for the serotypes covered by Conj-10 in the United States are the result of successful vaccination programs.

Inflammation is closely associated with the occurrence of cardiovascular complications (see Chapter 85) and immune dysfunction. When using the response to HBV vaccination as a surrogate for clinical immune function, there is a close correlation between inflammation and decreased immunity. This is confirmed by the finding that the IL10 gene polymorphism, which influences the extent of inflammation, also predicts vaccination responses in dialysis patients.19

IMMUNE CELL ABNORMALITIES

Monocytes

Vaccination

Recommendations for Adult Patients With Chronic Kidney Disease

TABLE 87.1

Vaccination Against Recommendation

HBV

Influenza
Streptococcus
pneumoniae
Tetanus
Diphtheria
Herpes zoster
Hepatitis A

All patients susceptible to HBV infection,
double dose (see Fig. 87.1)
Annually according to WHO recommendation,
standard dose
All patients, conjugate vaccine, can be
boosted by polysaccharide vaccine at 6 mo,
revaccination after 6 yr
All patients according to recommendations for
general population, standard dose
All patients according to recommendations for
general population, standard dose
All patients >60 years
Not routinely indicated, can be given prior to
travel to affected areas

HBV, Hepatitis B virus; WHO, World Health Organization.
Modified from Dinits-Pensy M, Forrest GN, Cross AS, Hise MK. The use of vaccines in adult patients with renal disease. Am J Kidney Dis. 2005;46:997–1011.

Monocytes are bone marrow–derived cells with specific functions in immune surveillance and antigen presentation. During their differentiation, they briefly circulate in the blood, produce cytokines, and then migrate into tissues to become macrophages.[20] Injury and infection lead to rapid enhancement of circulating monocyte numbers, which then migrate to the site of tissue injury and initiate the local immune response. Monocyte-derived macrophages are constituents of atherosclerotic plaques, and imaging studies have revealed that monocytes patrol along the vascular endothelium, where they detect endothelial defects.[21]

Monocyte subpopulations are defined by the expression of the lipopolysaccharide receptor CD14 and the immunoglobulin Fcy receptor CD16.[22] The classic monocytes only express CD14 and account for some 80% of all circulating monocytes in healthy individuals; intermediate monocytes express both CD14 and CD16 (~5%–7%), and nonclassic monocytes express high levels of CD16 while showing limited staining for CD14 (~10%–12%). Genetic analysis revealed that CD14++CD16+ intermediate monocytes particularly express markers related to antigen presentation, inflammation, and angiogenesis.[23]

In CKD, the intermediate and nonclassic monocyte subtypes are significantly expanded. This finding is related to the CV risk[24]; patients with the highest rate of CD14++CD16+ monocytes in blood had the lowest CV event-free survival.

Mouse models confirm differences between monocyte subpopulations in their ability to invade atherosclerotic plaques.25 In CKD the expansion of proinflammatory monocyte subsets and their epidemiologic association with CV events make a causal role of these cells for atherosclerotic disease likely. Furthermore, monocytes also express components of the angiotensin system. The angiotensin-converting enzyme (ACE) that turns angiotensin I (Ang I) into vasoactive angiotensin II (Ang II) is expressed in atherosclerotic plaques and colocalizes with monocyte-derived macrophages.26 ACE is also expressed on circulating monocytes, particularly on those with the CD14++CD16+ phenotype.27 Dialysis patients with high expression of ACE on intermediate monocytes have a dramatically enhanced CV mortality risk.27 Expression of ACE on monocytes is strongly upregulated by the uremic milieu.28 A consequence of this might be that monocytes transmigrate into the subendothelial space of arteries and provide high levels of ACE in the atherosclerotic plaque. The local production of Ang II through ACE is thought to contribute to further leukocyte attraction, inflammatory activation, and plaque growth. In addition, expression of ACE on monocytes alters their functional capacities. In vitro assays show that a higher expression of ACE leads to stronger endothelial adhesion and transmigration of the monocytes. This effect appears to be mediated via locally produced Ang II, because adhesion and transmigration could be inhibited by losartan.28

Monocytes also express ACE-2, a peptidase that degrades Ang II to Ang1–7, a vasodilatory peptide. Whereas CKD leads to the overexpression of ACE, the ACE-2 enzyme is downregulated compared with healthy individuals.29 Experimental overexpression of ACE-2 in a rodent model of atherosclerosis limited the progression of disease. These findings suggest that the uremic milieu alters monocyte function in a strongly proatherogenic way.

Monocytes are closely related to circulating blood dendritic cells. Dendritic cells are mainly found in organs and tissues, where they have strong capabilities in antigen presentation and activation of immune reactions. Their immature precursors circulate in blood in low numbers. There are different subtypes of circulating dendritic cells, but investigators have used different marker sets for their detection. This limits comparison among different studies, so that understanding of dendritic cell quantification and pathophysiology remains limited.

There is a relation between elevated numbers of CD14++CD16+ monocytes in the blood and the propensity of these cells to differentiate into dendritic cells in cell culture.30 Other studies31 found significantly lower numbers of dendritic cells in advanced CKD compared with healthy controls. The finding may be related to cardiovascular disease, because studies in patients with coronary heart disease and normal kidney function also reported reduced circulating numbers of dendritic cells.

T Lymphocytes

Impaired vaccination responses against viral antigens such as HBV or influenza, as well as reduced skin reaction in the Mantoux test, result from impaired T-cell activation. T cells are an important component of the antigen-specific adaptive immune defense. Their activation depends on antigen-presenting cells (APCs) that present foreign antigens with major histocompatibility complex and provide important costimulatory signals. Only T cells with specificity of their T-cell receptor toward the particular antigen are activated and proliferate.

Major APCs are dendritic cells, and their precursors are monocytes. Early studies showed that proliferative T-cell responses are impaired in dialysis patients, and this impairment is directly correlated with nonresponses to HBV vaccination. Both replacement of the patient’s APCs in in vitro assays with cells from healthy donors and overexpression of costimulatory molecules on the APCs normalize proliferation of T cells, indicating that the major defect leading to reduced T-cell activation is in the APC.32 However, these rather crude assays did not consider T-cell subpopulations. Helper T cells express the surface marker CD4 and interact with various other cell types. The CD4+ helper T cell is particularly needed for activation of B cells for antigenspecific seroresponses to viral antigens, as in HBV vaccination. The CD8+ cytotoxic T cells are important for antiviral defense because they are able to lyse infected host cells. In CKD the relation of CD4+/CD8+ T cells is reduced.

CD4+ helper cells can be further distinguished into cells that mainly support cellular immune reactions (helper T cells Type 1, Th1) and others that are more important for immunoglobulin production by members of the B-cell lineage (Th2). These cell types differ in the pattern of cytokines they produce, with interferon-γ being the major cytokine of Th1 and IL-4 the main cytokine of Th2 cells. CKD leads to a marked deviation of T cell differentiation toward the Th1 phenotype.33 Most likely the major cause is elevated production of IL-12 by monocytes and APCs in the context of their inflammatory activation.33

Another T-lymphocyte subpopulation is regulatory T cells (Tregs) that are important for the downregulation of immune responses once the aim of an antiinfectious response is reached. They prevent ongoing inflammation and the development of autoimmunity. The typical Treg cells originate in the thymus and have a distinct pattern of surface molecule expression. In patients with CKD the number of circulating Treg cells is unaltered, but their capacity to downregulate CD4+ helper T-cell activity is impaired.34

B Lymphocytes

Impaired vaccination efficacy in CKD suggests impaired function of immunoglobulin-producing B lymphocytes and plasma cells; thus a major dysfunction of this cell type might be expected. However, CKD patients have normal circulating immunoglobulin levels. Their B-cell lymphopenia is modest and probably not very clinically relevant. It is caused by a higher rate of apoptosis of these cells compared with healthy individuals.35 Lymphopenia appears to result from reduced numbers of the majority of B-cell subpopulations (naive B cells, memory B cells, etc.).36 Taken together, the alterations of B-lymphocytes in CKD appear to be less pronounced than alterations of other immune cell types. Impaired vaccination responses are caused by altered interaction of APCs, helper T lymphocytes, and the cytokine network in CKD rather than by abnormalities of B lymphocytes.

Granulocytes

Polymorphonuclear granulocytes (neutrophils) are components of the antigen-independent innate immune system. Their main activity is to kill and phagocytose invading pathogens via numerous enzymes that produce bactericidal substances. Among them are defensins, proteolytic enzymes, and enzymes that produce highly active oxygen species such as hypochlorous acid. In CKD patients, these nonspecific defense systems are highly activated, and the cells spontaneously release more reactive oxygen species.37 Inflammation, activation of different cell types, antiinfectious defense, and vascular disease are closely interwoven. Thus, the elevation of oxygen species H2O2 and malondialdehyde has predictive value for CV events and mortality in CKD.38

Another important function of granulocytes is phagocytosis, which is mildly compromised in CKD.39 Further, chemotactic attraction of the cells to the location of infection is modified by substances such as leptin that are retained in CKD.40

It is difficult to establish whether these abnormalities can be improved by dialysis. HD inevitably involves extensive contact between blood and foreign surfaces. When cellulose-based membranes were still in use, the activation of the complement system by these membranes led to marked depletion of circulating granulocytes within the first 20 minutes of a dialysis session.41 Newer synthetic membranes lead to minimal complement activation, and the leukocyte drop is much less pronounced. These findings on immune cells relate to CKD specifically, and some primary diseases (especially diabetes mellitus) further influence immune cell function.

PLATELET DYSFUNCTION AND PLATELET INHIBITORS IN CHRONIC KIDNEY DISEASE

Normal hemostasis begins with platelet adhesion to vascular endothelium and requires a relatively vasoconstricted vessel wall, integrity of platelet glycoproteins (GPs), and a normal quantity of large molecular weight, multimeric von Willebrand factor (vWF) (Figs. 87.3 and 87.4). Main platelet GPs are GPIb, the platelet receptor for vWF, involved in platelet adhesion, and GPIIb/IIIa, the platelet receptor for fibrinogen, involved in platelet aggregation.

Under static conditions, GPIb and vWF have no affinity for each other. However, these molecules develop a specific affinity for each other at high shear stress, resulting in arterial platelet adhesion. Aggregated fibrinogen-platelet mesh acts as a trap for binding and activation of other plasma clotting factors. The exposure of the preceding clotting factors to tissue factors, present on damaged endothelial cells, catalyzes the conversion of prothrombin to thrombin, which converts fibrinogen to fibrin. Subsequent cross-linking of insoluble fibrin results in a stable hemostatic plug.

Hemorrhagic Diathesis and Uremic Platelet Dysfunction

Patients with CKD have a high risk of bleeding. This hemorrhagic diathesis frequently has cutaneous (easy bruising, ecchymoses, or prolonged hemorrhage from needle puncture or postoperative sites) and mucosal (epistaxis; gastrointestinal or gingival bleeding) manifestations. More dramatic—albeit infrequent—manifestations are hemorrhagic pericarditis/hemopericardium, hemorrhagic pleural effusion/hemothorax, and intracranial and retroperitoneal bleeding.42

This hemorrhagic diathesis is not reflected in a prolongation of the prothrombin time or the partial thromboplastin time. Similarly, even though platelet counts may be moderately decreased because of platelet consumption outperforming platelet production, severe thrombocytopenia is rarely seen in uremia; the occurrence of very low platelet counts therefore requires a thorough search for alternative causes.43

Instead, platelet dysfunction is generally considered as the central contributor to the high bleeding risk, and a high number of pathophysiologic alterations have been suggested to contribute, comprising alterations in platelet function and structure, and extrinsic factors (see Table 87.1). Unfortunately, many studies on platelet functions in CKD date back to the early days of clinical nephrology, when clinical care and dialysis treatment were less sophisticated, and when less advanced laboratory methods were available for evaluation of hemostasis. For the various pathophysiologic alterations listed in Box 87.1, controversial data have been published.

In the search for uremic toxins inducing platelet dysfunction, a direct pathologic role of urea can be ruled out because no correlation exists between blood urea levels and bleeding time,44 and individuals with high serum urea levels but otherwise normal kidney function have no bleeding tendency.45

Among the different extrinsic factors that contribute to platelet dysfunction, the contribution of anemia has gained particular interest. Physiologically, erythrocytes occupy the center of a vessel, displacing platelets from the axial flow toward the vessel walls. This allows platelets to adhere to injured endothelial cells and initiate the formation of a platelet plug. In anemia, platelets are more dispersed, which impairs their adherence to the endothelium. Moreover, in CKD, red blood cells may affect coagulation by releasing adenosine diphosphate (ADP), by

Platelet Adhesion and Aggregation
von Willebrand
factor

Red blood cell

Fibrinogen

GPIIb/IIIa
Platelet

GPIIb
Fibrin
mesh
Platelet

Coagulation
IIa
cascade

Activated Inset expanded Tissue
Platelet
GPIIb/IIIa
in Fig. 87.4
factor
adhesion

Fig. 87.3 Platelet Adhesion and Aggregation. Platelets are pushed peripherally toward the vascular wall by red blood cells traversing centrally through the bloodstream. Damage to the vessel wall results in a disruption of the nonthrombogenic endothelial cell lining and exposure of subendothelial structures. Whereas collagen supports initial platelet adhesion (and subsequent aggregation), von Willebrand factor (vWF) deposition on the subendothelium serves as the main anchor for platelet adhesion through platelet glycoprotein (GP) IIb receptor. Postadhesion conformational change in platelet GPIIb/IIIa receptor (fibrinogen or vWF receptor) results in interlinking platelet aggregation.

Endothelial
cell

Collagen-laden
subendothelium

Clotting Cascade
Fibrinogen
IX

VII

X

VIIIa†

II

Cross-linking
Fibrin

Va†

*
Tissue
factor

VIIa

IIa*

(Thrombin)

VIIa IXa Xa
Endothelial cell

Fig. 87.4 Clotting Cascade. Expansion of the inset in Fig. 87.3 shows the clotting cascade that takes place at the damaged vessel wall. Exposure of subendothelial tissue factor, present on pericytes and fibroblasts, allows eventual activation of prothrombin (factor II) to thrombin. Thrombin converts fibrinogen to fibrin, activates fibrin cross-linking, stimulates further platelet aggregation, and activates anticoagulant protein C. Naturally occurring anticoagulants antithrombin III, protein C, and protein S help maintain control and counterbalance on coagulation. *Site of anticoagulant effect for antithrombin III. †Site of anticoagulant effect for protein C–protein S complex. (Courtesy James A. Sloand, MD, FACP, FASN, Baxter Healthcare Corporation, Deerfield, IL.)

Proposed Contributors to
Platelet Dysfunction in Uremia

BOX 87.1

Intrinsic Factors That Contribute to Platelet Dysfunction

- Dysfunction of glycoprotein IIb/IIIa
- Abnormal expression of platelet glycoprotein
- Altered release of adenosine monophosphate and serotonin from platelet α-granules
- Faulty arachidonic acid and depressed prostaglandin metabolism, decreased platelet thromboxane A2 generation
- Abnormal platelet cytoskeletal assembly with reduced incorporation of actin and diminished association of actin binding proteins (α-actin and tropomyosin) with the cytoskeleton

Extrinsic Factors That Contribute to Platelet Dysfunction

- The action of uremic toxins
- Anemia
- Increased nitric oxide and cyclic guanosine monophosphate production
- Functional von Willebrand factor abnormalities
- Decreased platelet production
- Abnormal interactions between the platelet and the endothelium of the vessel wall

Modified from Berns JS. Platelet dysfunction in uremia. UpToDate. https://www.uptodate.com/contents/platelet-dysfunction-in-uremia.

inactivating PGI_2, and by scavenging nitric oxide (NO), which are all central regulators of platelet function.[43]

Treatment of Uremic Platelet Dysfunction

Despite the previously discussed pathophysiologic considerations, few data establish the extent to which initiation of kidney replacement therapy reduces the risk for bleeding in CKD.

In the early decades of HD, the interaction of blood with cellulosebased dialyzer membranes resulted in complement activation and transient thrombocytopenia during the dialysis procedure. When using more biocompatible dialyzer membranes, such complement-induced platelet reduction no longer has clinical relevance. Nonetheless, HD treatment may still affect bleeding disorders; although potentially removing uremic toxins, which affect platelet function, it requires systemic anticoagulation and exposes patients to the potential risk for heparin-induced thrombocytopenia (HIT). Moreover, HD may disrupt the platelet cytoskeleton, induce repeated platelet stress, decrease the percentage of RNA-rich platelets, and reduce the percentage of available reticulated platelets.[46] As RNA-rich and reticulated platelets are more able to be activated, the accumulation of less RNA-rich and less reticulated platelets indicates the presence of less reactive platelets.

Although treatment of anemia may improve some parameters of platelet dysfunction,[46] it has not been demonstrated to ameliorate bleeding or risk for bleeding.

In summary, dialysis and anemia treatment will not completely normalize platelet function. Therefore, drug treatment should be considered for those patients who have active bleeding or are scheduled to undergo an invasive diagnostic or therapeutic procedure with bleeding risk.

Desmopressin

Desmopressin (1-deamino-8-d-arginine-vasopressin [DDAVP]) is a synthetic derivative of the antidiuretic hormone with little vasopressor activity. It acts by stimulating the release of large factor VIII–von Willebrand factor multimers from endothelial cells into the plasma and potentially by increasing the membrane glycoprotein expression of platelets.

At a dose of 0.3 μg/kg (if given intravenously [in 50 mL of saline over 15–30 minutes] or subcutaneously]), desmopressin may improve the bleeding time over the subsequent 4 to 8 hours.

Typical side effects include water retention, hyponatremia, moderate thrombocytopenia, facial flushing, mild transient headache, nausea, abdominal cramps, and mild tachycardia; thrombotic events are rarely observed.[42]

Although its efficacy on laboratory measures of platelet function is undisputed, its clinical efficacy for preventing or treating bleeding remains unproven. One study that recruited 162 participants without severely reduced kidney function who underwent ultrasound-guided kidney biopsy suggested that prebiopsy desmopressin administration may decrease the risk of bleeding and hematoma size.47 However, given this rather limited evidence for a clinical benefit of desmopressin, there is broad consensus that desmopressin is not mandatory before a routine kidney biopsy. Additionally, depletion of endothelial stores of the factor VIII–von Willebrand factor multimers after a second DDAVP injection may result in tachyphylaxis, which precludes its chronic use.

Cryoprecipitate

In many uremic patients, cryoprecipitate may improve the bleeding time within 1 hour after infusion. This effect is supposed to be mediated by the provision of factor VIII–von Willebrand factor multimers, fibrinogen, and by other factors that enhance platelet aggregation. However, this effect is short lasting (4–24 hours). Moreover, cryoprecipitate may have infectious, hemorrhagic, and anaphylactic complications, and not all patients respond to cryoprecipitate.42 43 46 Thus, use of cryoprecipitate should be limited to patients with life-threatening bleeding who are resistant to treatment with desmopressin and blood transfusions.

Tranexamic Acid

As an antifibrinolytic agent, tranexamic acid (TXA) is licensed for treatment of heavy bleeding, as well as before dental interventions in patients with coagulopathies. Its use in CKD has been reported in several (mostly small) cohort studies, which often focused on surrogate markers of hemorrhagic diathesis. Therefore, TXA may be considered for life-threatening bleeding events in CKD patients. However, it should be reserved for those in whom other treatments have failed to control bleeding, because kidney excretion is the main route of TXA clearance. TXA has an unpredictable pharmacokinetic profile in advanced CKD patients, who are at particular risk for neurologic side effects of TXA (i.e., seizures).48

RECOMBINANT ACTIVATED FACTOR VII

Recombinant activated factor VII (rFVIIa) was developed for treatment of hemorrhage in individuals with hemophilia with antibodies inactivating factor VIII or IV. Because of the central role of activated factor VII in coagulation, rFVIIa has been used off-label in a variety of other severe bleeding disorders, including some case reports that claimed successful use of rFVIIa for treatment of bleeding in CKD patients.43 This very limited evidence, together with a substantial risk for thromboembolic events, mandates very prudent use of rFVIIa, which should be considered only in very severe bleeding when other interventions have failed.

ESTROGENS

Estrogens may improve bleeding time in CKD patients in a dosedependent manner. Their mode of action involves a reduced production of l-arginine, which is a precursor of NO. Thus, estrogens may lower elevated NO production in CKD patients and subsequently reduce NO-induced guanylyl cyclase stimulation and cyclic guanosine monophosphate (cGMP) synthesis, which will finally increase thromboxane A and ADP availability. Estrogens may additionally lower hemorrhagic diathesis by affecting production of coagulation factors and their inhibitors.

Estrogens may be given intravenously, orally, or cutaneously. Compared with other approaches, estrogen treatment may affect bleeding tendency for a prolonged time. However, its long-term safety has again not been assessed in prospective studies.

IMPLICATIONS FOR ANTIPLATELET AGENT THERAPY

Uremic platelet dysfunction and the increased bleeding risk also imply that treatment with antiplatelet agents—particularly aspirin, clopidogrel, prasugrel, and ticagrelor—may induce more bleeding events among CKD patients than in the general population. At the same time, CKD patients are at high CV risk, and use of aspirin or other antiplatelet agents may reduce their risk for myocardial infarctions and stroke. A recent KDIGO guideline[9] recommends that “adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible CV benefits.” However, it remains unclear how to identify the patients who may benefit from antiplatelet agents, and risk scores from the general population work poorly among CKD patients.

Antiplatelet agents should not routinely be prescribed to all CKD patients because the increased risk for major bleeding appears to outweigh the CV benefits, at least in CKD patients with low risk for atherosclerotic events.[49] Their use among CKD patients with overt atherosclerotic vascular disease is strongly recommended (see Chapter 85). However, dual-antiplatelet therapy should be limited to the very early period after acute myocardial infarction or after coronary stenting among CKD patients, whose bleeding risk with dual-antiplatelet therapy is much higher than in patients with intact kidney function.

CIRCULATING COAGULATION FACTORS

Despite their elevated bleeding risk, patients with advanced CKD also may show features of a hypercoagulable state. Although general measures of the coagulation system—prothrombin time and partial thromboplastin time—are within normal ranges, venous thromboembolism (VTE) occurs more frequently in patients with low glomerular filtration rate and/or high albuminuria than among individuals with intact kidney function. A variety of factors may contribute, which include elevated levels of factor VIII and vWF, and a variety of comorbidities, including immobilization, congestive heart failure, and obesity. Iatrogenic factors may additionally play a part in CKD-associated hypercoagulation, such as drug treatment (erythropoietin, corticosteroids), intravascular interventions, and devices.

THERAPEUTIC INTERVENTION

Components of the coagulation system are targets of many drugs for prevention or treatment of thrombotic disease, including unfractionated and low-molecular-weight heparin (LMWH), vitamin K antagonists (VKAs), and non–vitamin K antagonist oral anticoagulants (NOACs).

First, heparin is routinely used during HD for preventing clotting in the extracorporeal circulation. Thus, nearly all HD patients are exposed to potential side effects of heparin, which include an increased bleeding risk and some less frequent adverse events, of which the development of HIT is the most serious complication. HIT is a clinical syndrome induced by antibodies that bind to heparin and platelet factor IV complexes on the platelet surface and thereby cause platelet activation. Clinically, HIT often manifests with arterial or venous thrombosis; less frequent complications are venous limb gangrene, adrenal hemorrhagic necrosis, necrotizing skin lesions at heparin injection sites, and acute systemic reactions within a few minutes after exposure to unfractionated heparin or LMWH injections. Of note, many patients have heparin-dependent antibodies without clinically apparent HIT. Therefore, to avoid overdiagnosing HIT, immunologic tests should not be ordered in patients with a low clinical likelihood but focused on patients in whom HIT is suspected clinically (as suggested by the 4T score; Table 87.2). This is of particular importance for HD patients, in whom an incorrect diagnosis may result in the withdrawal of heparin treatment during HD and in the initiation of less established (and more expensive) anticoagulation strategies. In the absence of CKD-specific pathways, the diagnosis of HIT should follow recommendations from the general population. Here, the likelihood

TABLE 87.2

4Ts Score to Determine the Likelihood of Heparin-Induced Thrombocytopenia

Thrombocytopenia: compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the percent of platelet fall (select only one option)

Timing (of platelet count fall or thrombosis[a])

Day 0 = First day of most recent heparin exposure (select only one option)

Score = 2

Score = 1

Score = 0

>50% platelet fall and nadir of ≥20,000/μL and no surgery within preceding 3 days

>50% platelet fall but surgery within preceding 3 days or any combination of platelet fall and nadir that does not fit criteria for score 2 or score 0 (e.g., 30%–50% platelet fall or nadir 10–19)

Consistent with platelet fall days 5–10 but not clear (e.g., missing counts)

Platelet fall within 1 day of start of heparin and exposure to heparin in past 31–100 days

Platelet fall after day 10

Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants

Suspected thrombosis (awaiting confirmation with imaging)

Erythematous skin lesions at heparin

injection sites
Possible other cause is evident: sepsis
without proven microbial source,
thrombocytopenia associated with
initiation of ventilator, other

<30% platelet fall
Any platelet fall with nadir <10

Platelet fall day 5–10 after start of
heparin
Platelet fall within 1 day of start of
heparin and exposure to heparin
within past 5–30 days

Thrombosis (or other clinical
sequelae) (select only one option)

Confirmed new thrombosis (venous
or arterial)
Skin necrosis at injection site
Anaphylactoid reaction to intravenous
heparin bolus
Adrenal hemorrhage

Other cause for
thrombocytopeniab (select only
one option)

No alternative explanation for platelet
fall is evident

aTiming

of HIT should first be estimated with clinical prediction tools, and use of antigen assays for confirmation of HIT antibodies should focus on patients with high and intermediate clinical likelihood (Fig. 87.5). Importantly, these antigen assays for detection of HIT antibodies have a high sensitivity but poor specificity. Wherever available, functional assays (serotonin release assays or heparin-induced platelet activation) should be used to confirm positive findings from antigen assays in the majority of patients with suspected HIT.

Once a patient has a high or intermediate clinical probability of HIT, all heparin treatment must be stopped and alternative anticoagulation initiated. The most relevant treatment options are listed in Table 87.3. Of note, no VKA should be initiated at this stage because these agents may reduce activation of anticoagulatory protein C and thus further perpetuate the prothrombotic state.

Platelet fall day 4 or earlier without
exposure to heparin in past 100
days

Thrombosis suspected

Probable other cause present:
Within 72 h of surgery
Confirmed bacteremia/fungemia
Chemotherapy or radiation within past
20 days
DIC as a result of non-HIT cause
PTP
Platelet count <20 and given a drug
implicated in causing D-ITPc (see

list)
Nonnecrotizing skin lesions at LMWH injection site (presumed DTH)
Other

of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions.
points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present.

cDrugs implicated in D-ITP: Relatively common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban), quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin. Less common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fusidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list. See Fig. 87.5 for interpretation of score results.

DIC, Disseminated intravascular coagulation; D-ITP, drug-induced immune thrombocytopenia; DTH, delayed-type hypersensitivity; HIT, heparininduced thrombocytopenia; LMWH, low-molecular-weight heparin; PTP, posttransfusion purpura.

Modified from Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e495S–e530S.

bTwo

Diagnostic Workup of Suspected Heparin-Induced Thrombycytopenia
Heparin-induced thrombocytopenia (HIT) suspected

4Ts score ≤ 3
Low clinical probability

4Ts score ≥ 4
High/intermediate clinical probability

Depends on physician preference

Discontinue heparin immediately
and start nonheparin
anticoagulant

Discontinue heparin immediately
and consider nonheparin
anticoagulant

HIT antigen assay

HIT antigen assay

Positive

Negative

Moderate/
low titer

HIT
confirmed

FA*

Negative

Optical density

Optical density

High titer

Positive

Continue
heparin

High titer

HIT
excluded

FA*

Moderate/
low titer

HIT excluded

Fig. 87.5 Diagnostic Workup of Suspected Heparin-Induced Thrombocytopenia (HIT). Because of the high number of patients with antibodies against heparin without clinical HIT, a diagnostic algorithm is needed to have a high a priori likelihood of HIT before ordering antibody tests. There is no algorithm specific to patients with chronic kidney disease, and the diagnosis should be made as in patients with normal kidney function. *Confirm with functional assay (FA), if available. “4T” refers to a risk score based on four clinical parameters (thrombocytopenia, timing of platelet count fall or thrombosis, thrombosis [or other clinical sequelae], and other cause for thrombocytopenia). See Table 87.2 for a detailed description.

Additionally, anticoagulants are approved for prevention of thromboembolic stroke in patients with atrial fibrillation, for prevention and treatment of VTE (particularly deep vein thrombosis and pulmonary embolism), and for prevention of clotting in patients with mechanical heart valves. In the latter case, the need for lifelong anticoagulation with VKA is indisputable. Similarly, in patients with proximal deep vein thrombosis and symptomatic pulmonary embolism, anticoagulation is indicated for a minimum of 3 months. Recommendations on extended anticoagulation are mainly derived from the general population, in whom indefinite anticoagulation with either VKA or (preferably) NOACs (Table 87.4) may be considered in patients with unprovoked proximal deep vein thrombosis and symptomatic pulmonary embolism, whereas anticoagulation should be stopped after 3 months in patients with provoked VTE with one or more transient risk factors. In patients with active cancer and VTE, data from the general population suggest indefinite anticoagulation with LMWH or NOACs.

When considering indefinite anticoagulation in patients with advanced CKD, their elevated bleeding risk must be considered. Therefore, if extended oral anticoagulation is decided after VTE in a CKD patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) should be considered after 6 months of therapeutic anticoagulation, which is supported both by evidence from randomized trials and by guidelines.50 This is of particular importance, as dose reductions of NOACs in CKD patients with VTE do not fully follow recommendations for CKD patients with atrial fibrillation. Particularly, no dosage adjustment is recommended, but “use with caution” is recommended by the manufacturers of apixaban and rivaroxaban for any degree of reduced kidney function in the treatment of deep vein thrombosis and/or pulmonary embolism, whereas the manufacturer of edoxaban recommends 30 mg instead of (standard-dose) 60 mg edoxaban in patients with creatinine clearance of 15 to 50 mL/min.

For patients with advanced CKD, the use of anticoagulants in atrial fibrillation is controversial (see Chapter 85). In the general population, patients who have one or more risk factors for cerebral stroke or systemic embolization (defined as a CHA2DS2-VASc score of ≥1 in men and ≥2 in women) should receive oral anticoagulation. Similarly, use of warfarin (if adjusted to target an international normalized ratio [INR] of 2.0–3.0) has been shown to reduce stroke risk substantially in patients with stage 3a/3b CKD.51 In these patients, NOACs are at least

TABLE 87.3 Characteristics of Anticoagulants Used to Treat Patients With
Heparin-Induced
Thrombocytopenia
Characteristic

Argatroban

Danaparoid

Bivalirudin

Fondaparinux

Target
Elimination
Approved for patients with
HITa
Method of administration
Monitoring

Thrombin
Hepatobiliary
Treatment/PCI

Factor Xa (predominantly)
Renal
Treatment

Thrombin
Enzymatic (80%)/renal (20%)
PCI/cardiac surgery

Factor Xa
Renal
No

IV, SC
Anti-Xa level

Antidote available
Dialyzable

No
20%

IV
aPTT
ACT or ECT (high doses)
++
Potentially cross-reactive
with antilepirudin Ab
No
25%

SC
Anti-Xa level

Effect on INR
Immunologic features

IV
aPTT
ACT
+++
None

0
5% cross-reactivity with
HIT Abb
No
Yes

0
May cause HITc
No
20%

aIn

some countries (check with local health regulatory authorities).
significance is uncertain and routine testing for cross-reactivity is not recommended.
cCase reports only.
Ab, Antibodies; ACT, activated clotting time; aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous.
Modified from Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e495S–e530S.
bClinical

TABLE 87.4

Absorption and Metabolism of Novel Oral Anticoagulants
Dabigatran

Apixaban

Edoxaban

Rivaroxaban

Bioavailability

3%–7%

50%

62%

Prodrug
Clearance nonrenal/renal,
percent of absorbed
dosea
Liver metabolism: CYP3A4
involved
Absorption with food

Yes
20%/80%

No
73%/27%

No
50%/50%

66% without food, almost
100% with food
No
65%/35%

No

Minimal (<4% of elimination)

No effect

Yes (elimination, moderate
contribution ~25%)
No effect

Intake with food
recommended?
Absorption with H2B/PPI

No

No

6%–22% more; minimal
effect on exposure
No

−12%–30% (not clinically
relevant)
+25%
Dyspepsia 5%–10%
12–17 h

No effect

No effect

No effect

No effect
No problem
12 h

No effect
No problem
10–14 h

No effect
No problem
5–9 h (young), 11–13 h
(elderly)

Dose if Asian ethnicity
GI tolerability
Elimination half-life

Yes (hepatic elimination
~18%)
+39% more
Mandatory

[a]For clarity, data are presented as single values, which are the midpoint of ranges as determined in different studies.
H2B, H2 blocker; GI, gastrointestinal; PPI, proton pump inhibitor.
Modified from Steffel J, Verhamme P, Potpara TS, et al. 2018 European Heart Rhythm Association Practical Guide on the use of non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330–1393.

as efficient as VKAs for prevention of thromboembolic events but may cause fewer intracerebral bleeding events. For patients with creatinine clearance less than 30 mL/min, few data demonstrate the efficacy (i.e., prevention of thromboembolic events) and safety (i.e., major bleeding events) of either VKAs or NOACs because most prospective clinical trials excluded patients with advanced CKD. The notable exception is very-low-dose edoxaban, which was tested in the ELDER-CARE study that also included patients with stage 4 CKD. In these patients, 15 mg edoxaban consistently protected against ischemic stroke without

causing a prohibitively high bleeding risk.52 Moreover, VKA accelerates vascular calcification53 54 and possibly also CKD progression, in particular in higher doses.55 In dialysis patients with atrial fibrillation, retrospective cohort studies yielded conflicting findings on whether oral anticoagulation lowers stroke incidence (see Chapter 85).56 57
For the time being, patients with atrial fibrillation and at least moderate risk for thromboembolism (defined by CHA2DS2-VASc score ≥2 for women, and ≥1 for men) should be offered NOACs if they have mild to moderate CKD (CKD 1–3b), unless they have prohibitive high

risk for bleeding. For stage 4 and 5 CKD patients with atrial fibrillation, lack of evidence precludes strong recommendations whether to use NOACs or no anticoagulation, with the potential alternative option of left atrial appendage closure. Based upon data from a first randomized clinical trial, VKAs appear inferior to dose-reduced NOACs in dialysis patients, but it is uncertain whether NOACs are preferable to no anticoagulation.57

Both LMWH and NOACs require dose adjustment in patients with CKD because they undergo renal excretion. As of 2022, only one NOAC (apixaban) has been licensed for use among dialysis patients in the United States, but not yet in Europe. Compared with other NOACs, apixaban is characterized by the least accumulation in

CKD, but still requires (like all NOACs) dose adjustment for kidney function. Notably, pharmacokinetic studies (and subsequent recommendations on NOAC dosages) used creatinine clearance estimated with the Cockcroft-Gault equation. In clinical practice, eGFR is now mostly calculated using the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease–Epidemiology (CKD-EPI) formula. Substituting the latter for the former may cause large dosage errors, particularly when physicians fail to consider that the more recent equations yield estimates standardized for a body surface area of 1.73 m2, and nonstandardized measures of kidney function (as provided by the Cockcroft-Gault equation) are suggested for dose adjustment.

SELF-ASSESSMENT QUESTIONS

1. Which of the following diagnostic findings is reliable (sensitive and specific enough to be useful) in patients with CKD even in the presence of their typical immune dysfunction?
A. Fever as a sign of bacteremia
B. Radiologic infiltration on chest radiograph for pneumonia
C. Mendel-Mantoux skin reaction for tuberculosis
D. Blood culture for bacteremia
E. C-reactive protein for infection
2. Viral hepatitis is a typical complication of hemodialysis treatment. Which statement correctly describes viral hepatitis in advanced CKD?
A. HBV infection leads to chronic infection in the majority of affected CKD patients.
B. Acute HBV infection in CKD patients is typically severe, characterized by jaundice and fever.
C. HBV infection can be easily prevented in CKD patients by vaccination, as recommended to the general population.
D. The clinical course of hepatitis C infection is largely different in CKD patients and those with normal kidney function.

E. Standard hygienic precautions have largely failed to reduce HBV transmission in dialysis centers. Only vaccination succeeded in preventing nosocomial transmission.
3. The hemorrhagic diathesis in CKD patients is typically mirrored by which of the following?
A. Prolongation of the prothrombin time
B. Prolongation of the partial thromboplastin time
C. Severely thrombocytopenia
D. Hyperchromic anemia
E. None of these
4. The spectrum of interventions that may allow reducing hemorrhages in advanced CKD does not include which of the following?
A. Desmopressin
B. Conjugated estrogens
C. Tranexamic acid

D. Cryoprecipitates
E. Clopidogrel

REFERENCES

1. United States Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
2. James MT, Quan H, Tonelli M, et al. CKD and risk of hospitalization and death with pneumonia. Am J Kidney Dis. 2009;54:24–32.
3. Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhiya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. Kidney Int. 2020;98:1530–1539.
4. Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. Am J Kidney Dis. 2009;53:475–491.
5. Sester M, Sester U, Clauer P, et al. Tuberculin skin testing underestimates a high prevalence of latent tuberculosis infection in hemodialysis patients. Kidney Int. 2004;65:1826–1834.
6. London WT, DiFiglia M, Sutnick AI, Blumberg BS. An epidemic of hepatitis in a chronic hemodialysis unit. N Engl J Med. 1969;281:571–578.
7. Janssen RS, Mangoo-Karim R, Pergola PE, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31:5306–5313.
8. Barraclough KA, Wiggins KJ, Hawley CM, et al. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: a prospective open-label randomized controlled trial in nonresponders to primary vaccination. Am J Kidney Dis. 2009;54:95.
9. Clinical KDIGO. Practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1.
10. Remschmidt C, Wichmann O, Harder T. Influenza vaccination in patients with end-stage renal disease: systematic review and assessment of quality of evidence related to vaccine efficacy, effectiveness, and safety. BMC Med. 2014;12:244.
11. Butler AM, Layton JB, Dharnidharka VR, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccine among patients receiving maintenance hemodialysis. Am J Kidney Dis. 2020;75:72–83.
12. Miller G, Schaefer H, Yoder S, et al. A randomized, placebo-controlled phase I trial of live, attenuated herpes zoster vaccine in subjects with end-stage renal disease immunized prior to renal transplantation. Transpl Infect Dis. 2018;20:e12874.
13. Fuchshuber A, Kuhnemund O, Keuth B, et al. Pneumococcal vaccine in children and young adults with chronic renal disease. Nephrol Dial Transplant. 1996;11:468–473.
14. Bond TC, Spaulding AC, Krisher J, McClellan W. Mortality of dialysis patients according to influenza and pneumococcal vaccination status. Am J Kidney Dis. 2012;60:959–965.
15. Miyamoto T, Carrero JJ, Stenvinkel P. Inflammation as a risk factor and target for therapy in chronic kidney disease. Curr Opin Nephrol Hypertens. 2011;20:662–668.
16. Kudo S, Goto H. Intrarenal handling of recombinant human interleukin1alpha in rats: mechanism for proximal tubular protein reabsorption. J Interferon Cytokine Res. 1999;19:1161–1168.
17. Chen LP, Chiang CK, Chan CP, et al. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? Am J Kidney Dis. 2006;47:815–822.
18. Missailidis C, Hallqvist J, Qureshi AR, et al. Serum trimethylamineN-oxide is strongly related to renal function and predicts Outcome in chronic kidney disease. PLoS One. 2016;11:e0141738.
19. Girndt M, Sester U, Sester M, et al. The interleukin-10 promotor genotype determines clinical immune function in hemodialysis patients. Kidney Int. 2001;60:2385–2391.
20. Ziegler-Heitbrock L. Blood monocytes and their subsets: established features and open Questions. Front Immunol. 2015;6:423.
21. Auffray C, Fogg D, Garfa M, et al. Monitoring of blood vessels and

tissues by a population of monocytes with patrolling behavior. Science. 2007;317:666–670.

22. Ziegler-Heitbrock L, Ancuta P, Crowe S, et al. Nomenclature of monocytes and dendritic cells in blood. Blood. 2010;116:e74–e80.
23. Zawada AM, Rogacev KS, Rotter B, et al. SuperSAGE evidence for CD14++CD16+ monocytes as a third monocyte subset. Blood. 2011;118:e50–e61.
24. Heine GH, Ulrich C, Seibert E, et al. CD14(++)CD16(+) monocytes but not total monocyte numbers predict cardiovascular events in dialysis patients. Kidney Int. 2008;73:622–629.
25. Tacke F, Alvarez D, Kaplan TJ, et al. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. J Clin Invest. 2007;117:185–194.
26. Diet F, Pratt RE, Berry GJ, et al. Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. Circulation. 1996;94:2756–2767.
27. Ulrich C, Heine GH, Seibert E, et al. Circulating monocyte subpopulations with high expression of angiotensin-converting enzyme predict mortality in patients with end-stage renal disease. Nephrol Dial Transplant. 2010;25:2265–2272.
28. Trojanowicz B, Ulrich C, Seibert E, et al. Uremic conditions drive human monocytes to pro-atherogenic differentiation via an angiotensindependent mechanism. PLoS One. 2014;9:e102137.
29. Trojanowicz B, Ulrich C, Kohler F, et al. Monocytic angiotensinconverting enzyme 2 relates to atherosclerosis in patients with chronic kidney disease. Nephrol Dial Transplant. 2016.
30. Dopheide JF, Zeller GC, Kuhlmann M, et al. Differentiation of monocyte derived dendritic cells in end stage renal disease is skewed towards accelerated maturation. Adv Clin Exp Med. 2015;24:257–266.
31. Agrawal S, Gollapudi P, Elahimehr R, et al. Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPSstimulated cytokine production. Nephrol Dial Transplant. 2010;25:737–746.
32. Girndt M, Köhler H, Schiedhelm-Weick E, et al. T-cell activation defect in hemodialysis patients: evidence for a role of the B7/CD28 pathway. Kidney Int. 1993;44:359–365.
33. Sester U, Sester M, Hauk M, et al. T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. Nephrol Dial Transplant. 2000;15:1217–1223.
34. Afzali B, Edozie FC, Fazekasova H, et al. Comparison of regulatory T cells in hemodialysis patients and healthy controls: implications for cell therapy in transplantation. Clin J Am Soc Nephrol. 2013;8:1396–1405.
35. Fernandez-Fresnedo G, Ramos MA, Gonzalez PM, et al. B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. Nephrol Dial Transplant. 2000;15:502–510.
36. Kim KW, Chung BH, Jeon EJ, et al. B cell-associated immune profiles in patients with end-stage renal disease (ESRD). Exp Mol Med. 2012;44:465–472.
37. Yoon JW, Pahl MV, Vaziri ND. Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. Kidney Int. 2007;71:167–172.
38. Kalantar-Zadeh K, Brennan ML, Hazen SL. Serum myeloperoxidase and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2006;48:59–68.
39. Anding K, Gross P, Rost JM, et al. The influence of uraemia and haemodialysis on neutrophil phagocytosis and antimicrobial killing. Nephrol Dial Transplant. 2003;18:2067–2073.
40. Ottonello L, Gnerre P, Bertolotto M, et al. Leptin as a uremic toxin interferes with neutrophil chemotaxis. J Am Soc Nephrol. 2004;15:2366–2372.
41. Craddock PR, Fehr J, Dalmasso AP, et al. Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. J Clin Invest. 1977;59:879–888.

42. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial. 2006;19:317–322.
43. Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. Semin Dial. 2009;22:279–286.
44. Steiner RW, Coggins C, Carvalho AC. Bleeding time in uremia: a useful test to assess clinical bleeding. Am J Hematol. 1979;7:107–117.

References

45. Linthorst GE, Avis HJ, Levi M. Uremic thrombocytopathy is not about urea. J Am Soc Nephrol. 2010;21:753–755.
46. Hedges SJ, Dehoney SB, Hooper JS, et al. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol. 2007;3:138–153.
47. Manno C, Bonifati C, Torres DD, Campobasso N, Schena FP. Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. Am J Kidney Dis. 2011;57:850–855.
48. Ma TK, Chow KM, Kwan BC, et al. Manifestation of tranexamic acid toxicity in chronic kidney disease and kidney transplant patients: a report of four cases and review of literature. Nephrology. 2016.
49. Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet therapy to prevent hemodialysis vascular access failure: systematic review and meta-analysis. Am J Kidney Dis. 2013;61:112–122.
50. Konstantinides SV, Meyer G, Becattini C, et al. ESC Scientific Document group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543–603.
51. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2599–2604.

52. Okumura K, Akao M, Yoshida T, et al. Low-dose edoxaban in very Elderly patients with atrial fibrillation. N Engl J Med. 2020;383:1735–1745.
53. van Gorp RH, Schurgers LJ. New Insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs). Nutrients. 2015;7:9538–9557.
54. De Vriese AS, Caluwé R, Pyfferoen L, et al. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie Study. J Am Soc Nephrol. 2020;31:186–19.
55. Bohm M, Ezekowitz MD, Connolly SJ, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY Trial. J Am Coll Cardiol. 2015;65:2481–2493.
56. Tan J, Liu S, Segal JB, et al. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. BMC Nephrol. 2016;17:157.
57. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146–1154.

88

Bone and Mineral Disorders in Chronic Kidney Disease

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DEFINITION

PATHOGENESIS

Disturbances of mineral metabolism are ubiquitous in chronic kidney disease (CKD) and lead to serious and debilitating complications unless these abnormalities are addressed and treated. The spectrum of the condition includes abnormal concentrations of serum calcium, phosphate, and magnesium as well as disorders of parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and vitamin D metabolism. These abnormalities and other factors related to the uremic state affect the skeleton and result in the complex disorders of bone known as renal osteodystrophy. This term should be used exclusively to define the bone disease associated with CKD, but it is important to acknowledge that aging-related and postmenopausal osteoporosis can exist in parallel. The clinical, biochemical, and imaging abnormalities previously identified as correlates of renal osteodystrophy are now defined more broadly as a syndrome called chronic kidney disease–mineral and bone disorder (CKD-MBD).1 The spectrum of skeletal abnormalities seen in renal osteodystrophy includes (Fig. 88.1):

- Osteitis fibrosa, a manifestation of hyperparathyroidism characterized by increased osteoclast and osteoblast activity, peritrabecular fibrosis, and increased bone turnover.
- Osteomalacia, a manifestation of defective mineralization of newly formed osteoid most often caused by aluminum deposition; bone turnover is decreased.
- Adynamic bone disease (ABD), a condition characterized by abnormally low bone turnover.
- Osteopenia or osteoporosis.
- Combinations of these abnormalities termed mixed renal osteodystrophy.
- Other abnormalities with skeletal manifestations (e.g., chronic acidosis, β2-microglobulin amyloidosis [Aβ2M amyloidosis]).

Several biochemical and hormonal abnormalities associated with CKD contribute to renal osteodystrophy and can be affected by efforts at prevention and treatment. The major factors may vary as CKD progresses (Fig. 88.3). Similarly, the predominance of one particular pathogenetic mechanism over another may contribute to the heterogeneity of bone disorders. We therefore discuss separately the two major entities: highand low-turnover osteodystrophy.

EPIDEMIOLOGY

The prevalence of the various types of renal osteodystrophy in patients with end-stage kidney disease (ESKD) is illustrated in Fig. 88.2 2 In patients on hemodialysis (HD), osteitis fibrosa is declining, whereas ABD is increasing in prevalence, at least in White patients.3 In Black patients on dialysis, osteitis fibrosa is still the most prevalent form. In patients on peritoneal dialysis (PD), those with diabetes, and the elderly, adynamic bone lesion has been the dominant form of renal osteodystrophy for decades. Osteomalacia represents only a small fraction of cases in either group but is more common in certain ethnic groups, particularly South Asians. Skeletal abnormalities associated with CKD can begin at relatively preserved levels of estimated glomerular filtration rate (eGFR; ~50 mL/min/1.73 m2).

OSTEITIS FIBROSA: HYPERPARATHYROIDISM—HIGH-TURNOVER RENAL BONE DISEASE

Elevated levels of PTH in blood, hyperplasia of the parathyroid glands, and elevations in FGF-23 are seen once eGFR declines below approximately 50 mL/min/1.73 m2. Although the level of free (i.e., non–protein bound) calcium in blood is normally the principal determinant of PTH secretion, several metabolic disturbances associated with CKD also alter the secretion of PTH.

Abnormalities of Calcium Metabolism

There are three main body pools of calcium: the bony skeleton (mineral component), the intracellular pool (mostly protein bound), and the extracellular pool (see Chapter 11). The calcium in the extracellular pool is in continuous exchange with that of bone and cells and is altered by diet and excretion. Calcium metabolism mainly depends on the close interaction of two hormone systems, PTH and vitamin D, although a minor and ill-defined role for calcitonin may exist as well. CKD leads to perturbations of both major systems, with adverse consequences on the skeleton. Total serum calcium tends to decrease in parallel with GFR because of phosphate retention, decreased kidney production of 1,25-dihydroxyvitamin D (calcitriol), reduced intestinal calcium absorption, and skeletal resistance to the calcemic action of PTH. However, free calcium levels remain within the normal range in most patients4 because of compensatory hyperparathyroidism. Because calcium is a major regulator of PTH secretion, persistent hypocalcemia is a powerful stimulus for development of hyperparathyroidism and also contributes to parathyroid growth.

Abnormalities of Phosphate Metabolism

With progressive CKD, phosphate is retained, at least, transiently, by the failing kidney. However, hyperphosphatemia usually does not become evident before stage 4 CKD. Until then, compensatory hyperparathyroidism and increases in circulating FGF-23 result in increased phosphaturia, maintaining serum phosphate levels in the normal range.5

Percentage of Patients Exhibiting
Elevated Circulating Levels of Calcium,
Phosphate, iPTH, 25OH-Vitamin D 3,
Calcitriol, and FGF-23 in Advancing CKD

Skeletal Abnormalities in
Renal Osteodystrophy
Adynamic bone
Osteomalacia

Normal

Mild

Osteitis fibrosa

100

Low
turnover

High
turnover

Calcium, calcitriol

Patients (%)

Mixed
Hyperparathyroidism

80
60

Calcium < 8.4 mg/dL (2.1 mmol/L)
Phosphate > 4.6 mg/dL (1.5 mmol/L)
iPTH > 65 pg/mL

40
20

Aluminum

0

Fig. 88.1 Spectrum of Renal Osteodystrophy. The range of skeletal abnormalities in renal bone disease encompasses syndromes with both high and low bone turnover.

60

100
Patients (%)

Prevalence of renal osteodystrophy in
patients with end-stage kidney disease

80

>80 79-70 69-60 59-50 49-40 39-30 29-20 <20
eGFR (mL/min/1.73 m2)
25(OH)D3 < 15 ng/mL

1,25(OH)2D3 < 22 pg/mL

60
40
20

50

0

40
30

100

20

80

10
0
1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005
Years
HPT

OM

MUO
ABD

Fig. 88.2 Prevalence of renal osteodystrophy in patients with end-stage kidney disease. ABD, Adynamic bone disease; HPT, high-turnover renal osteodystrophy; MUO, mixed uremic osteodystrophy; OM, osteomalacia. (Modified from Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: Analysis of 630 bone biopsies in black and white patients. J Bone Miner Res. 2011;26:1368–1376; and Malluche HH, Mawad H, Monier-Faugere MC. The importance of bone health in end-stage renal disease: Out of the frying pan, into the fire? Nephrol Dial Transplant. 2004;19[Suppl 1]:i9–13.)

Phosphate retention leads to hyperparathyroidism by decreasing serum free calcium, which, in turn, stimulates the secretion of PTH (Fig. 88.4). In addition, phosphate interacts with the calcium sensing receptors on parathyroid cells, attenuating the suppressive effects of calcium on PTH.6 Thus, a new steady state is achieved in which serum phosphate is restored to normal at the expense of a sustained high level of PTH. This cycle is repeated as kidney function declines until sustained and severe hyperparathyroidism is present. Second, phosphate retention leads to decreased kidney production of calcitriol, either directly or by increasing the levels of FGF-23 (which decreases the activity of 1α-hydroxylase).
The decrease in calcitriol allows increases in PTH gene transcription and also decreases intestinal calcium absorption, leading to hypocalcemia, which, in turn, also stimulates PTH secretion. Third, hyperphosphatemia

Patients (%)

% Patients/yr

1003

60

>80 79-70 69-60 59-50 49-40 39-30 29-20 <20
eGFR (mL/min/1.73 m2)
FGF-23 > 100 RU/mL

iPTH > 65 pg/mL
Phosphate > 4.6 mg/dL
(1.5 mmol/L)

40
20
0

>70 69-60 59-50 49-40 39-30 29-20 <20

eGFR (mL/min/1.73 m2)

Fig. 88.3 Percentage of patients exhibiting elevated circulating levels of calcium, phosphate, intact parathyroid hormone (iPTH), 25OH-vitamin D3, calcitriol, and fibroblastic growth factor-23 (FGF-23) in advancing chronic kidney disease (CKD). Particularly in early CKD stages, there is wide variability at the individual level, and some patients, for example, may exhibit increased FGF-23 and normal iPTH, whereas others may have elevated iPTH levels with normal FGF-23 or elevations of both. eGFR, Estimated glomerular filtration rate. (Data from Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int. 2007;71:31–; and Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011;79:1370–1378.)

is associated with resistance to the actions of calcitriol in the parathyroid glands, which also favors development of hyperparathyroidism and induces resistance to the actions of PTH in bone. Finally, phosphate per se appears to affect PTH secretion independently of changes in serum calcium or serum calcitriol.7 8 Phosphate may have an effect on parathyroid growth independent of serum calcium.9 10 Regardless of the mechanism by which phosphate retention causes hyperparathyroidism, experimental studies suggest that restriction of dietary phosphate in proportion to the

Phosphate Retention and Secondary Hyperparathyroidism
Hyperphosphatemia

Skeletal
PTH resistance

↑ Parathyroid
cell growth

Calcitriol resistance
in parathyroid glands

↓ Calcitriol

Parathyroid
resistance to calcium

Decreased intestinal
calcium absorption

Hypocalcemia
↑ PTH secretion

Fig. 88.4 Role of Phosphate Retention in the Pathogenesis of Secondary Hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone (PTH) secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol resistance. Hyperphosphatemia also has direct effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth.

decrease in GFR can prevent development of hyperparathyroidism, but it is uncertain whether this is clinically relevant. FGF-23 also appears to act directly on the parathyroid gland, with inhibitory effects on PTH secretion and parathyroid growth.[11,12] This effect is dependent on parathyroid presence of the coreceptor α-klotho, although expression of this coreceptor is reduced in CKD. Elevated FGF-23 levels also lead to a substantial reduction in calcitriol production, which, in turn, contributes to hyperparathyroidism. These various actions may partially explain the association between higher levels of FGF-23 and adverse clinical outcomes.[13]

Abnormalities of Vitamin D Metabolism

The conversion of 25-hydroxyvitamin D to its active metabolite 1,25-dihydroxyvitamin D occurs mainly in the kidney by the enzyme 1α-hydroxylase. Extrarenal production of calcitriol also occurs and contributes to the circulating levels of calcitriol. Kidney calcitriol production progressively declines in parallel with eGFR as a result of several mechanisms (Fig. 88.5).

Calcitriol production is compromised in CKD by a reduction in 25-hydroxyvitamin D levels[14] and the decrease in GFR, which further limits the delivery of 25-hydroxyvitamin D to the site of the 1α-hydroxylase in the proximal tubule. Early increases of FGF-23 in CKD likely have a prominent role on vitamin D metabolism because it inhibits 1α-hydroxylase activity but also promotes catabolism of vitamin D. Phosphate retention, besides increasing FGF-23, may also directly decrease the activity of 1α-hydroxylase. The ensuing reductions in calcitriol levels directly and indirectly contribute to the pathogenesis of hyperparathyroidism as described earlier (Fig. 88.6). Low levels of calcitriol directly release the gene for PTH from suppression by the vitamin D receptor and allow increased PTH secretion. In many tissues, vitamin D regulates its own receptor by positive feedback;

in CKD, the vitamin D receptor content is decreased in parathyroid tissue. Administration of calcitriol increases the vitamin D receptor content in the parathyroid glands coincident with the suppression of PTH secretion. Studies in vitro have shown that calcitriol is a negative growth regulator of parathyroid cells and therefore calcitriol deficiency in patients with CKD may facilitate parathyroid cell proliferation. Other direct consequences of low levels of calcitriol contributing to the pathogenesis of secondary hyperparathyroidism include an increase in the parathyroid set-point for calcium-regulated PTH secretion and possibly a decrease in the expression of calcium receptors.

Mechanisms Contributing to Decreased
Levels of Calcitriol in CKD
Kidney disease

↑ Pi

↓ GFR

↓ 25 (OH)D3

↑ FGF-23

↓ 1.25 (OH)2 D3

↑ C-PTH fragments

Fig. 88.5 Mechanisms contributing to decreased levels of calcitriol in chronic kidney disease (CKD). C-PTH, Carboxyl-terminal parathyroid hormone; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; Pi, inorganic phosphate.

Low levels of calcitriol also may indirectly promote the development of hyperparathyroidism by reducing intestinal absorption of calcium, leading to hypocalcemia and stimulation of PTH release.

Abnormalities of Parathyroid Gland Function

CKD is associated with intrinsic abnormalities in parathyroid gland function, in addition to those caused by hypocalcemia, low levels of calcitriol, and skeletal resistance to the actions of PTH (Box 88.1). Parathyroid hyperplasia is an early finding in CKD. In experimental models, hyperplasia begins within a few days after the induction of CKD and can be prevented by dietary phosphate restriction or by the use of calcimimetic agents.[10 15] Resected parathyroid glands from patients with severe hyperparathyroidism have nodular areas throughout the gland, which represent monoclonal expansions of parathyroid cells. Within these nodules, there is decreased expression of vitamin D receptors, calcium receptors, and α-klotho expression, the cofactor for FGF-23 signaling, reducing the ability of drugs such as active vitamin D and calcimimetics to bind to and treat the gland hyperplasia.

Calcitriol and Secondary Hyperparathyroidism
Low levels of calcitriol

Direct effects

Indirect effects

- Decreased repression of parathyroid hormone (PTH) gene transcription
- Decreased parathyroid vitamin D receptors
- Decreased repression of parathyroid cell proliferation
- Decreased expression of calcium receptor
- Increased set-point for calcium-regulated PTH secretion

- Decreased intestinal calcium absorption
- Skeletal resistance to the calcemic action of PTH

Abnormal parathyroid function

Hypocalcemia

Hyperparathyroidism

Fig. 88.6 Role of low levels of calcitriol in the pathogenesis of secondary hyperparathyroidism.

The parathyroid calcium receptor is centrally involved in the regulation of PTH secretion by calcium.[16] Its expression and synthesis are decreased in the parathyroid glands from hyperparathyroid patients. In addition, phosphate impairs the calcium sensitivity of the receptor. These mechanisms lead to increased concentrations of calcium to suppress PTH release from the parathyroid cells of uremic patients compared with healthy subjects. Thus, the presence of severe CKD appears to increase the concentration of calcium that is required to substantially decrease PTH release from the parathyroid.

Abnormal Skeletal Response to Parathyroid Hormone

In patients with CKD, there is an impaired response of serum calcium to the administration of PTH and a delay in the recovery from induced hypocalcemia in the presence of larger increments in PTH levels. Thus, in CKD the skeleton is relatively resistant to the calcemic actions of PTH. The resultant decrease in serum calcium levels stimulates PTH secretion and contributes to the pathogenesis of secondary hyperparathyroidism. Factors involved in the skeletal resistance to PTH in CKD include decreased levels of calcitriol, downregulation of the PTH receptor, and phosphate retention. In addition, circulating fragments of PTH, truncated at the N-terminus, have been suggested to oppose the calcemic actions of PTH, possibly acting at a presumed receptor for the C-terminal region of PTH.[17,18]

Clinical Manifestations of High-Turnover Renal

Osteodystrophy

Clinical manifestations of hyperparathyroidism are usually nonspecific and often preceded by biochemical or imaging abnormalities. One specific feature is the increased risk of fractures, typically of long bones, sometimes associated with brown tumors (see later discussion). Nonspecific aches and pains are more common; occur in the lower back, hips, and legs, aggravated by weight bearing; and can be debilitating. Acute, localized bone pain can occur and may be suggestive of acute arthritis. Pain around joints may be caused by acute periarthritis, which is associated with periarticular deposition of calcium phosphate crystals, especially in patients with marked hyperphosphatemia. The symptoms may be confused clinically with gout or pseudogout and often respond to nonsteroidal antiinflammatory drugs (NSAIDs).

BOX 88.1

Parathyroid Abnormalities in Chronic Kidney Disease

- Parathyroid gland hyperplasia: diffuse, nodular
- Decreased expression of vitamin D receptors
- Decreased expression of calcium receptors
- Decreased expression of α-klotho
- Increased set-point of calcium-regulated parathyroid hormone secretion

The gradual onset of muscle weakness is also common in patients with ESKD. Many factors are probably involved in its pathogenesis, including hyperparathyroidism and abnormalities of vitamin D. Aβ2M (see later discussion) should be considered in the differential diagnosis in very-long-term dialysis patients.

Bone abnormalities may occur in patients with severe hyperparathyroidism, particularly in children, and are manifested on radiographs by subperiosteal erosions, resorption of terminal digits. In adults, deformities arise as a result of fractures. Fractures of the axial skeleton can lead to kyphoscoliosis or chest wall deformities. Slipped epiphysis may occur in children, and frank rachitic features are occasionally evident. Growth retardation is also common in children, and although some improvement has been shown with calcitriol, this is not universal.

Extraskeletal calcifications are frequently encountered in patients with advanced CKD and are aggravated by persistent elevation of the calcium-phosphate product. Most commonly, vascular calcifications are seen, but calcifications may occur in other sites, such as the lung, myocardium, and periarticular areas (Fig. 88.7).

In the skin, hyperparathyroidism can manifest as pruritus (see Chapter 91). Rarely, it can also underlie the development of calciphylaxis (calcific uremic arteriolopathy; see Figs. 91.6 and 91.7).

Diagnosis and Differential Diagnosis

In addition to the clinical manifestations of renal osteodystrophy, a variety of biochemical and radiographic techniques are helpful to establish the specific diagnosis and guide the initiation and adjustment of therapy. Although bone biopsy is not widely used in clinical practice, it remains the gold standard for the diagnosis of renal osteodystrophy and the most specific guide for treatment decisions.

Serum Biochemistry

The levels of free calcium and phosphate in serum are usually normal in patients with mild to moderate CKD. Normally in stage 4 CKD the levels of serum calcium tend to fall and hyperphosphatemia manifests. Hypercalcemia may result from the administration of large doses of calcium-containing antacids or vitamin D metabolites or from severe hyperparathyroid bone disease. It is important to identify the cause of hypercalcemia in patients with CKD (see Chapter 11) because the management will vary greatly according to the cause. Also, the levels of serum calcium and phosphate, when used alone, are not useful in predicting the specific type of bone disease.

Parathyroid Hormone

Measurements of PTH are important for diagnostic purposes and therapeutic guidance in the management of renal osteodystrophy. With kidney impairment, there is accumulation of circulating PTH fragments, which complicates the interpretation of PTH assays, including the two-site immunometric assays, which were thought to measure

A

B

C

Fig. 88.7 Extraskeletal Calcification in Kidney Failure. (A) Arterial calcification (arrows). (B) Pulmonary calcification. (C) Periarticular calcification (arrows).

“intact” PTH (iPTH). Refinements in PTH assays have demonstrated that these iPTH assays also measure some large fragments of PTH, which are truncated at the N-terminus. More specific assays for socalled “biointact” PTH (PTH 1–84) have been developed that exclude these fragments from measurement, but their clinical superiority over iPTH is not established.19–21 Standardization needs to be improved among different PTH assays from various laboratories and various manufacturers of assay reagents. With existing iPTH assays (upper limit of the reference range, ~60 pg/mL), only values at the extremes are useful in the noninvasive diagnosis of renal osteodystrophy. In dialysis patients, iPTH levels greater than approximately 600 pg/mL are characteristic of patients with osteitis fibrosa. The threshold values for earlier stages of CKD are not well defined, but there is an element of skeletal resistance to PTH in patients with CKD, and higher levels of PTH promote phosphaturia. Therefore, supranormal levels of PTH appear to be adaptive even in earlier stages of CKD. Serial measurements of PTH are useful in the initial evaluation of patients with renal osteodystrophy and are essential to assess response to therapy and to avoid overtreatment and undertreatment because either can have detrimental effects on bone. There are marked differences among commercial PTH assay results so that precise recommendations of desired ranges cannot reliably be provided and results obtained in different laboratories cannot be easily compared.22

Vitamin D Metabolites

The levels of calcitriol in patients with CKD are not helpful in differentiating the histologic lesions of renal osteodystrophy. Measurements of calcitriol are not used routinely for diagnostic purposes unless extrarenal production of this metabolite is suspected, as in granulomatous disorders (see Chapter 11).

Vitamin D deficiency in CKD rarely results in osteomalacia in the United States and Europe but may contribute to hyperparathyroidism. In patients with CKD and marked proteinuria, there is loss of vitamin D–binding protein in the urine, which may result in decreased levels of 25-hydroxyvitamin D. Vitamin D deficiency may be encountered in patients with limited sun exposure, in those with intestinal malabsorption or malnutrition, and in susceptible racial groups, particularly South Asians. Assessment of vitamin D nutrition is by measurement of serum 25-hydroxyvitamin D3

Markers of Bone Formation and Bone Resorption

Levels of circulating alkaline phosphatase (AP) offer an approximate index of osteoblast activity in patients with CKD. High levels are commonly present in hyperparathyroid bone disease. The discriminatory power of AP measurements is enhanced by measurement of γ glutamyl transferase (γGT), which lowers the likelihood of the liver of source of elevated AP if γGT is normal, and bone-specific AP (BAP) isoenzyme, especially in conjunction with PTH values. Serial measurements of AP may be useful in assessing the progression of bone disease. Amino-terminal propeptide of type I procollagen (PINP) may be useful as a biomarker of bone formation, but the level of the monomeric form is dependent on kidney function, which complicates its interpretation in CKD. However, assays detecting trimeric (intact) P1NP do not have this limitation. Tartrate-resistant acid phosphatase and collagen degradation products are both markers of osteoclastic activity but are considered investigational at present.

Radiology of the Skeleton

Routine radiographic examination of the skeleton is relatively insensitive for the diagnosis of renal osteodystrophy, and radiographs can appear virtually normal in patients with severe histologic evidence of renal osteodystrophy. However, subperiosteal erosions are often present in severe secondary hyperparathyroidism, detected in the hands (Fig. 88.8), clavicles, and pelvis. Skull radiographs may show focal radiolucencies and a ground-glass appearance, known as pepper pot skull. Osteosclerosis of the vertebrae is responsible for the “ruggerjersey” appearance of the spine (Fig. 88.9). Very rarely, brown tumors, focal collections of giant cells and typical of severe hyperparathyroidism, are seen as well-demarcated radiolucent zones in long bones, clavicles, and digits (Fig. 88.10) and may be confused with osteolytic metastases. Looser zones or pseudofractures are characteristic of osteomalacia. Routine skeletal radiographs are not indicated unless there are symptoms. Novel imaging techniques such as magnetic resonance imaging (MRI), positron-emission tomography (PET), and highresolution peripheral quantitative computed tomography (CT; HRpQCT) are considered research tools, but some may find their way to clinical practice in the future.

Measurements of Bone Density

Dual-energy x-ray absorptiometry (DEXA) is widely used to assess bone density. Although DEXA does not identify the nature of the underlying osteodystrophy or distinguish this from osteoporosis, it does allow prediction of fracture risk in patients with any stage of CKD, including those after kidney transplantation. Vascular and soft tissue calcifications may contribute to errors in bone density measurements.

Fig. 88.8 Subperiosteal Erosions in Secondary Hyperparathyroidism. Severe subperiosteal erosions as a manifestation of hyperparathyroidism (arrows). The extensive scalloped appearance of the middle phalanx on the left (arrowheads) represents a small brown tumor.

Fig. 88.9 “Rugger-Jersey Spine” in Secondary Hyperparathyroidism. Vertebral bodies show the increased density of the ground plates and central radiolucency, which gives the striped appearance of a rugby jersey.

Bone Biopsy

Biopsy of bone and the microscopic analysis after double tetracycline labeling provide a deﬁnitive and quantitative diagnosis of renal osteodystrophy.[23] To standardize reports on bone histology, the Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Epidemiology Collaboration (CKD-MBD) work group proposed the TMV classiﬁcation, an assessment of turnover (T), mineralization (M), and bone volume (V).[1] Bone formation rate is assessed by the administration of two different tetracyclines spaced apart (e.g., tetracycline 500 mg three times daily for 2 days, followed by a 10-day interval, then demeclocycline 300 mg three times daily for 3 days, but several other labeling schemes exist) and biopsy 4 days later. Quantitation of bone mineralization rate is achieved by measuring the distance and surface between the two ﬂuorescent tetracycline bands. Although noninvasive testing is useful to distinguish low or normal from high bone turnover, there is considerable overlap, and therefore biopsy might be required for deﬁnitive diagnosis when biochemistry is not conclusive (e.g., PTH in recommended range but BAP elevated, hypercalcemia with PTH only modestly elevated, or bone pain), and especially so when treatment decisions depend on bone histology. Osteitis ﬁbrosa (hyperparathyroid bone disease) is characterized by increased bone turnover, increased number and activity of osteoblasts and osteoclasts, and variable amounts of peritrabecular ﬁbrosis (Fig. 88.11A). Osteoid may be increased but usually has a woven pattern distinct from the normal lamellar appearance. Osteomalacia is characterized by increased osteoid seam width, increase in the trabecular surface covered with osteoid, and decreased bone mineralization as assessed by tetracycline labeling (see Fig. 88.11D). The presence of aluminum can be detected on the mineralization front by speciﬁc staining (see Fig. 88.11C). Aluminum-related bone disease is deﬁned by aluminum staining exceeding 15% of the trabecular surface and a bone formation rate of less than 220 mm^2/day. Features of osteitis ﬁbrosa may occur together with features of osteomalacia; the combination is termed mixed renal osteodystrophy.

Fig. 88.10 Brown tumor (arrow) in a hemodialysis patient with severe hyperparathyroidism. The tumor can easily be confused with a lytic bone metastasis.

Treatment of High-Turnover Bone Disease

Prevention is the primary goal in management of renal osteodystrophy. Therapy for hyperparathyroidism ideally should be initiated in CKD stage 3 so parathyroid gland hyperplasia can be prevented. Because renal osteodystrophy is usually asymptomatic early in the course of CKD, the relevance of secondary hyperparathyroidism is frequently overlooked. By the time CKD is advanced, patients may have already developed signiﬁcant skeletal abnormalities or nodular parathyroid hyperplasia, and then more aggressive therapy is required to prevent the long-term consequences of renal osteodystrophy. The successful approach to the prevention and management of this disorder involves the integration of a variety of measures directed toward the suppression of PTH secretion and prevention of parathyroid hyperplasia.

Prevention of Hypocalcemia

Hypocalcemia should be corrected because it is a potent stimulus for PTH secretion. Low albumin may mask hypocalcemia unless free calcium is measured. The initial approach to therapy for hypocalcemia in patients with mild to moderate CKD is the administration of calcium supplements such as calcium carbonate, taken between meals with

*

B

A

C

D

Fig. 88.11 Bone Histology in Renal Osteodystrophy. (A) Osteitis fibrosa: characteristic manifestations of severe hyperparathyroidism with increased multinucleated osteoclasts and osteoblast activity and peritrabecular fibrosis (stained blue, arrow). (B) Adynamic bone disease: there is no cellular activity along the bone surface and no osteoid visible. (C) Mixed renal osteodystrophy: there is evidence of active osteoclasts on one bone surface (arrowhead) and evidence of thickened osteoid (stained red; asterisk) indicating a mineralization defect on the other. (D) Osteomalacia: marked excess of unmineralized osteoid (stained red) surrounding the mineralized bone (stained blue).

increasing doses as required. Vitamin D status should be assessed by measuring 25-hydroxyvitamin D, and deficiency should be corrected if the level is less than 30 ng/mL; 1,25-dihydroxyvitamin D has an 8-hour half-life and so is not helpful for assessing vitamin D status. The efficacy of therapy can be assessed with follow-up determinations of serum calcium and PTH. Adjunctive therapy with active vitamin D sterols should be considered if hyperparathyroidism or hypocalcemia persists. In patients with ESKD, active vitamin D sterols are often required. In dialysis patients, the goal is to achieve levels of iPTH that are approximately two to nine times greater than the upper limit of the assay used.24 Also, iPTH trends over time should be closely monitored. In CKD stages 3 to 5, progressive rises in iPTH above the normal range should be abrogated by correction of hypocalcemia, vitamin D deficiency, and hyperphosphatemia. The latter should be corrected before the correction of hypocalcemia.

Control of Phosphate

Control of phosphate is the cornerstone of effective management of secondary hyperparathyroidism. In mild to moderate CKD, a normal serum phosphate concentration does not necessarily indicate normal parathyroid status, and except for the late stages of CKD, normophosphatemia may be maintained at the expense of elevated serum PTH and FGF-23. Although it is debated whether phosphate-lowering strategies (like dietary restrictions and phosphate binders) are useful if phosphate levels are within the normal range, overt hyperphosphatemia clearly contributes to hyperparathyroidism.

Dietary Phosphate Restriction

Dietary phosphate restriction can prevent excessive PTH synthesis, secretion, and parathyroid cell proliferation in experimental animals with mild CKD, but the clinical effectiveness of this approach is not proven. Accordingly, restriction of dietary phosphate intake might be considered in patients with CKD stage 2 or 3. The input of a dietician is essential. Protein restriction and limiting dairy products, in particular processed foods containing high amounts of added phosphate, are the mainstays of the regimen. Phosphate-protein restriction increases the serum levels of calcitriol in patients with mild to moderate CKD. However, restriction of phosphate by severe dietary protein restriction below 0.8 g/kg/day may lead to protein-calorie malnutrition.

Phosphate Binders

Although dietary phosphate restriction is usually sufficient in early CKD to treat hyperphosphatemia, this becomes more difficult as kidney function deteriorates. Agents that bind ingested phosphate in the intestinal lumen to limit its absorption are then usually indicated, in addition to dietary restriction. Compounds used for this purpose include calcium-containing antacids; magnesium salts; non–calciumcontaining, non–aluminum-containing phosphate binders; and aluminum salts (Fig. 88.12). Several phosphate binders, especially in advanced CKD, have to be given in large numbers (often accounting for 50% of the daily pill burden) and consequently patient adherence with the medication is a major problem, especially because gastrointestinal (GI) side effects (e.g., nausea, vomiting, constipation, diarrhea) occur frequently.

Aluminum-containing antacids are effective phosphate binders, but their long-term use is discouraged in patients with CKD because of the risk for aluminum toxicity. Ingestion of aluminum-containing antacids together with foods containing citric acid (e.g., fruit juices and foods with sodium, calcium, or potassium citrate) may significantly increase aluminum absorption and therefore should be avoided.

Phosphorus Balance and Hemodialysis

Dietary phosphorus
intake
1000 mg/day
or
7000 mg/wk

Absorption
60%

Phosphorus
requiring
removal
4200 mg/wk

Removed by HD
3 × 800 mg
2400 mg/wk

Phosphorus balance
+1800 mg/wk

To achieve neutral phosphate balance,
binders must remove
1800/7 = 257 mg/day
Approximate potential phosphate-binding capacities of
commonly used agents:

- Calcium carbonate: 1 g binds 40 mg
- Calcium acetate: 1 g binds 45 mg
- Sevelamer: 1 g binds 36 mg
- Lanthanum carbonate: 1 g binds 93 mg
- Aluminum hydroxide (liquid): 1 g binds 60-75 mg
- Sucroferric oxyhydroxide: 1 g binds 100 mg

Fig. 88.12 Phosphate balance and phosphate binders used in hemodialysis (HD) patients.

Calcium carbonate or calcium acetate taken with meals effectively binds phosphates and limits their absorption. They are effective phosphate binders in 60% to 70% of patients on HD. The doses required to prevent hyperphosphatemia may vary according to patient compliance with dietary phosphate restriction as well as the CKD stage.
Hypercalcemia and calcium loading are potentially serious side effects. Current recommendations are to limit the ingestion of elementary calcium to 1500 mg/day. Consideration of overall calcium balance may be important with the use of calcium-containing phosphate binders.
Magnesium salts are effective phosphate binders for patients who become hypercalcemic with calcium-containing phosphate binders, but they should be administered with caution in CKD patients not on dialysis because hypermagnesemia may have serious adverse effects.
In patients on dialysis, magnesium carbonate (elemental magnesium 200–500 mg/day) has been used successfully, with prevention of hypermagnesemia through a reduction in dialysate magnesium concentration, or at least monitoring of magnesium levels.
Sevelamer carbonate is a nonabsorbable, calcium-free polymer, which provides effective phosphate control in a dose range of 2.4 to 4.8 g/day, but higher doses might be needed. Sevelamer may offer a advantage over calcium-containing phosphate binders in terms of limiting the calcium load. The use of sevelamer is associated with decreased progression of vascular calcification.[25] Sevelamer may be combined

with both calcium- and magnesium-containing phosphate binders if necessary. Lanthanum carbonate also is an effective phosphate binder. No significant toxicity has been observed, and like sevelamer, its use is associated with less progression of vascular calcification compared with calcium-containing phosphate binders.26 In general, pill burden is lower for lanthanum compared with sevelamer. Iron-containing phosphate binders include ferric citrate and sucroferric oxyhydroxide. Both compounds have comparable phosphate binding efficacy as lanthanum per pill. Ferric citrate allows significant oral iron uptake and therapy necessitates monitoring of iron stores, whereas iron uptake from sucroferric oxyhydroxide is low.25

Use of Vitamin D Metabolites

Calcitriol and other 1α-hydroxylated vitamin D sterols, such as 1α hydroxyvitamin D3 (alfacalcidol), 1α-hydroxyvitamin D2 (doxercalciferol), and 19-nor-1α,25-dihydroxyvitamin D2 (paricalcitol), are active forms of vitamin D and are effective for controlling secondary hyperparathyroidism. Calcitriol lowers PTH levels and improves bone histology. In patients with very high levels of PTH and markedly enlarged glands with severe nodular hyperplasia, the effectiveness of vitamin D metabolites may be limited because the expression of vitamin D receptor is low in such tissue. Accordingly, it appears rational to initiate treatment of secondary hyperparathyroidism with active vitamin D early in CKD when the parathyroid glands are more sensitive to such therapy and thereby prevent the progression to a refractory stage. Levels of 1,25 dihydroxycholecalciferol generally correlate with 25 hydroxycholecalciferol. Therefore, generally the first step in treatment of secondary hyperparathyroidism is correction of (native) vitamin D deficiency.

A beneficial effect of active vitamin D therapy in treatment of secondary hyperparathyroidism in patients with mild to moderate CKD has been shown, but the concern with initiation of active vitamin D therapy at this stage of CKD is acceleration of the progression of kidney disease, should hypercalcemia occur. Because of the effect of calcitriol to increase intestinal phosphate absorption, hyperphosphatemia and elevations in calcium-phosphate product may predispose patients to the development of metastatic calcification; however, it appears that doses of 1α-hydroxyvitamin D3 or calcitriol up to 0.5 µg/day are not commonly associated with hypercalcemia, hyperphosphatemia, or worsening kidney impairment. Another concern with the use of active vitamin D metabolites before dialysis is that oversuppression of PTH may increase the risk for adynamic bone. Accordingly, vitamin D therapy should be monitored carefully and should not be instituted without documentation of hyperparathyroidism, correction of 25-hydroxyvitamin D deficiency, and prior control of serum phosphate.

In patients with ESKD, indications for therapy with active vitamin D are better defined; however, hypercalcemia and aggravation of hyperphosphatemia are frequent complications of therapy. In these patients, the PTH suppressive effects of active vitamin D compounds are well established. Several, but not all, observational studies have suggested there may be a survival advantage associated with active vitamin D administration in patients with CKD and with ESKD.27 28 However, in a prospective Japanese clinical trial in HD patients with relatively low plasma iPTH levels, oral alfacalcidol therapy did not result in lower mortality or cardiovascular event rates.29 Thus, the principal indication to use active vitamin D is control of secondary hyperparathyroidism.

Role of Calcimimetics

An additional approach to the treatment of hyperparathyroidism in ESKD is the use of calcimimetic agents, such as the oral compounds cinacalcet and evocalcet (approved in Japan), or the intravenously administered etelcalcetide, which targets the calcium-sensing receptor and increases its sensitivity to calcium. In dialysis patients, cinacalcet results in a significant fall in PTH levels and can facilitate the control of hyperparathyroidism. The addition of cinacalcet to standard therapy, which included vitamin D sterols in most participants, in patients with iPTH serum levels exceeding 300 pg/mL while receiving standard therapy allowed significantly more dialysis patients to achieve guideline targets for calcium, phosphate, and iPTH.30 Cinacalcet is especially useful in patients with marginal or frank hypercalcemia or with hyperphosphatemia because it lowers these levels too. In addition, calcimimetics can be used in conjunction with other therapies and may even be more effective when combined with low-dose active vitamin D, which increases the expression of the calcium sensing receptor. Key side effects include hypocalcemia and nausea and vomiting; the latter can be somewhat improved by administering cinacalcet at night and possibly by switching to another calcimimetic. Cinacalcet may attenuate progression of cardiovascular (CV) calcification.31 A large clinical trial that examined the effect of cinacalcet compared with placebo on CV events and survival in HD patients with secondary hyperparathyroidism did not show statistical significance of treatment on the primary endpoint. However, this trial had a high risk of missing a beneficial effect of cinacalcet (type II error) because a substantial proportion of the placebo arm initiated commercial cinacalcet and because cinacalcet patients were older on average and thus at higher CV risk than those randomized to placebo.32 Nonetheless, cinacalcet significantly reduced rates of parathyroidectomies and of calciphylaxis compared with placebo.32 In CKD patients not on dialysis, the use of calcimimetics is accompanied by significant phosphate retention and is currently not recommended. The parenterally administered etelcalcetide offers improved patient adherence, but GI adverse events were similar to those with cinacalcet.33

Role of Parathyroidectomy

Although medical treatments are often effective for the control of hyperparathyroidism, there are patients in whom they are unlikely to be successful, have failed, or are contraindicated and parathyroidectomy should be considered (Box 88.2). Severe hyperphosphatemia in these patients precludes the use of vitamin D because of the risk for metastatic calcification. Some control of iPTH levels may be obtained with calcimimetics, but even these compounds may fail in severe hyperparathyroidism because of downregulated calcium-sensing receptors in the parathyroid glands. However, baseline levels of PTH do not predict response to calcimimetics. Some patients with severe hyperparathyroidism may become hypercalcemic. It is important to be certain that hypercalcemia represents severe hyperparathyroidism and is not caused by adynamic bone or other disease. In some cases, a bone biopsy may be required for a definite diagnosis before proceeding to surgical treatment of hyperparathyroidism. When hypercalcemia in a CKD patient is because of hyperparathyroidism, the level of iPTH generally exceeds 1000 pg/mL and BAP is usually elevated. Surgical parathyroidectomy might be considered in patients with very severe hyperparathyroidism who may receive a kidney transplant in the near future, particularly if they are female and have significant osteopenia. Parathyroidectomy in these patients can help avoid posttransplantation hypercalcemia and hypophosphatemia (caused by PTH-induced phosphaturia), as well as osteopenia. Avoiding hypercalcemia may lead to improved graft function and possibly to less intragraft calcification. Less severe hyperparathyroidism may subside spontaneously after kidney transplantation. Parathyroidectomy might be considered in patients with severe hyperparathyroidism who have evidence of metastatic calcification. The development of calciphylaxis is an urgent indication for parathyroidectomy if PTH levels are elevated (see Chapter 91).

The most commonly used surgical procedures are subtotal removal of the parathyroid glands and total removal of the parathyroid glands with reimplantation of parathyroid tissue in the forearm. Recurrence of hyperparathyroidism occurs in about 10% of patients. Total parathyroidectomy alone is less commonly performed because it results in hypoparathyroidism. Total parathyroidectomy with forearm implantation on the brachioradialic muscle, or subtotal parathyroidectomy in the neck, marking remaining tissue with clips, may be performed. Unregulated tumor-like growth of parathyroid tissue implants has been described and may be related to the monoclonal nature of the nodular hyperplasia of severe hyperparathyroidism. For patients with forearm implantation, it is important to consider which phlebotomy site is used for PTH levels because local levels may differ from systemic. Recurrence of hyperparathyroidism may respond to further medical therapy, but repeated surgery to remove the forearm implant or a second neck exploration to search for additional glands is often necessary and may be guided by parathyroid imaging.

Synthesis of Therapeutic Strategies

The general recommendations for the prevention and therapy of renal osteodystrophy are summarized in Fig. 88.13, in which therapeutic maneuvers are stratified according to the stage of CKD. Intervention should be considered in stage 2 or 3 CKD (GFR, 30–90 mL/min/1.73 m2), and dietary phosphate intake may be restricted once patients enter CKD stage 3. Levels of iPTH should be measured; if elevated above the normal range, the levels of 25-hydroxyvitamin D should be measured and corrected if less than 30 ng/mL. If relevant hyperparathyroidism persists, phosphate binders should be considered if phosphate levels are higher than normal. The effectiveness of calcium-containing phosphate binders in earlier stages of CKD is doubtful. As CKD progresses within stage 3, dietary phosphate restriction should be continued or intensified, with emphasis on inorganic

Indications for Parathyroidectomy

BOX 88.2

- Severe hyperparathyroidism
- With persistent hyperphosphatemia
- Unresponsive to calcitriol and calcium
- With hypercalcemia
- With intolerance or unresponsiveness to calcimimetics
- In kidney transplantation candidate if severe and unresponsive to calcitriol and calcimimetics
- With evidence of metastatic calcification

- If persistent and clinically relevant >18–24 months after kidney transplantation
- Calciphylaxis with evidence of hyperparathyroidism and no or modest response only to calcimimetic therapy

Treatment of Renal Osteodystrophy at Various Stages
of Chronic Kidney Disease
Monitor Ca/P/iPTH levels
Evaluate vitamin D status
and treat as necessary
Treat acidosis
Consider:
- Dietary Pi restriction
CKD 3
Consider:
Active vitamin D sterols
Limiting Ca intake
CKD 4
Consider:
P binders
Parathyroidectomy
Calcimimetic*
Dialysis regimen*
Dialysate calcium*
CKD 5

Fig. 88.13 Treatment of renal osteodystrophy at various stages of chronic kidney disease. Asterisk, Consider in CKD stage 5D (i.e., dialysis dependent) only. Ca, Calcium; CKD, chronic kidney disease; iPTH, intact parathyroid hormone; P, phosphate; Pi, inorganic phosphate. (Modified from Martin KJ, Gonzalez EA. Metabolic bone disease in chronic kidney disease. J Am Soc Nephrol. 2007;18:875–885.)

phosphate from food additives, and the doses of phosphate binders should be adjusted based on serial measurements of phosphate, with careful attention to avoid hypercalcemia or excessive calcium load. Acidosis, if present, should be treated with oral sodium bicarbonate because persistent acidosis has deleterious effects on the skeleton. The additional sodium load may require further salt restriction or increases in diuretics. Aluminum-based phosphate binders should be avoided.

If hyperparathyroidism (iPTH more than two to three times above the upper normal range of the assay) persists despite these measures, consideration should be given to the addition of calcitriol (0.25–0.5 μg/day), active vitamin D analogs, after restoring vitamin D (25OHvitamin D) deficiency. This therapy should be monitored carefully to avoid hypercalcemia and acceleration of progression of CKD.

In CKD stages 4 and 5, the preceding therapies may need to be intensified and larger amounts of phosphate binders may be required to treat hyperphosphatemia toward normal levels. In patients on dialysis, calcitriol therapy can be intensified, with attention to the serum levels of calcium and phosphate and monitoring of iPTH levels. In CKD stage 5, iPTH levels should be maintained approximately 2 to 9 times above the upper limit of the assay used to maintain normal bone turnover.24 Within this wide range, treatment decisions on PTH management depend on PTH trends and concurrent levels of phosphate, calcium, and BAP.24 Calcitriol or other analogs of active vitamin D may be administered orally either daily or intermittently (pulse therapy) or administered intravenously to patients on HD. During therapy with active vitamin D, it is imperative to ensure serum phosphate remains controlled and elevations of serum calcium are avoided. Cinacalcet provides additional effective control of hyperparathyroidism in patients with ESKD and may be used alone or in combination with the other strategies if iPTH levels do not fall into the target range. Parathyroidectomy should be considered in selected circumstances. Bone biopsy may be indicated in selected patients, particularly if biomarkers are inconclusive and important treatment decisions are needed (i.e., long-term use of antiresorptive agents or parathyroidectomy), hypercalcemia remains unexplained, or aluminum overload is suspected. Aluminum overload may require chelation therapy with deferoxamine in selected circumstances, especially if it is symptomatic, but in most patients preventing further aluminum exposure will lead to a gradual reduction in the serum levels of aluminum without the need for chelation. During therapy with potent vitamin D compounds, attention should be given to the dialysate calcium concentrations because higher concentrations may aggravate hypercalcemia. However, the increasingly frequent use of lower dialysate calcium levels, such as 1.25 mmol/L, requires careful monitoring of the patient to ensure compliance with calcium-containing phosphate binders and vitamin D metabolites to avoid progressive negative calcium balance and ongoing stimulation of PTH. Dialysate calcium should remain within the range of 1.25 to 1.50 mmol/L and, when possible, should be individually prescribed.24

LOW-TURNOVER (ADYNAMIC) BONE DISEASE

Adynamic bone disease (ABD) describes the morphologic consequences of low-turnover osteopathy in CKD. As CKD progresses, hyperparathyroidism initially develops as an adaptive response to counteract the increasing skeletal PTH resistance and phosphate overload. ABD mainly results from too rigorous suppression of this adaptive response. ABD is increasingly important in CKD-MBD because of the high percentage of affected individuals (>40% in CKD stage 5) and because of its association with CV calcification and mortality.34 35

Pathogenesis of Adynamic Bone Disease

Better phosphate control

Diabetes

Diabetes

↑ Age

↑ Age
↑ Aluminum
Vitamin D therapy

Uremic toxins
Relative
hypoparathyroidism

Decreased bone
formation rate

Malnutrition

VDR polymorphism
CAPD

Altered growth
factors and cytokines
↑ Aluminum

↑ Serum Ca

Vitamin D therapy
↓ PTH-1 receptor

↑ Calcium intake

Fig. 88.14 Pathogenesis of adynamic bone disease. Ca, Calcium; CAPD, continuous ambulatory peritoneal dialysis; PTH, parathyroid hormone; VDR, vitamin D receptor. (Modified from Couttenye MM, D'Haese PC, Verschoren WJ, et al. Low bone turnover in patients with renal failure. Kidney Int Suppl. 1999;73:S70–S76.)

Furthermore, fracture incidence is estimated to be twice as high in individuals with low than in those with high bone turnover. ABD prevalence is markedly increasing in bone biopsy registries of dialysis patients, which may relate to the increasing prevalence of its key risk factors—advanced age and diabetes mellitus. PD also represents a risk factor for ABD, possibly because of a more continuous exposure to high dialysate calcium as opposed to the cyclic exposure associated with HD.

Pathogenesis of Adynamic Bone Disease

Given that the bone develops a relative resistance of the PTH-1 receptor to its ligand PTH as CKD progresses, PTH levels above the normal range are required to maintain adequate bone turnover. Unfortunately, there are no definite ranges of elevated PTH levels that can reliably differentiate an adaptive response (normal bone turnover) from a maladaptive response (increased bone turnover) because PTH resistance individually varies and because it depends on the stage of CKD. Accordingly, ABD is a consequence of inadequately low PTH levels, which cause suppression or cessation of both osteoblast and osteoclast activities, resulting in a reduced bone formation rate and low bone mass. Iatrogenic oversuppression of PTH in CKD mainly results from high-dose active vitamin D analog treatment, from calcium loading (high doses of calcium-containing phosphate binders, high dialysate calcium concentration), or after parathyroidectomy.

The effects of calcimimetic treatment on bone turnover have been prospectively evaluated in HD patients, and patients in this cohort had significant high-turnover osteopathy at baseline (average iPTH > 1200 pg/mL). Therapy with cinacalcet decreased elevated bone formation rate and improved bone histologic status.36 ABD occurred only if iPTH was suppressed below the KDIGO target range of two to nine times the upper reference range of the assay. Finally, diabetes, uremic toxins, malnutrition, and, potentially, C-terminal PTH fragments may be additional factors favoring a state of low bone turnover (Fig. 88.14).

Diagnosis and Differential Diagnosis

Serum Biochemistry

Low iPTH levels (<100–150 pg/mL) are almost always indicative of low bone turnover in CKD stage 5D. However, histologically proven ABD may occur in many dialysis patients with iPTH levels of up to 300 pg/mL and, in exceptions, of up to 600 pg/mL.37 38 Therefore, PTH levels alone do not reliably identify ABD. Serum levels or activities of AP or BAP are usually normal or low; downward trends may indicate the development of ABD. Serum calcium and phosphate can be normal or elevated, dependent on the choices of cotreatment (phosphate binders, vitamin D metabolites) and nutritional status. Particularly in instances of calcium and phosphate loading, hypercalcemia and hyperphosphatemia may be pronounced because adynamic bone is less able to buffer calcium and phosphate loads by osseous deposition (Fig. 88.15).

Extraskeletal Calcification in
Adynamic Bone Disease
Normal bone turnover
Deposition

Mobilization

Ca2+
Bone
PO4

Low bone turnover
(adynamic bone)

Ca2+
Bone
PO4

Fig. 88.15 Bone Turnover in Adynamic Bone Disease. Reduced bone turnover leads to increased extraskeletal calcification. Ca2+, Calcium ion; PO4, phosphate.

In CKD stages 3 and 4, there are uncertainties about the diagnosis of ABD and its clinical consequences. It is unclear which PTH levels are required to maintain adequate bone turnover in these stages. It seems reasonable to correct vitamin D deficiency, hyperphosphatemia, and hypocalcemia when PTH levels start to rise, but beyond that, no firm recommendations can be given.

Bone Biopsy

The gold standard for diagnosis of ABD is bone biopsy. According to the TMV classification (see earlier discussion),[1] ABD is characterized by low turnover, normal (or high secondary) mineralization, and low bone (osteoid) volume. The individual indication to perform bone biopsy should be considered in symptomatic patients based on inconsistencies of biochemical parameters associated with unexplained

The Value of Bone Density Measurements
in the Assessment of CKD-Related Bone Disease
Clinical Situation:

Normal bone

Normal
bone mass
Bone
Composition:

Measured BMD:
Densitometry
Report:

Osteoporosis
Low bone
mass

Normal
primary
mineralization

Normal
primary
mineralization

1.250 g/cm2

0.625 g/cm2

Normal BMD

Osteomalacia

Adynamic
Bone Disease

Normal
bone
mass

Low bone
mass

Abnormal
primary
mineralization

High
secondary
mineralization

0.625 g/cm2

0.625 g/cm2

Secondary Hyperparathyroidism
Normal or
increased

bone mass
Decreased
secondary
mineralization
Increased
osteoid volume
0.625 g/cm2

“Osteoporosis”

Fig. 88.16 Value of bone density measurements in the assessment of chronic kidney disease (CKD)-related bone disease. Pink boxes indicate mineralized bone; red boxes indicate osteoid. BMD, Bone mineral density.
(Courtesy Prof. M.H. Lafage-Proust, St. Etienne, France.)

fractures, bone pain, progressive extraosseous calcifications, or hypercalcemia. The KDIGO initiative recently investigated more than 492 bone biopsy samples and concomitant serum samples to identify biomarker patterns that may allow noninvasive assessment of bone turnover status. ABD was quite strongly associated with low-normal to low BAP levels. In general, PTH and BAP could distinguish low from nonlow and high from non-high bone formation rate.39 However, there is considerable heterogeneity between the extremes. Aluminum toxicity is a relevant differential diagnosis versus ABD. Thus, if the patient’s history suggests significant aluminum exposure, aluminum bone deposition should be excluded by measurement of serum aluminum and specific staining of a bone biopsy specimen.

Radiology and Measurements of Bone Density

There are no typical features of ABD in conventional bone radiographs or DEXA. In the latter, bone density may be low, normal, or high, depending on the primary or secondary mineralization state, but it never reflects the actual turnover and is therefore not a helpful diagnostic test (Fig. 88.16). A very high CV calcification burden on conventional radiographs may raise the suspicion of a low bone turnover state, if accompanying biochemical parameters are compatible with this diagnosis. Biopsy-proven ABD is associated with the highest magnitude of vascular calcification in dialysis patients.34

Treatment of Adynamic Bone Disease

The key therapeutic approaches in the treatment of ABD are to avoid PTH overexpression and restore adequate PTH levels, without triggering the progressive development of secondary hyperparathyroidism. Such a stepwise treatment approach may include reduction or avoidance of calcimimetics, reduction or avoidance of active vitamin D metabolites, reduction or avoidance of calcium-containing phosphate binders, and reduction of the dialysate calcium concentration (usually to 1.25 mmol/L), first of all based on the magnitude and development of serum PTH levels. Indeed, a recent randomized controlled trial found a histologic improvement of low bone turnover when the dialysate calcium concentrations were decreased from 1.5 or 1.75 mmol/L to 1.25 mmol/L.40 Any aluminum should be withdrawn. After these interventions, biochemical parameters (PTH, calcium, phosphate, perhaps AP, and especially BAP) should be monitored more frequently than usual.

Studies comparing calcium-containing with non–calciumcontaining phosphate binders in dialysis patients38 41 found that the administration of calcium-containing phosphate binders was associated with a higher proportion of individuals who developed ABD. This development was associated with a fall in serum PTH because of the higher calcium load. In an observational study, high-dose calciumcontaining phosphate binder intake was associated with both low bone turnover and increased aortic calcification.42

Other therapeutic approaches to ABD have not been systematically studied. They include optimized diabetes control, a change from PD to HD to facilitate a more flexible dialysate calcium prescription, and calcilytics (agents that antagonize the calcium receptor and thus increase endogenous PTH).43 At present, many patients with ABD remain refractory to these treatments.

Future options for treatment might include recombinant PTH (teriparatide, 1–84 PTH), especially in cases of “irreversible” ABD (i.e., after total parathyroidectomy). Supportive study data on relevant clinical features (e.g., bone histomorphometry, bone mineral density, hypercalcemia) are becoming increasingly available from case reports and non-CKD populations,44–46 but this approach would be considered an “off-label” treatment for ABD.

OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE

Although abnormal bone is common and fracture risk is increased in CKD patients, the relative contribution of classic osteoporosis (as defined by World Health Organization [WHO] criteria) to the CKDMBD complex is not well defined. Data from studies of antiosteoporosis agents are mostly available for patients in CKD stages 1 to 3, and subjects with features of CKD-MBD were largely excluded. Nevertheless, postmenopausal women and elderly men are highly prevalent in late-stage CKD populations, and it is thus likely that classic osteoporosis also contributes to their bone disease.

Pathogenesis of Osteoporosis in Chronic Kidney Disease

Osteoporosis may be associated with low, normal, or high bone turnover and is characterized by thin and disconnected trabeculae and loss of the plate-like bone structure. Many patients with CKD have abnormal mineralization and increased osteoid, which is quite atypical for osteoporosis.

Typical pathogenetic factors of osteoporosis, including older age, low estrogen levels, immobilization, and corticosteroid use, are frequent in CKD patients, although some postmenopausal women with late-stage CKD may have relatively normal estrogen levels. However, secondary hyperparathyroidism, relative hypoparathyroidism (as in ABD), and 25-hydroxyvitamin D, as well as 1,25-dihydroxyvitamin D deficiencies, may dominate and “overrule” the bone phenotype of osteoporosis even if classic risk factors are present.

Diagnosis and Differential Diagnosis

initiation, if bone turnover markers and repeat DEXA scans indicate a clinical response.

ß2-MICROGLOBULIN–DERIVED AMYLOID

Aβ2M amyloidosis, also termed dialysis-associated amyloidosis, exclusively and rarely affects patients with long-standing stage 5 CKD. Although the process is systemic, clinical manifestations are largely confined to the musculoskeletal system. Aβ2M amyloidosis in CKD stage 5 should not be confused with a rare hereditary systemic amyloidosis derived from the Asp76Asn variant of β2-microglobulin, which manifests in the absence of CKD.

Osteoporosis diagnosis relies on an areal bone mineral density (BMD) evaluated by DEXA at the spine or hip below −2.5 standard deviation (SD) from the BMD in young women (T-score). BMD as assessed by DEXA predicts fractures in patients with CKD G4 to G5D but likely also underestimates the actual risk in patients with CKD G4 to G5D because it does not account for impaired bone quality.47 Furthermore, in advanced CKD, BMD measurements do not differentiate classic osteoporosis versus other CKD-MBD–related bone disease, and low BMD can be found in CKD-MBD–induced high-turnover bone disease, ABD, and osteomalacia (see Fig. 88.16). The value of biomarkers for diagnosing osteoporosis in advanced CKD is not well established; if monitoring is attempted, analytes should be preferred that do not exhibit major kidney retention, such as BAP, intact procollagen type I N-propeptide (PINP; marker of bone collagen synthesis), and tartrate-resistant acid phosphatase 5b (TRAP5b; marker of osteoclast activity). Peripheral quantitative tomography (pQCT) of the radius may be a superior methodology for assessment of CKD patients in the future but awaits validation in sufficiently large patient cohorts.48 The only reliable methodology to diagnose osteoporosis and discriminate it from other bone manifestations in CKD patients is bone biopsy. In a large bone biopsy study, including 1429 samples from dialysis patients, osteoporosis was diagnosed in 52% of individuals, and 49% of them also had ABD.49 These proportions may be quite different in patients in earlier CKD stages, but there are no systematic data available on such cohorts.

Histologic studies from the 1990s observed amyloid deposits in 100% of dialysis patients treated for more than 13 years.58 Most amyloid deposits never cause clinical problems. Aβ2M amyloid–related symptoms presently are largely confined to patients who have been dialyzed for more than 15 years.

Treatment of Osteoporosis in Chronic Kidney Disease

Clinical Manifestations and Diagnosis

Nonpharmacologic approaches to osteoporosis in CKD (i.e., sufficient calcium supply, exercise, fall prevention) do not differ from the general population. Post-hoc analyses indicate that antiosteoporotic medications are safe and efficacious for treatment of postmenopausal women in stages CKD 1 to 3 and high risk for fractures (according to WHO criteria or using the Fracture Risk Assessment [FRAX] tool) and no features of CKD-MBD.50–53 In such populations, bisphosphonates, denosumab, raloxifene, and teriparatide appear to be feasible therapeutic options. The former three drugs antagonize high bone turnover with an antiresorptive mode of action; teriparatide exerts bone anabolic effects (PTH analog). Bisphosphonates may lead to oversuppression of osteoclasts, but only in patients with advanced CKD. A recent subanalysis of patients in CKD stages 2 to 4 from the Following Rehabilitation, Economics and Everyday-Dialysis Outcomes Measurements (FREEDOM) trial demonstrated a significantly reduced fracture risk with denosumab treatment versus placebo, independent of the stage of CKD.54 In CKD patients with ABD, bisphosphonates and denosumab may aggravate osteoclast paralysis. In CKD patients with secondary hyperparathyroidism, these antiresorptive agents may upregulate PTH secretion. Patients with advanced CKD (stages 4 and 5) may develop particularly severe hypocalcemia when treated with denosumab; coadministration of vitamin D analogs and calcium may be required to blunt this effect. However, because antiresorptive therapies may be effective in patients with advanced CKD,47 and the lack of definite evidence that these drugs induce ABD in this population, it may not be necessary to perform a bone biopsy before treatment

Aβ2M amyloidosis mainly manifests at osteoarticular sites, particularly synovial membranes; visceral manifestations are rare.55 Carpal tunnel syndrome is often bilateral and usually requires surgery. Osteoarthropathy of peripheral joints, resulting from amyloid deposition in periarticular bone and the synovial capsule (Fig. 88.17), is

Pathogenesis

Fibrils of Aβ2M amyloid are derived from the circulating precursor protein β2-microglobulin, the nonvariable light chain of the human leukocyte antigen (HLA) class I complex. The pathogenesis appears to involve three events:

1. Pronounced kidney retention of β2-microglobulin (11.8 kDa), leading to plasma levels that can be elevated up to 60-fold in dialysis patients55; however, even massive overproduction of β2-microglobulin in mice was not sufficient to induce amyloid deposits and thus further steps must be important.56
2. Modifications of the β2-microglobulin molecule that render it more amyloidogenic.57
3. Local factors that contribute to and determine the spatial localization of the amyloidosis.

Epidemiology

Fig. 88.17 β2-Microglobulin (Aβ2M) Amyloid Deposition in the Femoral Head. Postmortem specimen from a patient who had undergone long-term hemodialysis. Two large lesions (arrowheads), partly filled with grayish amyloid and partly cystic, are noted in the femoral head. Also note the marked thickening of the synovial capsule from amyloid deposition (arrow).

A

B

Fig. 88.18 β2-Microglobulin (Aβ2M) Amyloidosis–Associated Spondyloarthropathy. (A) Destruction of an intervertebral disk (arrow) in the neck vertebrae of a long-term hemodialysis patient. (B) Magnetic resonance image of the same patient. Note destruction of the intervertebral space and protrusion of material into the spinal canal (arrow).

characterized by recurrent or persistent arthralgias, stiffness of large and medium-sized joints, and swelling of capsules and adjacent tendons. Recurrent joint effusions and synovitis, often in the shoulders and knees, may occur. The clinical presentation may vary from frank, acute arthritis to slow, progressive destruction of the affected joints. Destructive spondyloarthropathy (Fig. 88.18) resulting from Aβ2M amyloidosis can manifest as asymptomatic deposits, radiculopathy, stiffness, “mechanical ache,” and, finally, medullary compression with resulting paraplegia or cauda equina syndrome. Other manifestations include camptodactyly (a flexion deformity resulting in bent fingers that cannot completely extend or straighten) resulting from amyloid deposits along the flexor tendons of the hands (Fig. 88.19). Patients undergoing dialysis also can have subcutaneous tumorous deposits of Aβ2M amyloid.

Clinically relevant organ manifestations in patients treated with HD for more than 15 years have described heart failure, odynophagia (painful swallowing), intestinal perforation of both small and large bowel, GI bleeding and pseudo-obstruction, gastric dilation, paralytic ileus, persistent diarrhea, macroglossia or functional tongue disturbances (abnormal taste, mobility, articulation), ureteral stenosis, and nephrolithiasis.

Diagnosis

Serum levels of β2M do not distinguish between patients with amyloidosis and those without. Ultrasound can detect synovial Aβ2M amyloidosis as thickening of the joint capsules and tendons and the presence of echogenic structures between muscle groups and joint effusions.[55 57] On radiologic examination, affected joints may present with single or multiple juxta-articular, “cystic” (i.e., amyloid-filled) bone radiolucencies (Fig. 88.20; see also Fig. 88.17). Such bone defects are prone to pathologic fractures. Diagnostic criteria for Aβ2M amyloid–induced cystic bone radiolucencies include (1) diameter of lesions more than 5 mm in wrists and more than 10 mm in shoulders and hips, (2) normal joint space adjacent to the bone defect, (3) exclusion of small subchondral cysts in the immediate weight-bearing area of the joint and of defects of the “synovial inclusion” type, (4) increase of defect diameter of more than 30% per year, and (5) presence of defects in at least two joints.[59] Scintigraphy, using either radiolabeled serum amyloid P component or β2-microglobulin,[60] offers more specific detection of

Fig. 88.19 Hand Involvement in β2-Microglobulin (Aβ2M) Amyloidosis. Hand of a long-term hemodialysis patient showing maximal extension. Note the prominence of shrunken flexor tendons (arrows). This is also known as the guitar string sign.

amyloid deposits but is not widely available. The definitive diagnosis of Aβ2M amyloidosis relies on histologic findings. Fat aspiration and rectal biopsy are not helpful in Aβ2M amyloidosis, but diagnostic material can be obtained from synovial membranes, synovial fluid, or bone lesions.

Treatment and Prevention

Therapy for established Aβ2M amyloidosis is symptomatic. NSAIDs and physical and surgical measures, such as carpal tunnel decompression, endoscopic coracoacromial ligament release, and bone stabilization in areas of cystic destruction, are all used.55 Dialytic removal of β2M is probably of no therapeutic value in established Aβ2M amyloidosis. Kidney transplantation is the preferred treatment because it leads to rapid symptomatic improvement and halts further progress of the disease, but whether this can actually lead to regression of established Aβ2M amyloid deposits is uncertain.

A number of strategies exist for prevention of the clinical manifestations of Aβ2M amyloidosis.55 The risk for carpal tunnel syndrome is reduced by 40% to 50% in patients treated with high-flux hemo(dia)

A

B

C

D

Fig. 88.20 Peripheral Bone Cystic Radiolucencies in β2-Microglobulin (Aβ2M) Amyloidosis. Radiographic findings in a long-term hemodialysis patient. (A) Multiple cystic lesions (arrows) are present in the hand bones. (B) Large cysts (arrows) in the neck of the femur and adjacent pelvic bones. (C–D) Anterior and lateral views of the head of the tibia with two very large, cystic lesions (arrows) resulting in posterior bulging of the tibial plateau.

filtration and minimal in patients receiving online hemodiafiltration. A dramatic reduction in the prevalence of carpal tunnel syndrome occurred in patients dialyzed with ultrapure dialysate. In another study, an 80% reduction of amyloid signs in a chronic HD population appeared to relate to dialysate factors such as microbiologic purity and the use of bicarbonate buffer.

SELF-ASSESSMENT QUESTIONS

1. A 56-year-old White woman with ESKD secondary to presumed hypertensive nephrosclerosis has been on maintenance HD for 3.5 years. She reports to dialysis treatments regularly and is being adequately dialyzed. Laboratory data over the past few months reveal that intact PTH levels have ranged from 360 to 545 pg/mL, serum calcium 9.5 to 10.5 mg/dL (2.4–2.6 mmol/L), and phosphorus 5.5 to 7.0 mg/dL (1.83–2.33 mmol/L). She has been treated with increasing doses of paricalcitol, dietary phosphate restriction, and calcium carbonate as a phosphate binder. A few days ago, she was seen by her internist regarding vague symptoms that included abdominal pain. At that time, blood tests showed serum phosphorus 7.6 mg/dL (2.5 mmol/L) and calcium 10.1 mg/dL (2.5 mmol/L). The rest of the metabolic profile was within normal limits. A kidney, ureter, and bladder (KUB) film of the abdomen showed calcification of the abdominal aorta. What is the most appropriate next step in the management of this patient’s CKD-MBD?

A. Increase the dose of paricalcitol.
B. Increase the dose of calcium carbonate to improve phosphate control.
C. Stop calcium carbonate and add a non–calcium-containing phosphate binder.
D. Refer for parathyroidectomy.
E. Decrease dialysate calcium.

2. A 75-year-old White man on HD because of diabetic nephropathy exhibits rapid progression of vascular calcification. His total serum calcium fluctuates around the upper limit of normal, with occasional episodes of mild hypercalcemia. Serum phosphorus is around 7 mg/dL (2.3 mmol/L) despite various changes of his phosphate binder medication. The latest intact PTH level is 105 pg/mL (previous levels ranged from 90–180 pg/mL). Current medication includes fluvastatin, calcium acetate, low-dose aspirin, a β-blocker, and insulin. What is the most appropriate next step in the management of this patient’s CKD-MBD?

A. Continue the described therapy.
B. Increase the dose of calcium acetate to improve phosphate control.
C. Repeat dietary counseling.
D. Add low-dose calcitriol (e.g., 0.25 μg/day).
E. Replace calcium acetate with a calcium-free phosphate binder.

3. A 68-year-old White woman with an eGFR of 25 mL/min/1.73 m2 as a result of presumed hypertensive nephrosclerosis presents for a regular checkup. She has no specific complaints. Medication consists of an ACE inhibitor, a loop diuretic, a β-blocker, and low-dose

aspirin. Current laboratory values include intact PTH level 90 pg/mL (reference range <60), serum calcium 8.1 mg/dL (2.0 mmol/L) and phosphorus 5.7 mg/dL (1.8 mmol/L), 25(OH)-vitamin D3 17 μg/L (target range 30–100). What step in the management of this patient’s CKD-MBD is not appropriate?
A. Educate the patient about phosphate content in food.
B. Initiate therapy with a phosphate binder.
C. Initiate substitution of 20,000 IU vitamin D3 every second week.
D. Educate the patient about food additives.
E. Initiate therapy with a low dose of a calcimimetic.

REFERENCES

1. Moe S, Drueke T, Cunningham J, et al. Improving global O. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69:1945–1953.

2. Sherrard DJ, Hercz G, Pei Y, et al. The spectrum of bone disease in endstage renal failure-an evolving disorder. Kidney Int. 1993;43:436–442.

3. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. J Bone Miner Res. 2011;26:1368–1376.

4. Martinez I, Saracho R, Montenegro J, et al. The importance of dietary calcium and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. Am J Kidney Dis. 1997;29:496–502.

✓ 5. ✓ Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005;16:2205–2215.

6. Centeno PP, Herberger A, Mun HC, et al. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. Nat Commun. 2019;10:4693.

✓ 7. ✓ Almaden Y, Canalejo A, Hernandez A, et al. Direct effect of phosphorus on PTH secretion from whole rat parathyroid glands in vitro. J Bone Miner Res. 1996;11:970–976.

8. Slatopolsky E, Finch J, Denda M, et al. Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. J Clin Invest. 1996;97:2534–2540.

9. Denda M, Finch J, Slatopolsky E. Phosphorus accelerates the development of parathyroid hyperplasia and secondary hyperparathyroidism in rats with renal failure. Am J Kidney Dis. 1996;28:596–602.

10. Naveh-Many T, Rahamimov R, Livni N, et al. Parathyroid cell proliferation in normal and chronic renal failure rats. The effects of calcium, phosphate, and vitamin D. J Clin Invest. 1995;96:1786–1793.

11. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, et al. The parathyroid is a target organ for FGF23 in rats. J Clin Invest. 2007;117:4003–4008.

12. Krajisnik T, Bjorklund P, Marsell R, et al. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. J Endocrinol. 2007;195:125–131.

✓ 13. ✓ Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359:584–592.

14. Gonzalez EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol. 2004;24:503–510.

✓ 15. ✓ Wada M, Furuya Y, Sakiyama J, et al. The calcimimetic compound NPS R-568 suppresses parathyroid cell proliferation in rats with renal insufficiency. Control of parathyroid cell growth via a calcium receptor. J Clin Invest. 1997;100:2977–2983.

16. Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. Nature. 1993;366:575–580.

17. Murray TM, Rao LG, Divieti P, Bringhurst FR. Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxylterminal region and related biological actions of carboxyl- terminal ligands. Endocr Rev. 2005;26:78–113.

18. Slatopolsky E, Finch J, Clay P, et al. A novel mechanism for skeletal resistance in uremia. Kidney Int. 2000;58:753–761.

19. Coen G, Bonucci E, Ballanti P, et al. PTH 1-84 and PTH “7-84” in the noninvasive diagnosis of renal bone disease. Am J Kidney Dis. 2002;40:348–354.

20. Martin KJ, Akhtar I, Gonzalez EA. Parathyroid hormone: new assays, new receptors. Semin Nephrol. 2004;24:3–9.

21. Monier-Faugere MC, Geng Z, Mawad H, et al. Improved assessment of bone turnover by the PTH-(1-84)/large C-PTH fragments ratio in ESRD patients. Kidney Int. 2001;60:1460–1468.

22. Souberbielle JC, Boutten A, Carlier MC, et al. Inter-method variability in

PTH measurement: implication for the care of CKD patients. Kidney Int. 2006;70:345–350.

23. Malluche HH, Monier-Faugere MC. The role of bone biopsy in the management of patients with renal osteodystrophy. J Am Soc Nephrol. 1994;4:1631–1642.
2✓ 4.✓ KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017; 7:1–59.
25. Floege J. Phosphate binders in chronic kidney disease: a systematic review of recent data. J Nephrol. 2016;29:329–340.
26. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: a pilot randomized controlled trial. Nephrology (Carlton). 2011;16:290–298.
27. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Association of activated vitamin D treatment and mortality in chronic kidney disease. Arch Intern Med. 2008;168:397–403.
2✓ 8.✓ Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in nondialyzed CKD. J Am Soc Nephrol. 2008;19:1613–1619.
29. Investigators JD, Shoji T, Inaba M, et al. Effect of oral alfacalcidol on clinical outcomes in patients without secondary hyperparathyroidism receiving maintenance hemodialysis: the J-DAVID Randomized Clinical Trial. JAMA. 2018;320:2325–2334.
30. Moe SM, Chertow GM, Coburn JW, et al. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. Kidney Int. 2005;67:760–771.
31. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant. 2011;26:1327–1339.
32. Investigators ET, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367:2482–2494.
33. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: a randomized clinical trial. JAMA. 2017;317:156–164.
34. London GM, Marty C, Marchais SJ, et al. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004;15:1943–1951.
35. Malluche HH, Mawad H, Monier-Faugere MC. The importance of bone health in end-stage renal disease: out of the frying pan, into the fire?. Nephrol Dial Transplant. 2004;19(suppl 1):i9–i13.
36. Behets GJ, Spasovski G, Sterling LR, et al. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015;87:846–856.
37. Barreto FC, Barreto DV, Moyses RM, et al. K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients. Kidney Int. 2008;73:771–777.
3✓ 8.✓ Ferreira A, Frazao JM, Monier-Faugere MC, et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. J Am Soc Nephrol. 2008;19:405–412.
39. Sprague SM, Bellorin-Font E, Jorgetti V, et al. Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis. Am J Kidney Dis. 2016;67:559–566.
4✓ 0.✓ Ok E, Asci G, Bayraktaroglu S, et al. Reduction of dialysate calcium level reduces progression of coronary artery calcification and improves low bone turnover in patients on hemodialysis. J Am Soc Nephrol. 2016;27:2475–2486.
4✓ 1.✓ D'Haese PC, Spasovski GB, Sikole A, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl. 2003:S73–S78.

42. London GM, Marchais SJ, Guerin AP, et al. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. J Am Soc Nephrol. 2008;19:1827–1835.
43. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT Plus. 2008;1:135–147.

References

44. Sumida K, Ubara Y, Hoshino J, et al. Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study. Osteoporos Int. 2016;27:1441–1450.
45. Peugh J, Khalil A, Chan MR, Hansen KE. Teriparatide treatment for hypercalcemia associated with adynamic bone disease. JBMR Plus. 2019;3:e10176.
46. Rubin MR, Zhou H, Cusano NE, et al. The effects of long-term administration of rhPTH(1-84) in hypoparathyroidism by bone histomorphometry. J Bone Miner Res. 2018;33:1931–1939.
47. Evenepoel P, Cunningham J, Ferrari S, et al. European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4-G5D. Nephrol Dial Transplant. 2021;36:42–59.
48. Jamal SA, West SL, Miller PD. Fracture risk assessment in patients with chronic kidney disease. Osteoporos Int. 2012;23:1191–1198.
49. Ballanti P, Wedard BM, Bonucci E. Frequency of adynamic bone disease and aluminum storage in Italian uraemic patients-retrospective analysis of 1429 iliac crest biopsies. Nephrol Dial Transplant. 1996;11:663–667.
✓50.✓ Ishani A, Blackwell T, Jamal SA, et al. The effect of raloxifene treatment in
postmenopausal women with CKD. J Am Soc Nephrol. 2008;19:1430–1438.
51. Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res. 2007;22:503–508.
52. Miller PD, Roux C, Boonen S, et al. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the

53.

54.

55.
56.

57.
58.

59.

60.

Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res. 2005;20:2105–2115.
Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–1441.
Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res. 2011;26:1829–1835.
Floege J, Ketteler M. beta2-microglobulin-derived amyloidosis: an update. Kidney Int Suppl. 2001;78:S164–S171.
Zhang P, Fu X, Sawashita J, et al. Mouse model to study human A beta2M amyloidosis: generation of a transgenic mouse with excessive expression of human beta2-microglobulin. Amyloid. 2010;17:50–62.
Corlin DB, Heegaard NH. beta(2)-microglobulin amyloidosis. Subcell Biochem. 2012;65:517–540.
Jadoul M, Garbar C, Noel H, et al. Histological prevalence of beta 2-microglobulin amyloidosis in hemodialysis: a prospective post-mortem study. Kidney Int. 1997;51:1928–1932.
van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J. Effect of dialysis membrane and patient’s age on signs of dialysis-related

amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int. 1991;39:1012–1019.
Ketteler M, Koch KM, Floege J. Imaging techniques in the diagnosis of dialysis-related amyloidosis. Semin Dial. 2001;14:90–93.

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Neurologic Complications of Chronic Kidney Disease

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Disorders of the nervous system may coexist with kidney disease in patients with systemic disorders (e.g., hypertensive encephalopathy, thrombotic microangiopathies, atheroembolic and atherosclerotic disease, vasculitides) and fluid and electrolyte abnormalities. Neurologic complications accompany acute kidney injury (AKI) in the intensive care setting and in outpatients with chronic kidney disease (CKD).
A recent meta-analysis revealed that cognitive impairment is evident across the stages of CKD independent of age-related changes.[1] Furthermore, patients with CKD are at increased risk for toxin- and pharmacologic agent–induced neurotoxicity. This chapter focuses on the direct neurologic consequences of CKD.

UREMIC ENCEPHALOPATHY

The syndrome of uremic encephalopathy (UE) involves a spectrum of brain abnormalities that may range from nearly imperceptible changes to coma.

Pathogenesis

The brain in CKD has decreased metabolic activity and oxygen consumption.[2,3] As long as the underlying kidney disease has not affected cerebral hemodynamics and responsiveness to carbon dioxide, these functions appear intact, but subtle disturbances have been detected after dialysis.
Among the known uremic toxins listed in the European (EUTox) database, 9% (7 of 75 solutes) are associated with neurologic effects.[4]
The balance of excitatory and inhibitory neurotransmitters may be disrupted by organic substances,[5] in particular guanidino compounds, which are increased in cerebrospinal fluid.[6,7] These compounds antagonize γ-aminobutyric acid (GABAA) receptors and at the same time have agonistic effects on N-methyl-d-aspartate glutamate receptors, leading to enhanced cortical excitability. Asymmetric dimethylarginine,[8] which is increased in CKD, inhibits endothelial nitric oxide synthase, and levels correlate with cerebrovascular complications in uremia. The serum level of neuropeptide Y (NPY), a peptide associated with orexigenic (hyperphagic) food intake, was found to be elevated in CKD patients. NPY can diffuse across the blood-brain barrier, and elevated NPY levels in blood promote endothelial dysfunction and regulate neural progenitor cells.[9,10] Disturbances in monoamine metabolism include a depletion of norepinephrine and suppression of central dopamine, which has been linked to the impairment of motor activity in uremic rats. Myoinositol, carnitine, indoxyl sulfate, and polyamine content, as well as disrupted solute transport and permeability, have been implicated in the neuronal dysfunction of uremia. Metabolites of drugs such as cimetidine and acyclovir are increased in uremia because of inhibition of organic anion transporter 3 (OAT3) and may result in neurotoxic syndromes.[11] Levels of opiates, in particular metabolites of meperidine, are increased in plasma because of decreased

excretion through renal cation secretory transport, with subsequent neurotoxicity.[12]
Secondary hyperparathyroidism also may play a role in UE[13,14] because brain calcium is increased in CKD, and calcium transporters within neurons are sensitive to parathyroid hormone (PTH).
Increased cellular calcium may play a role in neuroexcitation, while PTH may increase alkaline phosphatase levels in the brain, therefore indirectly causing cognitive impairment in CKD patients. High levels of alkaline phosphatase in the brain might promote the binding of

tau protein to muscarinic receptors in the hippocampus, leading to a significant increase in cellular calcium level and neuronal cell death.15 High fibroblast growth factor (FGF)-23, directly through its interaction with α-klotho, was associated with a higher risk of dementia in the Framingham study.16 On the other hand, low α-klotho levels were associated with increased risk of dementia.17

Appetite regulation is abnormal in uremia (see Chapter 90). A high rate of tryptophan entry across the blood-brain barrier may increase the synthesis of serotonin, a major appetite inhibitor.18 High levels of cholecystokinin, a powerful anorectic, and low levels of NPY, an appetite stimulant, have been observed. Cachexia may result from anorexia, acidosis, and inflammation. Inflammatory cytokines such as leptin, tumor necrosis factor-α, and interleukin-1 may signal anorexigenic neuropeptides such as proopiomelanocortin and α-melanocyte–stimulating hormone in the arcuate nucleus of the hypothalamus.

Clinical Manifestations

Whereas 20% of critically ill patients with AKI developed neurologic impairment in a study,19 the syndrome in CKD is more subtle, not correlating closely to the level of kidney function.20 Numerous studies with long-term follow-up in CKD patients suggest that cognitive impairment is greater in patients with albuminuria.21,22 Cross-sectional studies in hemodialysis (HD) patients found cognitive impairment in 30%, with about 10% exhibiting severe impairment. Neurocognitive deficits may have special implications for CKD in early childhood, adversely affecting development of the brain.23

UE can manifest as complex mental changes or motor disturbances (Box 89.1). The full-blown syndrome is a risk factor for morbidity and mortality.2,3 Mental findings include emotional changes, depression, disturbing and disabling cognitive and memory deficits, and, in the most severe form, a generalized disorder characterized by delirium, psychosis, seizures, coma, and ultimately death. Severe motor symptoms or signs are rare. Depression, anxiety, and even suicide are important underdiagnosed and undertreated aspects of uremia and may be related to metabolic or poor nutritional state and fear of dialysis or death. Other known causes of depression should always be sought.

Stable UE manifests with fine action tremor, myoclonus, asterixis, and hyperreflexia. Asterixis is characterized by intermittent loss of muscle tone in antigravity muscles. It is distinguished from tremor by the fact that it is not an oscillation but rather an intermittent loss of tone. Myoclonus is also seen in patients with UE. It is similar in timing to asterixis (10–100 ms) but is caused by activation of antigravity muscles. For this reason, some consider asterixis to be a form of negative myoclonus. The distinction between asterixis and myoclonus is not as important as once thought, because both or either may be present in many metabolic encephalopathies and some structural brain diseases as well. Asterixis and myoclonus may be elicited with the hands outstretched but detection may be enhanced by looking at the protruded tongue or the index finger raised with the hand resting on a firm surface. Asterixis and myoclonus may be seen in patients with kidney impairment who have received drugs such as metoclopramide, phenothiazines, antiepileptic drugs including gabapentin, and opioids, especially meperidine. It is imperative for the treating physician to understand the life-threatening complications of such drugs for the patient with CKD before and after initiation of dialysis12 (Table 89.1). Metabolic acidosis may produce an indistinguishable encephalopathy, as can aluminum toxicity. Therefore, a careful search for other causes is required before features potentially consistent with UE are attributed to advanced uremia requiring kidney replacement therapy (KRT).

Clinical Manifestations of Uremic Encephalopathy

BOX 89.1

Early Encephalopathy

Mental Changes
- Mood swings
- Impaired concentration, loss of recent memory
- Insomnia, fatigue, apathy

Motor Changes
- Hyperreflexia
- Tremor, asterixis
- Dysarthria, altered gait, clumsiness, unsteadiness

Late Encephalopathy

Mental Changes
- Altered cognition and perception
- Illusions, visual hallucinations, agitation, delirium
- Stupor, coma

Advanced UE is usually characterized by a reduced level of consciousness, anorexia, asterixis, myoclonus, and upper motor neuron signs such as spasticity, dysarthria, and gait disturbance.

Diagnosis and Differential Diagnosis

Severe UE is unlikely to occur in patients with CKD who are followed closely before initiation of KRT (see Chapter 95). UE is more likely to occur in patients who initially present with kidney failure or dialysis patients after missing many treatments. The blood urea nitrogen concentration most commonly exceeds 200 mg/dL. Hypertension is often present, and the manifestation may be mistaken for hypertensive encephalopathy. The diagnosis of UE is based on clinical findings and their improvement after adequate therapy (see next section). If the patient develops more insidious signs of cognitive impairment while undergoing dialysis, inadequate dialysis treatment must be distinguished from dialysis-associated dementia, Alzheimer disease, or other causes of chronic cognitive impairment. Lumbar puncture, electroencephalography, and imaging procedures largely serve to exclude other causes in patients in whom the clinical diagnosis is doubtful. In UE the cerebrospinal fluid is often abnormal, sometimes demonstrating a modest pleocytosis (usually <25 cells/µL) and increased protein (usually <100 mg/dL). The electroencephalogram is usually abnormal but nonspecific. Generalized slowing in the theta and delta wave ranges is found.[24] Brain imaging often shows cerebral atrophy and enlargement of the ventricles (Fig. 89.1).

The differential diagnosis of UE is shown in Table 89.2. Seizure activity may be secondary to UE, hypertensive encephalopathy, cerebral embolism, cerebral venous thrombosis, or electrolyte and acidbase abnormalities. Tetany can develop when treatment involves alkalinization of an acidemic patient with kidney disease and hypocalcemia. Severe electrolyte abnormalities, including hypocalcemia, hypomagnesemia, hyponatremia, and hypophosphatemia, may manifest with delirium.

Treatment

Most nephrologists consider advanced cognitive or memory impairment an indication for initiation of KRT. Most of the manifestations of central nervous system (CNS) involvement are reversible with dialysis within days or weeks, but mild signs of UE may persist. Patients who do not manifest severe signs of encephalopathy often notice improvement in cognitive function once they start KRT. Some may describe this as a “fog lifting.” In dialyzed patients with persistent or recurrent

Motor Changes
- Myoclonus, tetany
- Hemiparesis
- Seizures

TABLE 89.1

Opioid Use in End-Stage Kidney Disease

Drug

Active Metabolites

Comments

Codeine
Hydrocodone
Meperidine
Morphine

Morphine
Hydromorphone
Normeperidine
Morphine-3-glucuronide,
Morphine-6-glucuronide
Hydromorphone-3glucuronide
Oxymorphone
Noroxycodone
No active metabolites

Active metabolites accumulate in patients with kidney failure; should avoid in dialysis. Meperidine should not be used in chronic kidney disease because normeperidine causes central nervous system toxicity (seizures, opisthotonos) in kidney disease.

Active metabolites accumulate in patients with kidney failure; can cause myoclonus and respiratory depression; mostly replaced by hydromorphone.

Mostly metabolized in liver. Active metabolites removed by dialysis, but small amounts accumulate in patients with kidney failure.

Hydromorphone
Oxycodone
Fentanyl
Methadone

Metabolized in liver; not removed by dialysis.
Fecal excretion; not removed by dialysis.

symptoms, increasing the delivered dialysis dose may improve clinical findings. Successful kidney transplantation usually results in resolution of the UE syndrome within days.

Correction of anemia with recombinant erythropoietin in the dialysis patient (see Chapter 86) may be associated with improved cognitive function[25] and decreased slowing on the electroencephalogram.[26]

Too rapid overcorrection of anemia may be associated with seizures.

Treatment of psychosis in kidney disease must consider the pharmacokinetics of the specific agent. For example, risperidone may be useful,

but dose reduction is necessary because of the prolonged half-life in CKD.

Of note, intensive blood pressure (BP) control may not improve cognitive impairment in CKD patients. A subset of patients (n = 670) in the large SPRINT study received magnetic resonance imaging follow-up. Surprisingly, there was an increase in white-matter lesion volume and a decrease in total brain volume in the intensive antihypertensive treatment group compared with the standard treatment group.[27]

PERIPHERAL NEUROPATHY

Fig. 89.1 Magnetic Resonance Imaging Findings in Uremic Encephalopathy. Axial T2-weighted (fluid-attenuated inversion recovery) scan from a 40-year-old woman. The extensive hyperintense lesion involves the cortical and subcortical areas of both occipital lobes and, in a more focal distribution, the basal ganglia and the frontal white matter (arrows). The volume of the affected brain parenchyma is increased. Reversibility of the MRI changes was noted 2 weeks after the initiation of regular dialysis. (Courtesy A. Thron, Aachen, Germany.)

TABLE 89.2

Patients with CKD are susceptible to both polyneuropathies and mononeuropathies. The pathophysiologic process of polyneuropathy involves axonal degeneration in a length-dependent fashion. Primary demyelinating neuropathies are rare in the context of CKD except when the underlying kidney disease also causes demyelination (e.g., multiple myeloma). Mononeuropathies in CKD may be caused by nerve entrapment with compression of metabolically weakened nerves, particularly in wheelchair users or bed-bound patients. Mononeuritis multiplex should raise the possibility of vasculitic neuropathy, especially when systemic vasculitis (e.g., antineutrophil cytoplasmic antibody–positive small-vessel vasculitis or polyarteritis nodosa) is causing the CKD. Functional sparing of small-diameter axons in uremia is suggested by relatively intact thermal thresholds (hot and cold thermal threshold testing is a surrogate for pain threshold). The modestly slowed nerve conduction velocities in the polyneuropathies of uremia may be related to the reversible inhibition of the sodium-potassium adenosine triphosphatase by a uremic toxin. According to the middle molecule hypothesis, accumulated toxins in the range of 300 to 12,000 Da, including peptide hormones and polyamines, may lead to progression of neuropathy in HD patients.[6,13,14] Lower limb motor axons in uremic patients are depolarized before but not after dialysis, consistent with a role of hyperkalemia in the development of altered nerve excitability.[28] Elevated magnesium levels will also slow nerve conduction velocity. In vitro, extracellular acidosis contributes to decreased sodium conductance in large sensory neurons. Very slow nerve conduction velocities (i.e., less than half normal) suggest a demyelinating

Differential Diagnosis of Uremic Encephalopathy

Differential Diagnosis

Comment

Hemodynamic or Vascular Encephalopathy
Systemic inflammatory response syndrome
Observed in septic patients.
Systemic vasculitis
Vasculitis or lupus with cerebral involvement.
Cerebral atheroembolic disease
Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity
cyanosis, livedo reticularis, and eosinophilia.
Drug-Induced Neurotoxicity
Analgesics
Meperidine, codeine, morphine, gabapentin.
Antibiotics
High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and
aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy).
Psychotropics
Lithium, haloperidol, clonazepam, diazepam, chlorpromazine.
Immunosuppressants
Cyclosporine, tacrolimus.
Chemotherapeutics
Cisplatinum, ifosfamide.
Others
High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum metoclopramide (myoclonus, dystonia).
Subdural Hematoma
Posterior reversible encephalopathy
Observed particularly after kidney transplantation as a result of reversible, abnormal permeability of the blood-brain
syndrome
barrier.
Often manifests with headache followed by mental depression, visual loss, and seizures in the context of volume
expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors.
Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies.

neuropathy, a finding that should lead the physician to seek a specific cause (e.g., a paraprotein).

Uremic neuropathy may progress rapidly in advanced CKD.2 28 29 Characteristic symptoms and signs are sensory loss, pain, paresthesias, and insensitivity to temperature, particularly cold. Motor findings such as foot drop can also occur. Phrenic neuropathy may cause dyspnea because of poor diaphragmatic movement, whereas hiccups are more likely a result of the CNS effects of uremia. The distal lower extremities are usually affected first because axonal polyneuropathies are length dependent. Decrease in vibratory sensation and position sense and Romberg sign (i.e., greater instability of stance with eyes closed than with eyes open) are common signs. Muscle stretch reflexes are reduced or absent. In the patient with diabetes who is on dialysis and has progressive neuropathy, it is important to establish adequacy of dialysis, as well as glucose control. Uremic polyneuropathy is aggravated by malnutrition, inadequately controlled hypertension, certain comorbid conditions (e.g., diabetes mellitus, alcohol use, atherosclerotic vascular disease), and medications (e.g., nitrofurantoin, isoniazid, hydralazine). The diagnosis of uremic polyneuropathy can usually be made from clinical findings. If electromyography and nerve conduction tests are performed, they should not be done in an extremity bearing an arteriovenous fistula because vascular access surgery may cause local nerve injury, which can complicate the interpretation of these studies.28 Nerve conduction velocity is modestly reduced, and needle electromyography shows evidence of chronic denervation and sometimes reinnervation.

Lead polyneuropathy should be considered, particularly when there is a known exposure history. A lower motor neuron syndrome caused by lead toxicity may be mistaken for amyotrophic lateral sclerosis. A bone lead scan using K-line x-ray fluorescence spectroscopy of the tibia is a promising new noninvasive test that may become useful. Serum lead values and red cell protoporphyrin levels may be normal if exposure is remote. There may be associated depression, the so-called saturnine temperament, which takes its name from the ancient belief that Saturn was made of lead and was associated with a melancholy disposition. Gout, hypertension, glycosuria, and microcytic anemia also may be caused by lead toxicity.

Other conditions in the differential diagnosis of mixed polyneuropathy include other heavy metals (e.g., arsenic, mercury), nutritional deficiencies (e.g., pyridoxine, folate, thiamine, niacin), HIV-related neuropathy, amyloid, vasculitis, sarcoid, lupus, and a paraneoplastic syndrome.

Progressive polyneuropathy may be an indication for initiation of dialysis or kidney transplantation. Symptoms usually will not deteriorate further or may even show a slow improvement thereafter. If polyneuropathic symptoms worsen in a dialysis patient, the dialysis dose should be increased. Physical therapy is an important component of the management. Patients experiencing neuropathic pain may be treated with tricyclic antidepressants (e.g., amitriptyline 10–25 mg, increasing to 75–150 mg at bedtime) or antiepileptic drugs (e.g., carbamazepine 200–400 mg initially, increasing to 1200 mg maximally; phenytoin 100–200 mg initially, maximally 600 mg).2 3 Gabapentin may result in sedation and myoclonus in CKD because of marked prolongation of the drug’s half-life, and should be prescribed at reduced doses. Deficiencies of cobalamin (vitamin B12), folate, and pyridoxine may be reflected in an elevated serum homocysteine level. Methylmalonic acid may be elevated in vitamin B12 deficiency, and it is critical to promptly diagnose this deficiency because irreversible changes to the nervous system may develop within months. Loss of balance and position sense may be mistaken for neuropathy in pernicious anemia. Vitamin B12 deficiency and folate deficiency manifest with a megaloblastic or macrocytic anemia. If folate is given to a patient deficient in vitamin B12, acute posterior and lateral column findings of subacute combined degeneration of the spinal cord may develop as the low store of vitamin B12 is used to correct the anemia. Thiamine deficiency, often associated with malnutrition, can aggravate neuropathy, but whether replacement of any of these vitamins is effective in preventing or curing polyneuropathy in uremic patients is not well established. Thiamine deficiency is the cause of Wernicke encephalopathy in dialysis or malnourished patients. This syndrome is suspected when the triad of mental change (often amnesia), ataxia (most often affecting gait), and oculomotor disturbances (most often abducens palsies with gaze-evoked nystagmus) is seen in any patient whose diet is deficient in B vitamins. When amnesia is combined with a polyneuropathy, the term Korsakoff syndrome applies. In malnourished patients, the cause of Korsakoff syndrome is usually multiple subclinical attacks of Wernicke encephalopathy, hence the term Wernicke-Korsakoff disease.

Specific mononeuropathic syndromes include ulnar nerve entrapment, associated with uremic tumoral calcinosis and subsequent ischemia, and carpal tunnel syndrome, for example, caused by β2-microglobulin–derived amyloidosis (see Chapter 88) or by an arteriovenous fistula.2,29 These syndromes may be treated with antiinflammatory agents, antiepileptic drugs, and surgical decompression. It is important to ensure adequacy of dialytic treatment.

Pruritus in the uremic patient may be severe and is not primarily a skin disorder (see also Chapter 91). Rather, it may represent a form of sensory neuropathy. This symptom usually improves with KRT. Antihistamines, with their sedating effect, are not always effective. Gabapentin and carbamazepine block the afferent pathway in uremic neuropathic itch. Gabapentin and pregabalin inhibit calcitonin gene–related peptide from primary afferent neurons by inhibiting GABA and opioid receptor antagonists (naloxone and naltrexone) and may antagonize transmission of itch. Antidepressants also have been successful, possibly by interfering with reuptake of serotonin and norepinephrine to reduce pruritus perception.30

AUTONOMIC NEUROPATHY

Autonomic neuropathy is also very common in patients with advanced CKD, probably because diabetes is a common cause of CKD. Hyperglycemia may be more difficult to control in CKD because glucose filtration is decreased. Amyloidosis, a less common cause of CKD, is associated with autonomic neuropathy. A typical manifestation is orthostatic hypotension, which is most severe in patients with diabetes mellitus or amyloidosis as a cause of CKD. Some dopaminergic drugs used in Parkinson disease or parkinsonism itself may cause orthostasis. Some patients have peripheral neuropathy and may manifest hyporeninemic hypoaldosteronism with hyperkalemia and renal tubular acidosis. Hypotension or orthostasis may preclude treatment with angiotensin antagonists and may complicate fluid removal during dialysis. CKD patients were thought to have decreased baroreceptor function, but normal baroreceptor responses to graded decrements in mean arterial BP have been described.31 Instead, CKD patients have sympathetic hyperactivity, which contributes to hypertension, more rapid progression to kidney failure in the predialysis patient, and greater cardiovascular (CV) risk. Accordingly, α- and β-adrenergic blockade has been advocated in CKD.31 Autonomic neuropathy is caused by axonal disease and thus is length dependent. For that reason, the longest autonomic nerve, the vagus nerve, is usually the first affected, resulting in the loss of the normal sinus arrhythmia, significant reductions of day-night BP variation, and possibly sudden cardiac death related to the loss of the balance between the sympathetic and parasympathetic limbs of the autonomic nervous system. Reports of gastrointestinal problems include gastroparesis, which is particularly problematic for the diabetic patient. In the

predialysis patient, nausea and early satiety associated with gastroparesis may be confused with uremia. Several medical regimens have been used for the uremic patient with gastroparesis; they include erythromycin, which can activate the gastric motilin receptor. Levodopa-carbidopa, as a dopamine agonist, may be effective, as may metoclopramide 10 mg before sleep or domperidone 10 to 20 mg. Nocturnal diarrhea is another consequence of vagal neuropathy. Erectile dysfunction and incontinence (urinary more commonly than fecal) also may be related to autonomic neuropathy.

CRANIAL NEUROPATHIES

Cranial nerve involvement is most often vestibulocochlear. Hearing loss needs to be distinguished from drug-induced ototoxicity or the neurosensory deafness of hereditary nephropathy.2 3 Bilateral vestibular failure leads to inability to stand or to walk normally without vertigo or nystagmus. It is often related to the use of aminoglycoside antibiotics in the patient with CKD. N-Acetylcysteine given with aminoglycosides may reduce the risk for cochlear toxicity. Sulfa-based loop diuretics, often used at high doses in patients with CKD, may cause vestibular or cochlear damage. Decreased olfactory function, especially a reduced ability to discriminate among and identify odors, and dysgeusia are commonly seen in patients with CKD.

SLEEP DISORDERS

Sleep disorders in CKD include daytime sleepiness, insomnia, sleep apnea and restless legs syndrome.32 Many HD and peritoneal dialysis patients exhibit obstructive sleep apnea that is independent of obesity.33 The associated sleep deprivation contributes to fatigue and cognitive impairment and increases the risk for CV complications.33

Both obstructive and central sleep apnea are prevalent in patients with CKD,34 but the clinical predictive scores used to screen for sleep apnea have poor specificity in CKD patients32; diagnostic testing with polysomnography and actigraphy systems may be preferable. Obstructive sleep apnea is a condition in which blockage of the upper airway can interfere with nocturnal breathing. Nighttime oxygen and continuous positive airway pressure (CPAP) may help. Treatment of obstructive sleep apnea is effective, including use of CPAP (as in nonuremic individuals)35 and conversion to nocturnal HD.36 37 Central sleep apnea, often accompanied by heart failure, causes prolonged apneic episodes38 and may respond to oxygen. Initiation of dialysis may be helpful.

Daytime sleepiness is common and underdiagnosed in patients with CKD and contributes not only to worsened hypertension and increased CV risk but also to social dysfunction. Whether obstructive sleep apnea and its associated excessive daytime sleepiness is an independent risk factor for the progression of kidney failure is not yet settled. It is assessed by a multiple sleep latency test; that is, the duration of time from “lights out” to the onset of sleep. Sleep latency less than 5 minutes is consistent with sleep deprivation. There was also a reduced proportion of rapid eye movement sleep. An increased arousal frequency is related to periodic limb movements during sleep and the presence of sleep apnea.

Sleep-wake complaints are common in patients on dialysis, with an incidence of up to 80%. Contributors include peripheral neuropathy, pain, and pruritus.

RESTLESS LEGS SYNDROME (EKBOM SYNDROME)

Restless legs syndrome (RLS), described by K.A. Ekbom in 1944, is frequent in CKD, particularly in women. It may result from a decrease in dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and increased spinal cord excitability. RLS is characterized by unpleasant “creeping” sensations in the extremities and a compulsive need to move the limbs, usually the legs.[39,40] The movement is worsened by periods of rest or inactivity and is relieved by walking or stretching. Symptoms are worse at night and may lead to insomnia and consequent daytime sleepiness and reduced quality of life. Nocturnal muscle cramps are common in CKD and should be distinguished from RLS. The Ekbom syndrome consists of restless legs plus other obsessive-compulsive–like disorders including various pica behaviors, such as pagophagia (ice eating), geophagia (clay eating), and amylophagia (starch eating).

Periodic limb movement disorder is characterized by episodes of involuntary repetitive extension of the big toe and dorsiflexion of the ankle, as well as flexion of the knee and hip.[40] This disorder is more likely to occur in those with RLS.

Iron deficiency or iron transport into the CNS plays a central role in RLS. Iron is a cofactor for the enzyme tyrosine hydroxylase, the ratelimiting step in the biosynthesis of dopamine, possibly explaining the link between iron deficiency and dopamine deficiency in RLS. Overt iron deficiency is easily diagnosed and should be treated.[40] In patients with normal red blood cell indices and serum iron and total ironbinding capacity, serum ferritin should be tested. Transferrin saturation ratio may be an even more sensitive indicator of iron deficiency.

Although not clinically indicated for RLS, analysis of spinal fluid ferritin may reveal a subtle CNS iron deficiency syndrome. RLS often persists after initiation of dialysis but may improve after transplantation and has been linked to abnormalities in calcium and phosphorus metabolism as well as to anemia. Iron replacement should be initiated if there is any indication of iron deficiency. Intravenous iron may be required (see Chapter 86). Dopaminergic treatment is often helpful, usually starting with the dopamine receptor agonists pramipexole and ropinirole. Levodopa combined with decarboxylase inhibitors (e.g., carbidopa-levodopa) may be used as well as gabapentin, opioids, and benzodiazepines.[39,40] As mentioned earlier, gabapentin should be used cautiously. Older dopamine receptor agonists, such as bromocriptine and pergolide, are rarely used now for RLS.

NEUROLOGIC SYNDROMES ASSOCIATED WITH KIDNEY REPLACEMENT THERAPY

KRT is associated with an increased incidence of subdural hematoma and intracranial hemorrhage, presumably connected to hypertension and anticoagulation with HD as well as Wernicke encephalopathy (see earlier discussion).[2,3] A syndrome of muscle weakness has been attributed to l-carnitine depletion from dialysis, leading to decreased mitochondrial fatty acid usage.

Dialysis disequilibrium syndrome is a rare complication of rapid metabolic changes occurring with HD, usually affecting patients in whom HD is being initiated (see Chapter 100).[41] It is most common in patients with severe uremia of long duration and with severe hypertension. Characterized by acute onset of headache, nausea, vomiting, disorientation, a state of confusion, and seizures, it is a diagnosis of exclusion. It usually results from acute changes in osmolality during HD, in which the rapid decrease in urea in the extracellular fluid favors water movement into brain cells, resulting in cerebral edema. Alternatively, other intracellular osmolytes within brain cells may draw water from the extracellular fluid. The syndrome normally reverses spontaneously after a period of regular HD. If no improvement is seen after a month of HD, one should investigate for other possible causes of the clinical syndrome by imaging the brain, obtaining an electroencephalogram, and examining the spinal fluid. Dialysis disequilibrium syndrome may be prevented by decreasing HD length to 2 to 3 hours, dialyzing daily, providing mannitol during the dialysis run (such as 25 g IV every 90 minutes) and reducing HD efficacy during the first sessions.

Dialysis encephalopathy (formerly called dialysis dementia) is probably a multifactorial syndrome occurring in sporadic-endemic and epidemic types. In particular, in the epidemic type, aluminumbased phosphate binders and exposure to dialysate containing more than 20 μg of aluminum per liter are considered to be major causes.42 43 Aluminum transferred to the nervous system by transferrin results in a characteristic clinical condition with prominent stuttering that

usually worsens toward the end of a dialysis session and encephalopathy, initially responding well to IV benzodiazepines but then becoming unresponsive, leading to severe encephalopathy and death. With the almost universal preparation of dialysate water by reverse osmosis and the marked reduction in aluminum-containing phosphate binder use, aluminum-induced encephalopathy has virtually disappeared. If it is present, aluminum toxicity is treated with deferoxamine (see Chapter 88). Kidney transplantation is an effective treatment for dialysis dementia.

SELF-ASSESSMENT QUESTIONS

1. A 50-year-old man with chronic hypertension, CKD, and eGFR of 8 mL/min/1.73 m^2 who is not yet on dialysis presents with confusion, lethargy, and myoclonus. Which of the following factors may contribute to these neurologic changes?
A. Use of gabapentin for neuropathic pain
B. Poorly controlled secondary hyperparathyroidism
C. Poorly controlled anemia with iron deficiency
D. Poor dietary protein intake resulting in decreased blood urea level
E. A and D
F. All of the above

2. A 25-year-old woman has hypertension, seizures, and encephalopathy believed to be caused by uremia. Her blood pressure is 200/120 mm Hg. Her blood chemistry reveals Na 120 mEq/L, K 4 mEq/L, Cl 80 mEq/L, and HCO_3 15 mEq/L. The anion gap is 25 mEq/L, glucose 70 mg/dL, and BUN 200 mg/dL. Which of the following is the best answer?

A. Hypotonic hyponatremia may contribute to the altered neurologic picture.
B. The seizures may be from severe hypertension.
C. This presentation is characteristic of uremic encephalopathy.
D. The BUN should be decreased to normal promptly with dialysis.
E. Both A and D are incorrect.
F. A, B, and C are correct.

3. Findings associated with restless legs syndrome include all of the following except:
A. obsessive-compulsive behavior.
B. amylophagia (starch craving).
C. iron overload and deposition in the basal ganglia.
D. response to dopaminergic medication.
E. commonly, improvement during daytime hours and with exercise.

REFERENCES

1. Brodski J, et al. A systematic review of cognitive impairments associated with kidney failure in adults before natural age-related changes. J Int Neuropsychol Soc. 2019;25(1):101–114.
2. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. Clin Neurol Neurosurg. 2004;107(1):1–16.
3. Burn DJ, Bates D. Neurology and the kidney. J Neurol Neurosurg Psychiatry. 1998;65(6):810–821.
4. Viggiano D, et al. Mechanisms of cognitive dysfunction in CKD. Nat Rev Nephrol. 2020;16(8):452–469.
5. Smogorzewski MJ. Central nervous dysfunction in uremia. Am J Kidney Dis. 2001;38(4 suppl 1):S122–S128.
6. Vanholder R, et al. New insights in uremic toxins. Kidney Int Suppl. 2003;(84):S6–S10.
7. De Deyn PP, et al. Endogenous guanidino compounds as uremic neurotoxins. Kidney Int Suppl. 2001;78:S77–S83.
8. De Deyn PP, Vanholder R, D’Hooge R. Nitric oxide in uremia: effects of several potentially toxic guanidino compounds. Kidney Int Suppl. 2003;(84):S25–S8.
9. Choi B, et al. Elevated neuropeptide Y in endothelial dysfunction promotes macrophage infiltration and smooth muscle foam cell formation. Front Immunol. 2019;10:1701.
10. Geloso MC, et al. Cellular targets for neuropeptide Y-mediated control of adult neurogenesis. Front Cell Neurosci. 2015;9:85.
11. Ohtsuki S, et al. Role of blood-brain barrier organic anion transporter 3 (OAT3) in the efflux of indoxyl sulfate, a uremic toxin: its involvement in neurotransmitter metabolite clearance from the brain. J Neurochem. 2002;83(1):57–66.
12. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613–624.
13. Fraser CL, Arieff AI. Nervous system complications in uremia. Ann Intern Med. 1988;109(2):143–153.
14. Lockwood AH. Neurologic complications of renal disease. Neurol Clin. 1989;7(3):617–627.
15. Díaz-Hernández M, et al. Tissue-nonspecific alkaline phosphatase promotes the neurotoxicity effect of extracellular tau. J Biol Chem. 2010;285(42):32539–32548.
16. McGrath ER, et al. Circulating fibroblast growth factor 23 levels and incident dementia: the Framingham heart study. PLoS One. 2019;14(3):e0213321.
17. Kuriyama N, et al. Association between α-klotho and deep white matter lesions in the brain: a pilot case control study using brain MRI. J Alzheimers Dis. 2018;61(1):145–155.
18. Aguilera A, et al. Eating behavior disorders in uremia: a question of balance in appetite regulation. Semin Dial. 2004;17(1):44–52.
19. Mehta RL, et al. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. Kidney Int. 2004;66(4):1613–1621.
20. Tyler HR. Neurologic disorders seen in the uremic patient. Arch Intern Med. 1970;126(5):781–786.
21. Ekblad LL, et al. Albuminuria and microalbuminuria as predictors of cognitive performance in a general population: an 11-year follow-up study. J Alzheimers Dis. 2018;62(2):635–648.

22. Martens RJ, Estimated GFR, et al. Albuminuria, and cognitive performance: the maastricht study. Am J Kidney Dis. 2017;69(2):179–191.
23. Gipson DS, et al. The nervous system and chronic kidney disease in children. Pediatr Nephrol. 2004;19(8):832–839.
24. Balzar E, et al. Quantitative EEG: investigation in children with end stage renal disease before and after haemodialysis. Clin Electroencephalogr. 1986;17(4):195–202.
25. Vinothkumar G, et al. Correlation between abnormal GSK3β, β amyloid, total tau, p-tau 181 levels and neuropsychological assessment total scores in CKD patients with cognitive dysfunction: impact of rHuEPO therapy. J Clin Neurosci. 2019;69:38–42.
26. Stivelman JC. Benefits of anaemia treatment on cognitive function.

Nephrol Dial Transplant. 2000;15(suppl 3):29–35.

27. Nasrallah IM, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. JAMA. 2019;322(6):524–534.

28. Krishnan AV, et al. Altered motor nerve excitability in end-stage kidney disease. Brain. 2005;128(Pt 9):2164–2174.

29. Krishnan AV, et al. Sensory nerve excitability and neuropathy in end stage kidney disease. J Neurol Neurosurg Psychiatry. 2006;77(4):548–551.

30. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. Am J Kidney Dis. 2007;50(1):11–20.

31. Koomans HA, Blankestijn PJ, Joles JA. Sympathetic hyperactivity in chronic renal failure: a wake-up call. J Am Soc Nephrol. 2004;15(3):524–537.

32. Maung SC, et al. Sleep disorders and chronic kidney disease. World J Nephrol. 2016;5(3):224–232.

33. Hanly P. Sleep apnea and daytime sleepiness in end-stage renal disease. Semin Dial. 2004;17(2):109–114.

34. Lin CH, Lurie RC, Lyons OD. Sleep apnea and chronic kidney disease: a state-of-the-art review. Chest. 2020;157(3):673–685.

35. Marrone O, et al. Fixed but not autoadjusting positive airway pressure attenuates the time-dependent decline in glomerular filtration rate in patients with OSA. Chest. 2018;154(2):326–334.

36. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344(2):102–107.

37. Tang SC, et al. Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 2006;17(9):2607–2616.

38. Yumino D, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation. 2010;121(14):1598–1605.

39. Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med. 2003;348(21):2103–2109.

40. Barrière G, et al. The restless legs syndrome. Prog Neurobiol. 2005;77(3):139–165.

41. Arieff AI. Dialysis disequilibrium syndrome: current concepts on pathogenesis and prevention. Kidney Int. 1994;45(3):629–635.

42. Alfrey AC. Dialysis encephalopathy. Kidney Int Suppl. 1986;18. S53–7.

43. Nayak P. Aluminum: impacts and disease. Environ Res. 2002;89(2):101–115.

90

Nutrition in Chronic Kidney Disease

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LIFESTYLE ADVICE: NUTRITION

In the early stages of chronic kidney disease (CKD), the emphasis of disease management is on lifestyle interventions. This includes maintaining or achieving a healthy body weight, ensuring good blood glucose control if diabetes is present, and providing dietary interventions to improve blood pressure (BP) and lipid levels. A healthy diet as set out by the World Health Organization (WHO) encourages:

- A variety of vegetables, fruits, legumes, nuts, and whole grains
- Limiting energy intake from fats (with unsaturated fats being preferable to saturated fats)
- Limiting total energy intake from free sugars
- Reducing salt intake

There has been much discussion about reducing protein in the diet and the extent to which it may help slow progression of CKD. Although most would promote moderating protein intake (0.8–1 g/kg body weight/day), opinions differ regarding the ideal level of protein intake as CKD advances.

Multiple levels of protein restriction have been proposed for patients with CKD stages 3 to 5 not on dialysis, with different recommendations for those with or without diabetes[1–4] (Table 90.1). However, a Cochrane review outlines the complexity of this evidence and highlights the need for further research before these dietary approaches can be recommended for widespread use.[5] This therefore remains under discussion.

In people with a solitary kidney (e.g., after nephrectomy) or at high risk for CKD, consider moderating protein to 0.8 to 1.0 g/kg body weight as indicated in the International Society of Nutrition and Metabolism (ISRNM) Commentary.[3,6] Certain patient populations, such as patients with polycystic kidney disease, appear to benefit less from a low protein diet,[1] but even these patients should avoid high dietary protein intake greater than 1.0 g/kg/day.[6] A higher protein intake of 1.0 to 1.2 g/kg body weight/day is recommended for dialysisdependent patients.[1]

When advising patients with CKD about their protein requirements, factors to consider include diagnosis, CKD stage, comorbidity, nutritional status, food preferences, motivation, cooking skills, and dietetic resources. Lower levels of protein may be advised for those who are motivated, otherwise well/stable, and able to be closely monitored. Low-protein diets can be difficult to implement, in practice requiring adequate resourcing of specialist renal dieticians to allow clinical judgment to be exercised. Individuals need careful monitoring of nutritional status to help prevent malnutrition while acknowledging patient preferences and adherence.

More recently, a plant-dominant (PLADO) low-protein diet has also been proposed, where more than 50% of protein is sourced from plants with a total daily protein intake in the range of 0.6 to 0.8 g/kg body weight/day. This diet was designed for people with CKD who do not need dialysis and may be of interest for the future.[7]

The determination of body weight for diet prescription, whether it be ideal body weight, body mass index (BMI), usual or current, or adjusted depends on clinical judgment because adjustment must be considered for people who are severely underweight or obese.[1]

Malnutrition: Protein-Energy Wasting

Protein-energy wasting (PEW) is defined as a state of nutritional and metabolic derangements in patients with CKD that may negatively affect nutritional status and lean body mass, leading to frailty.8 Inflammation often coexists, and nutrition intervention in isolation may not successfully reverse the loss of skeletal muscle and fat mass.9 PEW is common among patients with CKD, especially those undergoing maintenance dialysis,10,11 and is associated with increased morbidity and mortality. Several factors contribute to the high incidence of PEW:

✓ • ✓ Inadequate dietary protein and energy intake: There is a spontaneous reduction in nutrient intake that parallels the decrease in glomerular filtration rate (GFR) and is largely driven by anorexia.12 Anorexia in CKD may be caused by impaired taste acuity and diminished olfactory function, medications, autonomic gastroparesis, psychological and socioeconomic factors, and inadequate dialysis. Suboptimal intake can be further compounded by frailty, poverty, advanced age, and multiple acute or chronic comorbidities.

✓ • ✓ Inappropriate or overzealous dietary restrictions may have been recommended, which is particularly relevant for patients with endstage kidney disease (ESKD).13,14

✓ • ✓ Protein and amino acid losses occur during dialysis treatment. For those on peritoneal dialysis (PD), these losses may increase during episodes of peritonitis.

✓ • ✓ Metabolic acidosis and periods of acute or chronic illnesses may induce protein catabolism. This is mediated in large part through the ubiquitin-proteasome pathway of protein degradation.15

✓ • ✓ Protein catabolic effects that can further compromise patients early after transplantation include large doses of corticosteroids, the stress response to surgery, and delayed graft function.

✓ • ✓ Chronic inflammation may contribute to both an increase in nutritional needs and anorexia. Alterations in intestinal microbiota and increased permeability of the intestinal barrier may contribute to the pathogenesis of inflammation (see Chapter 83).16

✓ • ✓ Endocrine disorders, such as insulin resistance (associated with increased muscle breakdown), vitamin D deficiency, and increased parathyroid hormone concentrations have long been considered contributors to protein energy wasting, although the data remain inconclusive regarding the exact mechanisms involved. There is

Guidelines for Levels of Dietary Protein Intake for Chronic Kidney Disease (Stages 3–5) Not on Dialysis

TABLE 90.1

Protein (g/kg BW/day)[a]

Comments

0.8–1.0 g/kg/day
0.8 g/kg/day

Widely adopted to moderate protein for CKD patients
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[4] (CKD [stages 4–5] patients with or without diabetes)
KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease[2] (CKD patients with diabetes)
KDOQI clinical practice guideline for nutrition in CKD:2020 update[1] (CKD patients with diabetes under close supervision)
ISRNM Commentary on the KDOQI clinical practice guideline for nutrition in CKD 2020[3] (suggests a more streamlined target for CKD patients with or without diabetes under close supervision)
KDOQI clinical practice guideline for nutrition in CKD:2020 update[1] (CKD patients without diabetes who are metabolically stable and under close supervision)

0.6–0.8 g/kg/day

0.55–0.6 g/kg/day or 0.28–0.43 g/kg/day (supplemented
with essential keto acid/amino acid analogs to meet
protein requirements (0.55–0.60 g/kg body weight/day)

[a] Determination of body weight depends on clinical judgment. 1

BW, Body weight; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Clinical Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; ISRNM, International Society of Nutrition and Metabolism.

some evidence of an association between fibroblast growth factor-23 (a phosphate-regulating hormone) and inflammation in CKD.[17]

Obesity Paradox in Chronic Kidney Disease

Although there is a high prevalence of PEW in patients with CKD, which is associated with poorer outcomes, paradoxically, a higher BMI is associated with better survival in patients receiving hemodialysis (HD). This is termed reverse epidemiology (see Chapter 84). This relationship does not hold for morbid obesity in patients receiving HD, which may be used as a predictor of higher mortality.[1]

Of note, obesity in some centers can prevent a patient being activated on the transplant list, and support to achieve an acceptable BMI is often needed.

Assessment of Nutritional Status

The measurement of nutritional status does not lend itself to one simple test, and a panel of measures is required. Table 90.2 summarizes some of the methods used for the assessment of nutritional status.

ESTIMATION OF INTAKE

Diet history, recall, and food diaries are the mainstays for estimation of dietary nutrient intake. In dialysis-dependent patients, a gradual decrease in blood urea nitrogen (BUN) and reduced phosphate and potassium levels may indicate a decrease in protein intake, and a low serum cholesterol level may indicate a poor calorie intake.

In HD, the protein catabolic rate (PCR), also known as the protein equivalent of total nitrogen appearance (PNA), can be estimated from interdialytic changes in BUN concentration in serum. The interdialytic appearance of urea is determined by measuring the BUN at the end of one dialysis session and just before the start of the next dialysis session. Among patients who have low BUN, measuring the change in BUN between dialysis sessions distinguishes adequate dialysis as a cause of low BUN from poor intake resulting from inadequate dialysis. The PCR is expressed as g/day. Usually, the PCR is normalized to the patient’s body weight (nPCR), which is expressed as g/kg/day. Assuming that nitrogen excretion equals nitrogen intake in steady state, nPCR can be used to approximate dietary protein intake in the short term but results should be interpreted with caution. The PCR in patients treated with HD is calculated by various urea kinetic modeling

TABLE 90.2

Status
Area

Assessment of Nutritional

Assessments

Physical Examination
Assessment of
Diet history, food diaries, appetite assessment
dietary intake
questionnaires
Anthropometric
Body weight, height, body mass index
measurements
Percentage weight change
Skinfold thickness
Mid arm muscle circumference
Waist circumference
Body composition Bioelectrical impedance
DEXA
Near-infrared reactance
Neutron activation
Total body potassium
Biochemical
Serum electrolytes
determinations
Serum proteins
PNA, PCR
Serum cholesterol
Creatinine indexa
Nutritional
Subjective Global Assessment, Malnutrition Inflammation
scoring
Score (MIS), Dialysis Malnutrition Score (DMS)
systems
Geriatric Nutritional Risk Index (GNRI)
Immunologic

Blood lymphocyte count
assays
Delayed cutaneous hypersensitivity tests
Functional tests
Grip strength
aThe

creatinine index is measured as the sum of creatinine removed from the body (measured from the creatinine removed in dialysate, ultrafiltrate, and/or urine), any increase in the body creatinine pool, and the creatinine degradation rate. See also www.kidney.org/professionals/kdoqi/pdf/KDOQI2000NutritionGL.pdf.
DEXA, Dual-energy x-ray absorptiometry; PCR, Protein catabolic rate (mathematically identical to PNA); PNA, protein equivalent of total nitrogen appearance.

software programs. (Urea kinetic modeling and adequacy of dialysis are further discussed in Chapters 99 and 101.)
The use of PCR to estimate protein intake has a number of limitations. It may be considered as a complementary tool to assess

nutritional status but should not be interpreted in isolation because it can be influenced by nonnutritional factors.[1]

If a computer program is not available, the following simple formula will give a good estimate of the nPCR:

$$\text{nPCR (g/kg/day)} = 0.22 + \frac{(0.036 \times \text{interdialytic rise in BUN [mg/dL]} \times 24)}{\text{interdialytic interval (hours)}}$$

Among patients with residual kidney function, total urea lost in the urine must also be measured from urine collected during the interdialytic period. Using this measurement, the following term is added to the equation for nPCR[17a]:

$$+ \frac{\text{Urinary urea nitrogen (g)} \times 150}{\text{Interdialytic interval (hours)} \times \text{Weight (kg)}}$$

where the urinary urea nitrogen is all of the urea nitrogen excreted in a urine collection obtained from the end of one dialysis to the beginning of the next (i.e., in the interdialytic interval).

Fig. 90.1 Routine Measurement of Skinfold Thickness. The dominant arm, which does not have an arteriovenous fistula or graft, is used in patients with kidney failure.

Body Mass Index

BMI (weight [kg]/height^2 [m^2]), also known as the Quetelet index, is the most commonly used parameter for nutritional assessment; however, because weight does not distinguish between muscle and fat mass or acknowledge hydration status, it may not be representative.

Body Composition

A range of techniques can distinguish body compartments based on physical characteristics providing information about nutritional state (body lean tissue and fat content) and hydration. Some are costly, less accessible, and used more for research purposes, and the usefulness of the results depends on the availability of reference data from a population of same age, race, sex, and disease status. A few of the more widely available techniques are mentioned in the following discussion.

Triceps skinfold thickness can be used as an indicator of fat mass, and mid-arm muscle circumference (MAMC) as a surrogate measure of fatfree mass. The midpoint of the upper dominant arm is used because this is the arm less likely to have an arteriovenous fistula (Fig. 90.1).

$$\text{MAMC (cm)} = \text{Mid-arm circumference (cm)} - [3\ 14 \times \text{Triceps skinfold}]\ \text{(cm)}$$

The measurement is taken after dialysis for patients on HD. Although these anthropometric parameters are inexpensive and relatively easy to measure, they are limited by relatively wide ranges of inter- and intrapatient variability. An estimation of BMI can be made from the mid–upper arm circumference and there are reference values available, but caution is needed because these are not disease specific. Nevertheless, serial measures over time can be useful to track changes in the same patient when they are used in conjunction with other nutritional indices.

An unintentional weight loss of 5% to 10% would be interpreted as a greater than normal intraindividual variation and an earlier indicator of increased risk of undernutrition, and greater than 10% would be interpreted as clinically significant.[18]

Observation of trends using serial measures of bioelectrical impedance are increasingly being used as an adjunct to the day-to-day clinical assessment of hydration status and body composition management of dialysis patients. Assessments are best obtained after dialysis treatment when fluid compartment levels are balanced. Bioelectrical impedance is not routinely available in all facilities and is not without its limitations. Further prospective controlled trials are required to determine the best role for this technology in clinical practice.19–21

Fig. 90.2 White Nails in Hypoalbuminemia. The white band grew during a transient period of hypoalbuminemia caused by nephrotic syndrome.

Serum Albumin, Prealbumin, and Transferrin

Serum albumin, prealbumin, and transferrin represent the so-called visceral protein. Fluid status, impaired liver function, age, and acute inflammatory conditions can affect serum albumin levels; however, despite its relatively long half-life (20 days), albumin remains an important measure of the nutritional status and health of the patient. Clinically, it may be possible to observe the growth of white nails when there has been a transient period of hypoalbuminemia (Fig. 90.2). Other serum protein markers of nutritional status are difficult to interpret because of the influence of factors other than nutrition. Serum transferrin is linked to body iron stores and may be altered with changes in iron status. Serum prealbumin (transthyretin) levels can be increased by CKD because of impaired metabolism in the kidney but also decline rapidly during episodes of acute inflammation.

Tools to Diagnose Protein-Energy Wasting and Assess Nutritional Status

Given the low specificity and sensitivity of many of the anthropometric and biochemical markers, a range of measurements is needed to assess nutritional status in addition to the evaluation of the subjective wellbeing of the patient (Table 90.3).

Four main established categories are recommended for the screening for PEW: serum biochemistry, body mass, muscle mass, and dietary intake.8 Subjective global assessment (SGA) is a reliable nutritional

TABLE 90.3

Some Indices of Malnutrition

Assessment

Indices

Biochemical
parameters

Serum albumin below the normal range
Serum prealbumin < 300 mg/L (30 mg/dL) (for maintenance dialysis patients only because levels may vary according to GFR level for CKD stages 2–5)
Low predialysis serum creatinine, phosphate, potassium, urea levels
Serum total cholesterol < 150 mg/dL (3.8 mmol/L)
Low creatinine index
Low PNA, PCR
Continuous decline in weight, skinfold thickness, mid-arm muscle circumference
WHO classification for BMI:
<18.5 kg/m2 underweight (<20 kg/m2 for some classification systems; note that ISRNM suggests a lower threshold of 23 kg/m2)[7]
<18.5–24.9 kg/m2 normal weight
<25–29.9 kg/m2 overweight
>25 kg/m2 obese
Body weight < 90% of ideal
Abnormal muscle strength

Anthropometric
parameters

GFR, Glomerular filtration rate; ISRNM, International Society of Renal Nutrition and Metabolism; PCR, protein catabolic rate; PNA, protein equivalent of total nitrogen appearance; WHO, World Health Organization.

assessment tool for patients on dialysis.[22] Questions about recent changes in nutrient intake are used alongside simple observations of the patient’s body weight and muscle mass to assess the nutritional status of the individual; patients are classified as well nourished, mild to moderately malnourished, or severely malnourished. Figs. 90.3 and 90.4 show muscle wasting in a patient on HD who was classified by SGA as severely malnourished. The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends the use of the 7-point SGA for assessing nutritional status in adults on dialysis.[1] The dialysis malnutrition score (DMS) and the malnutrition inflammation score (MIS), which are fully quantitative adaptations of the SGA, as well as the International Society of Renal Nutrition and Metabolism (ISRNM) PEW definition criteria and the geriatric nutritional risk index, are alternative tools used by some centers and continue to be evaluated and refined.

Nutritional Guidelines, Monitoring, and Treatment

Renal dieticians, or their equivalent in different regions of the world, have the unique knowledge and skills to nutritionally assess, tailor advice, and prioritize goals according to the patient’s clinical condition. The renal dietician is trained in behavioral methods to help reduce barriers, can impart practical information, and may have an extended role, such as with the management of CKD-related bone disease. Latest guidance from KDOQI recommends that a registered dietician, nutritionist, or regional equivalent collaborate closely with the multiprofessional team to help tailor nutrition advice to patients with CKD.[1]

Guidelines are useful, but it is important that dietary restrictions are not unnecessarily imposed and that advice is tailored to the individual and altered as circumstances dictate. Table 90.4 summarizes the nutritional recommendations for CKD.

Historically, dietary advice for patients with CKD has focused on individual nutrients, such as phosphorus, potassium, salt, and protein, which can be complex, challenging to adhere to, and may lead to unbalanced diets. Consequently, particular dietary patterns, including the Mediterranean diet, the Dietary Approach to Stop Hypertension (DASH), and plant-based diets that are high in fruit and vegetables, are increasingly of interest because they are linked with reduced chronic cardiovascular (CV) disease (CVD) and mortality risk in the healthy population.[23] A recent meta-analysis looked at seven studies where healthy dietary patterns (generally higher in fruit, vegetables, fish, legumes, whole grain, and fiber and lower in red meat, salt, and refined sugars) were consumed by adults with CKD and demonstrated that these eating patterns were consistently associated with lower mortality.[24]

Fig. 90.3 Severely malnourished hemodialysis patient.

Although traditionally there has been fear of hyperkalemia from plant-based foods, recent studies suggest that a higher intake of dietary fibers from more plant-based sources can enhance bowel movement and gastrointestinal (GI) potassium loss and have an alkalizing affect, which may reduce hyperkalemia.[6]

The safety and acceptability of various diet patterns must be determined on an individual basis in the advanced stages of CKD, especially with regard to serum potassium control and adequacy of protein and energy. More large-scale clinical trials implementing DASH/Mediterranean style and plant-based diets, including PLADO diet, in people with CKD are needed.

Monitoring of patients with CKD involves a combination of nutritional assessment, noting relevant biochemistry (potassium, phosphate, and lipids), checking dialysis adequacy, and observing fluid status. The challenge comes in balancing the potential dietary restrictions of CKD providing IDPN to malnourished HD patients,28 but a more recent RCT demonstrated IDPN therapy increased prealbumin levels and was superior to nutrition counseling after 16 weeks.29 Further clinical research is needed in this area, although the high cost of the therapy is a barrier to performing adequately powered clinical trials.

Intraperitoneal amino acids (IPAAs) can be used in PD. A 1.1% amino acid solution is substituted for glucose in PD fluid, and about 80% of the amino acids are absorbed in a 4-hour period.30 Because the long-term effects of IPAAs on nutritional status and clinical outcomes are not known, the solution is often used to reduce glucose exposure.

Expert opinion on the use of these approaches is inconsistent. KDOQI has suggested that IPAAs (for PD) or IDPN (for HD) should be considered for patients who are unable to tolerate adequate oral supplements or tube feeding and have evidence of protein or energy malnutrition.1 The European Society of Enteral and Parenteral Nutrition (ESPEN) has provided criteria for use of IDPN.31 Conversely, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends that IDPN not be used as a nutritional supplement in malnourished HD patients because studies so far are not convincing.32

Appetite Stimulants

Fig. 90.4 Severely Malnourished Hemodialysis Patient. There is marked wasting of the quadriceps and calf muscles. In addition, note skin lesions from scratching because of uremic pruritus.

against the risk for compromising nutritional status. When anorexia is present, compromising food intake, nutrient intake may be maximized by one or more of the methods discussed in the following sections.

Enteral Supplementation

If food fortification advice is insufficient, supplements, in the form of high-protein, high-calorie drinks, powders, and puddings, should be considered when there are signs of PEW or its high-risk factors, especially in dialysis patients.1 Enteral tube feeding is an option if nutrient intake cannot be increased sufficiently using oral supplements.1 Kidney-specific tube feeds and supplements are available that are lower in fluid and electrolytes. A systematic review suggested that enteral multinutrient support increases serum albumin concentration and improves total dietary intake in patients receiving maintenance dialysis.25 In addition, where maintenance HD patients with albumin levels of up to 3.5 g/dL received intradialytic oral nutritional supplements in a large retrospective matched-cohort study, despite limitations, significantly better survival was seen in the supplemented group versus similarly matched patient controls.26 27

Supplementation of Intradialytic Parenteral Nutrition and Dialysate Fluids

The GI route is the preferred choice for nutritional supplementation; however, intradialytic parenteral nutrition (IDPN), where a concentrated hypertonic solution is infused into the venous blood line three times weekly over approximately 4 hours during HD treatments, has been used to provide intensive parenteral nutrient therapy for patients who cannot tolerate oral or enteral administration of nutrients. IDPN typically provides 800 to 1200 kcal three times weekly, in the form of glucose and fat emulsion and 30 to 60 g of protein, and so will be only supplementary rather than providing full nutritional needs.

A systematic review concluded that there was insufficient evidence to demonstrate either a net benefit or a net harm associated with

Despite megestrol acetate, a progesterone derivative, improving appetite moderately in HD patients in small studies, it can have adverse effects, and larger trials are required before recommendations can be made for CKD patients.[33]

In some countries, mirtazapine, an antidepressant with the side effect of increasing appetite, and cannabis-based agents can be considered, but research data in their support are insufficient. It is important to note that the licensing and restrictions of these drugs/agents plus ethical considerations are likely to vary between countries, which will affect their usage and suitability for recommendation.

More studies are also required for ghrelin, an orexigenic hormone, and melanocortin-receptor antagonists.

Vitamins, Minerals, and Trace Elements

Vitamin, mineral, and trace element abnormalities in CKD are related to dietary restriction, dialysate losses, and the necessity of intact kidney function for normal metabolism; however, the dietary requirements for patients with CKD are not clear-cut.

Protein and potassium restrictions can lead to inadequate intakes of pyridoxine, vitamin B12, folic acid, vitamin C, iron, and zinc. The use of recombinant human erythropoietin may increase the requirement for iron and folic acid (see Chapter 86).

Elevated total homocysteine levels have been identified as a risk factor for CVD in the general population. Homocysteine levels in the blood are influenced by blood levels of folic acid; however, evidence from randomized trials does not support supplementation in secondary prevention.

Hyperhomocysteinemia is common in patients with ESKD. As observed in those with normal kidney function, lowering homocysteine levels with folic acid, vitamin B12, and pyridoxine supplements had no effect on mortality or risk of CV events in dialysis patients.[34]

A variety of available vitamin preparations contain a recommended water-soluble vitamin profile for dialysis patients. In the absence of firm guidance, it is prudent to have a low threshold for commencing such a water-soluble vitamin preparation. The European Best Practice (www.european-renal-best-practice.org) on nutrition gives opinion-based recommendations for patients on HD[35] and KDOQI give a statement of guidance:

In adults with CKD 3 to 5D or post transplantation, it is reasonable for the registered dietician, nutritionist, or international equivalent, in close collaboration with a physician

TABLE 90.4

Nutritional Recommendations in Chronic Kidney Disease a

Daily Intake

CKD Not on Dialysis

Protein (g/kg BW/day)

0.6–1.0
Level depends on the view of the nephrologist.
1.0 for nephrotic syndrome (see Table 90.1)

Energy (kcal/kg BW)
Sodium (mmol)
Potassium

Phosphorous

Hemodialysis

Peritoneal Dialysis

1.0–1.21
1.0–1.21
Recommendations are in conjunction with an adequate energy intake. Requirements may be higher during illness because of multiple comorbidities or during acute periods of infection, including peritonitis.
25–351
25–351
25–351
<1001 (more if salt wasting)
<1001
<1001
Reduce if hyperkalemic
Reduce if hyperkalemic
Reduce if hyperkalemic; potassium restriction is generally not required.
May need to increase potassium intake if hypokalemic.
If hyperkalemic, patients will be advised to moderate intake of certain foods (e.g., some fruits and vegetables) and given information about cooking methods.
Adjust dietary phosphate intake to maintain serum phosphate levels in the normal range. Patients will be advised to moderate intake of certain foods (e.g., dairy, offal, some shellfish) as well as processed foods with high content of added phosphates, and given information about the timing of binders with high-phosphorus meals and snacks.

aRecommendations

are for typical patients but always should be individualized on the basis of clinical, biochemical, and anthropometric indices.
BW, Body weight; CKD, chronic kidney disease.
Determination of body weight depends on clinical judgment. 1

or physician assistant, to assess dietary vitamin intake periodically and to consider multivitamin supplementation for individuals with inadequate vitamin intake. In adults with CKD 5D who exhibit inadequate dietary intake for sustained periods of time, it is reasonable to consider supplementation with multivitamins, including all the watersoluble vitamins, and essential trace elements to prevent or treat micronutrient deficiencies.[1]

High-dose vitamin C supplements should not be taken by people with CKD because of the increased risk for secondary tissue oxalate deposition.

A review on fat-soluble vitamins in advanced CKD concluded that supplementation with vitamin A is generally not recommended (unless a patient is receiving total parenteral nutrition) because deficiencies are rare, dialysis losses are minimal, and accumulation leading to toxicity can occur.[36] Vitamin E may have antioxidant properties and beneficial effects for patients with CKD,[37] but appropriately powered studies with longer follow-up are needed for confirmation.

Vitamin K is a cofactor for the enzyme γ-glutamyl carboxylase and may inhibit vascular calcification (see Chapters 84 and 88). Evidence suggests most dialysis-dependent patients have subclinical vitamin K deficiency, and there is no known toxicity. Research is ongoing to determine whether vitamin K supplementation may prevent vascular calcification and reduce mortality in patients with advanced CKD.[38]

KDOQI suggests that patients receiving anticoagulant medicines known to inhibit vitamin K activity (e.g., warfarin compounds) should not receive vitamin K supplements.[1]

Guidelines for vitamin D, phosphorus, and calcium are summarized in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (see Chapter 88).

Recommendations for sodium, potassium, and phosphorus are shown in Table 90.4

Gut-Targeted Therapeutics

There is accumulating evidence that the GI tract may be a major source of chronic inflammation in CKD. It is hypothesized that altered diets (low potassium, phosphorus, and fiber) may affect the gut microbiome, resulting in overgrowth of bacteria that produce uremic toxins and a leaky epithelial barrier, allowing toxins into the circulation, whereas plant-based diets may have a salutary effect.

Prebiotic and probiotic formulations may lower serum levels of uremic toxins, but more trials investigating gut-targeted therapeutics are needed before they can be recommended for use in clinical practice.

Metabolic Acidosis

Although some trials have shown no detrimental effect of mild metabolic acidosis, many others have reported that normalization of serum bicarbonate concentration (see Chapter 13) is beneficial for nutritional status and bone metabolism. Current guidelines recommend the correction of acidosis in dialysis-dependent patients[9,39,40] and KDOQI states that in adults with CKD 3 to 5D, it is reasonable to maintain serum bicarbonate levels at 24 to 26 mmol/L.[1]

Exercise

There is a large body of research on exercise training for adults with CKD that shows significant benefits on physical fitness, CV parameters, well-being, and nutritional markers.[41] Trials are ongoing, and the future is likely to hold more guidance in this area for clinical practice.

SELF-ASSESSMENT QUESTIONS

1. A 60-year-old woman began hemodialysis 6 years ago. At a recent outpatient appointment, she reported breathlessness. Predialysis BP was 150/80 mm Hg.

✓ • ✓ Dialysis: 4 hours three times per week
✓ • ✓ Target weight: Stable for last 2 years at 55 kg

✓
✓
✓
✓

- ✓
- ✓
- ✓
- ✓

Height: 1.47 m
Body mass index (BMI): 25 kg/m2
Intradialytic weight gain average: 0.9 kg
Passes small amounts of urine

Monthly laboratory testing reveals blood results as follows:

Predialysis
Postdialysis

Creatinine
(mg/dL)

Urea
(mg/dL)

Phosphate
(mg/dL)

Potassium
(mmol/L)

Albumin
(g/dL)

Cholesterol
(mg/dL)

Hemoglobin
(g/dL)

5.3
1.54

27
7.86

3.16
1.30

4.5
2.9

3.5

100

13.85

What would your next course of action be?
A. Reduce the dialysis time because she is receiving more dialysis than required.
B. Investigate dietary intake, in particular protein and calorie intake, and assess target weight.
C. Increase target weight.
D. Start diuretics and fluid restriction.
2. A 38-year-old White man with progressive CKD is feeling tired and reporting weight loss, nausea, and a metallic taste in the mouth. His BP is 156/90 mm Hg, and urinalysis reveals +++ protein and traces of blood. There are no signs of peripheral edema. He trains at the gym three times per week.
✓ •✓ Weight: 78 kg
✓ •✓ Height: 1.7 m
✓ •✓ BMI: 27 kg/m2
✓ •✓ Amlodipine 5 mg/day begun

✓ •✓ Sodium bicarbonate begun
✓ •✓ Diet history reveals an average daily protein intake of 120 g, an approximate calorie intake of 2600 kcal, and sodium intake of 190 mmol/day.Laboratory findings are as follows:

What would your next course of action be?
A. Put the patient on a reduced-calorie diet.
B. Start dialysis.
C. Moderate protein and salt intake.
D. Start a low-potassium diet.
3. A 59-year-old man with ESKD resulting from type 1 diabetes has been treated with continuous ambulatory peritoneal dialysis for 12 months. He reports reduced appetite, occasional nausea, and feeling full only midway through modest-sized meals; he has lost 3.3 kg over the previous 2 months. He weighs 79.2 kg and has a BMI of 34 kg/m2. He dialyzes with four exchanges of volume, 2 L each. Measurement of dialysis clearances shows a weekly Kt/V for urea of 1.8 (target minimum 1.7). What would your next course of action be?
A. Reduce dialysis fluid volumes in case they are contributing to his gastrointestinal symptoms.
B. Advise weight reduction because BMI may be contributing to feelings of fullness.
C. Start amino acid-containing peritoneal dialysate.
D. Start a prokinetic agent.

Glomerular
filtration rate (mL/min)

Creatinine
(mg/dL)

Urea
(mg/dL)

Phosphate
(mg/dL)

Calcium
(mg/dL)

Potassium
(mmol/L)

Bicarbonate
(mEq/L)

13

5.1

74

4.96

10.02

5.1

16

REFERENCES

1. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD:2020 update. Am J Kidney Dis. 2020;76:S1–S107.

2. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1–S115.

3. Kistler BM, Moore L, Benner D, et al. The international society of renal nutrition and metabolism Commentary on the National kidney Foundation and Academy of nutrition and dietetics KDOQI clinical practice guideline for nutrition in chronic kidney disease. J Ren Nutr. 2020:1–6.

4. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;1(3):1–150.

5. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease (Review). Cochrane Database Syst Rev. 2020;10:CD001892.

6. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. NEJM. 2017;377(18):1765–1776.

7. Kalantar-Zadeh K, Joshi S, Schlueter R, et al. Plant-dominant lowprotein diet for conservative management of chronic kidney disease. Nutrients. 2020;12(7):1931.

8. Fouque D, Kalantar-Zadeh K, Kopple J, et al. Proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–398.

9. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23(2):77–90.

10. Kalantar-Zadeh K, Ikizler TA, Block G. Malnutrition-inflammation complex syndrome in dialysis patients; causes and consequences. Am J Kidney Dis. 2003;42:864–881.

11. Churchill DN, Taylor DW, Keshaviah PR. The CANUSA Peritoneal Dialysis Study Group: adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol. 1996;7:198–207.

12. Kopple JD, Greene T, Chumlea W. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD Study. Int Soc Nephrol. 2000;57:1688–1703.

13. Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84. 1096, 109.

14. Saatino A, Regolisti G, Karupaiah T. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. Clin Nutr. 2017;36(3):663–671.

✓ 15. ✓ Rajan V, Mitch WE. Ubiquitin, proteasomes and proteolytic mechanisms activated by kidney disease. Biochim Biophys Acta. 2008;1782:795–799.

✓ 16. ✓ Lau WL, Kalantar-Zadeh K, Vaziri ND. The gut as a source of inflammation in chronic kidney disease. Nephron. 2015;130:92–98.

17. Mendoza JM, Isakova T, Ricardo AC, et al. Fibroblast growth factor 23 and inflammation in CKD. Clin J Am Soc Nephrolo. 2012;7:1155–1162.

17a. Jindal KK, Goldstein MB. Urea kinetic modelling in chronic hemodialysis: benefits, problems, and practical solutions. Semin Dial. 1988;1(2):82–85.

18. Elia M, ed. The MUST Report: Nutritional Screening in Adults: A Multidisciplinary Responsibility. Development and Use of the Malnutrition Universal Screening Tool (MUST) for Adults. A Report by the Malnutrition Advisory Group for the British Association of Parenteral and Enteral Nutrition (BAPEN). Redditch, UK: BAPEN; 2003. bapen.org.uk/pdfs/must/must-report.pdf.

19. Davies S, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int. 2014;86:489–496.

20. Marcelli D, Wabel P, Wieskotten S, et al. Physical methods for evaluating the nutrition status of hemodialysis patients. J Nephrol. 2015;28:523–530.

21. National Institute for Health and Care Excellence. Multiple Frequency

Bioimpedance Devices to Guide Fluid Management in People with Chronic Kidney Disease Having Dialysis; 2017. nice.org.uk/guidance/dg29.

22. Steiber A, Kalantar-Zadeh K, Secker D, et al. Subjective global assessment in chronic kidney disease: a review. J Ren Nutr. 2004;14(4):191–200.

23. Salehi-Abargouei A, Maghsoudi Z, Shirani F, et al. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases-incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29(4):611–618.

24. Kelly JT, Palmer SC, Wai SN, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: a meta-analysis of cohort studies. CJASN. org. 2017;12:272–279.

2✓ 5.✓ Stratton RJ, Bircher G, Fouque D, et al. Multinutrient oral supplements and tube feeding in maintenance dialysis: a systematic review and metaanalysis. Am J Kidney Dis. 2005;46:387–405.

2✓ 6.✓ Lacson Jr E, Wang W, Zebrowski B, et al. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: a quality improvement report. Am J Kid Dis. 2012;60:591–600.

27. Weiner DE, Tighiouart H, Ladik V, et al. Oral intradialytic nutritional supplement use and mortality in hemodialysis patients. Am J Kidney Disease. 2014;63(2):276–285.

28. Sigrist MK, Levin A, Tejani AM. Systematic review of the use of intradialytic parenteral nutrition in malnourished hemodialysis patients. J Ren Nutr. 2010;20:1.

29. Marsden TA, Beer J, Mann H. Intradialytic parenteral nutrition in maintenance hemodialysis patients suffering from protein-energy wasting. Results of a multicenter, open, prospective, randomized trial. Clin Nutr. 2017;36:107–117.

30. Bruno M, Gabella P, Ramello A. Use of amino acids in peritoneal dialysis solutions. Perit Dial Int. 2000;20(suppl 2):s166–s171.

31. Cano NJ, Aparicio M, Brunori G, et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. Clin Nutr. 2009;28(4):401–414.

3✓ 2.✓ Brown RO, Compher C. American Society for Parenteral and Enteral Nutrition Board of Directors. ASPEN clinical guidelines: nutrition support in adult acute and chronic renal failure. JPEN J Parenter Enteral Nutr. 2010;34:366–377.

3✓ 3.✓ Wazny LD, Nadurak S, Orsulak C, et al. The efficacy and safety of megestrol acetate in protein-energy wasting due to chronic kidney disease: a systematic review. J Ren Nutr. 2016;26(3):168–176.

34. Nigwekar SU, Kang A, Zoungas S, et al. Interventions for lowering plasma homocysteine levels in dialysis patients. Cochrane Database Syst Rev. 2016;5. CD004683, 1469–493X.

35. Fouque D, Vennegoor M, ter Wee P, et al. EBPG guideline on nutrition. Nephrol Dial Transplant. 2007;22(suppl 2):ii45–ii87.

3✓ 6.✓ Holden RM, Ki V, Morton AR, Clase C. Fat-soluble vitamins in advanced CKD/ESKD: a review. Semin Dial. 2012;25:334–343.

37. Jun M, Vekataraman V, Razavian M, et al. Antioxidants for chronic kidney disease. Cochrane Database Syst Rev. 2012;10:CD008176.

38. Kaesler N, Schurgers LJ, Floege J. Vitamin K and cardiovascular complications in chronic kidney disease patients. Kidney Int. 2021;100(5):1023–1036.

39. Dombros N, Dratwa M, Feriani M, et al. The efficacy and safety of guidelines for peritoneal dialysis. 8. Nutrition in peritoneal dialysis. Nephrol Dial Transplant. 2005;20(suppl 9):ix28–ix33.

40. Dobre M, Rahman M, Hostetter TH. Current status of bicarbonate in CKD. J Am Soc Nephrol. 2015;26:515–523.

41. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev. 2011;10:CD003236.

91

Dermatologic Manifestations of Chronic Kidney Disease

Pieter Evenepoel, Dirk R. Kuypers

Cutaneous disorders are common in patients with chronic kidney disease (CKD). Many of these cutaneous disorders are caused by the underlying kidney disease, whereas others relate to the severity and duration of uremia. CKD patients have a high incidence of skin lesions associated with cutaneous aging, including wrinkling, senile purpura, actinic keratoses, and hair loss.

Improved treatments in dialysis patients have resulted in changes in the frequency and types of skin disorders observed in conjunction with end-stage kidney disease (ESKD). Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid now rarely occur. Pigmentary alterations, xerosis, ichthyosis, half-and-half nails, acquired perforating dermatosis, bullous dermatoses, pruritus, and calcific uremic arteriolopathy (CUA) remain prevalent, whereas nephrogenic systemic fibrosis (NSF) is a rare and waning entity now that the causative agent has been identified (Fig. 91.1). The last four prevalent skin disorders are the focus of this chapter because they are associated with significant morbidity or mortality and/or represent an ongoing diagnostic or therapeutic challenge.

UREMIC PRURITUS

Clinical Manifestations

Uremic pruritus (UP) is a frequent symptom of ESKD, with a prevalence ranging from 22% to 48%. Although its incidence in adult dialysis patients declined as a result of improved dialysis efficacy and the introduction of so-called “biocompatible” dialysis membranes, UP still causes serious discomfort and skin damage, often associated with disturbance of day and night rhythm, sleeping disorders, depression, anxiety, and diminished quality of life.1,2 The intensity and spatial distribution of UP vary significantly among patients and over time throughout the course of kidney disease. Excoriations, induced by uncontrollable scratching with or without superimposed infection, occur in severely affected patients and, rarely, lead to prurigo nodularis—a treatment-resistant lichenified or excoriated papulonodular chronic skin eruption (Fig. 91.2). The most frequently involved body areas are the back, limbs, chest, and face; 20% to 50% of patients report generalized pruritus.3

Pathogenesis

Factors thought to contribute to UP include parathyroid hormone (PTH) and divalent ions (calcium, phosphate, magnesium) because itching is a frequent symptom accompanying severe secondary hyperparathyroidism and elevated calcium-phosphate product. However, the lack of consistent correlations between serum and skin levels of PTH, calcium, phosphorus, and magnesium with the severity of UP indicates that other factors also contribute to its development. The number of dermal mast cells is increased in uremic patients, and higher tryptase and histamine plasma concentrations are reported in severe cases. Histamine release is triggered by substance P, a neurotransmitter involved in itch sensation. The role of elevated serotonin (5-hydroxytryptamine [5-HT3]) levels in dialysis patients with UP is debated; clinical trials using a selective inhibitor of 5-HT3 have yielded conflicting results (see later discussion). Xerosis is a common skin problem in dialysis patients (60%–90%) that predisposes to UP. Skin dryness is caused by primary dermal changes associated with uremia, such as atrophy of sweat glands with impaired sweat secretion, disturbed stratum corneum hydration, sebaceous gland atrophy, and abnormal arborization of free cutaneous nerve fiber endings.

There are two major hypotheses concerning the pathogenesis of UP.

The opioid hypothesis proposes that UP is caused by overexpression of opioid μ-receptors and decreased κ opioid receptor expression in dermal cells and lymphocytes. Consistent with this hypothesis, activation of the κ opioid system using a κ-receptor agonist was efficient in reducing UP in a mouse model. In contrast, the immune hypothesis considers UP an inflammatory systemic disease rather than a local skin disorder. Studies examining the beneficial effects of ultraviolet B (UVB) light exposure on pruritus showed that UVB attenuates the development of Th1 helper cells in favor of Th2 helper cells. Indeed, the number of CXCR3expressing and interferon-γ–secreting CD4+ cells (indicating Th1 differentiation) is significantly increased in the circulation of dialysis patients with UP compared with those without. Levels of serum markers of inflammation, such as (high sensitivity) C-reactive protein, interleukin (IL)-2, IL-31, and IL-6, are also higher in patients with UP.

Treatment

Common causes of UP in CKD and dialysis patients, such as primary skin disorders (e.g., urticaria, psoriasis, atopic and contact dermatitis), liver disease (e.g., hepatitis), and endocrine diseases (e.g., hypothyroidism, diabetes mellitus) should be ruled out and adequately treated.
The treatment approach to UP is shown in Fig. 91.3.

Optimizing Dialysis and Mineral Metabolism Therapy

Optimizing dialysis biocompatibility and efficacy, using medium cutoff dialyzers, and improving nutritional status may reduce the prevalence and severity of UP. Controlling calcium and phosphorus serum concentrations by short-term use of dialysate with low calcium and magnesium concentrations has sometimes ameliorated UP symptoms but may lead to worsening of renal osteodystrophy in cases of prolonged use. Parathyroidectomy is not advocated for relief of UP because no consistent beneficial effects have been demonstrated.

Skin Emollients

Emollients continue to be the primary treatment given by nephrologists, although the overall efficacy of this approach is uncertain.
Simple emollients without perfumes or other additives are preferred.
Continuous bath oil therapy containing polidocanol, a mixture of

B
A

D

C

Fig. 91.1 Cutaneous Disorders in Patients With End-Stage Kidney Disease. (A) A spectrum of pigmentary alterations occurs in dialysis patients, with brownish hyperpigmentation in sun-exposed areas being the most prevalent. (B) Xerosis, a dry or roughened skin texture, is seen in up to 75% of dialysis patients. (C) Acquired perforating dermatosis affects approximately 10% of the dialysis population. The lesion is usually asymptomatic and consists of grouped dome-shaped papules and nodules, 1 to 10 mm in diameter. The trunk and the extremities are most commonly involved. (D) Half-and-half nails (also termed red and white nails) occur in as many as 40% of patients on dialysis. The nails exhibit a whitish or normal proximal portion and an abnormal brown distal portion.

monoether compounds of lauryl alcohol and macrogol, seems to help some patients. Sericin, a biopolymer protein from the silkworm (Bombyx mori), contains 32% serine, is the main amino acid of the natural moisture factor in human skin, and suppresses the release of proinflammatory cytokines. Sericin effectively reduced UP in a randomized, double-blind, placebo-controlled 6-week study in 50 dialysis patients.4

Antihistaminic Drugs

Classic antihistamines have similar efficacy compared with emollients; newer, second-generation antihistamines (e.g., desloratadine) might have some effect in UP. Ketotifen (2–4 mg/day), a putative mast cell stabilizer, was beneficial in one small study.

Phototherapy

UV light, especially UVB (wavelength 280–315 nm), is effective for treatment of UP and is well tolerated except for occasional sunburn. The duration of the antipruritic effect of thrice-weekly total body UVB therapy (total of 8–10 sessions) is variable but may last for several months. Potential carcinogenic effects of UV radiation require serious consideration, and its prolonged use (>12 weeks) is contraindicated in patients with a fair complexion (skin phototypes I and II).

mg nalfurafine were equally effective in reducing UP scores compared with placebo during a 2-week treatment period in 337 dialysis patients.6 A subsequent 1-year study (n = 211) confirmed the sustained beneficial effect of 5 mg nalfurafine on UP, with the most frequently reported adverse events being insomnia (19%), constipation (7%), and increased blood prolactin concentrations.7 Difelikefalin, a peripherally restricted and selective kappa opioid receptor agonist, has been approved for treatment of moderate to sevier pruritus associated with CKD in adults undergoing hemodialysis. This drug reduced UP intensity in a significantly larger proportion of dialysis patients (51.9% vs. 30.9% in controls) than placebo when administered thrice-weekly intravenously for 12 weeks.8 UP-related quality of life improved in the active treatment arm, but diarrhea, dizziness, and vomiting were more commonly observed.8

Fig. 91.2 Prurigo nodularis. (Courtesy I. Macdougall, London, UK.)

Sequential Approach to the Uremic Patient With Pruritus
Uremic pruritus
Rule out primary skin disorder
Universal measures
- Ensure optimal dialysis efficacy and control of PTH, calcium and phosphate
- Optimize skin moisturisation and barrier function

Persistent pruritus
Itch-specific therapy

Difelikefalin

Gabapentinoids

UVB/SSRI/other

Fig. 91.3 Sequential approach to the uremic patient with pruritus. PTH, Parathyroid hormone; SSRI, Selective serotonin reuptake inhibitor; UVB, Ultraviolet B.

Gabapentin

Gabapentin, an anticonvulsant drug administered after dialysis (300 mg), was effective in reducing UP. A reduced dose is required if it is given chronically to patients with ESKD because it has a narrow therapeutic window and can accumulate and cause neurotoxic side effects.9 The UP score was significantly reduced in two controlled studies after 4 weeks of gabapentin therapy at a dose of 100 to 300 mg administered thrice weekly after dialysis. Gabapentin was well tolerated; no patients stopped therapy because of side effects, which were limited to dizziness, somnolence, fatigue, and nausea. Similar effects were demonstrated in a smaller study using pregabalin and recent randomized trials comparing gabapentin with doxepin and ondansetron.10,11

IMMUNOMODULATORS AND IMMUNOSUPPRESSIVE AGENTS

A 7-day course of thalidomide reduced the intensity of UP by up to 80% in a placebo-controlled crossover study of 29 HD patients. Because of its strong teratogenic properties, thalidomide should be reserved for therapy-resistant severe UP in individuals outside the reproductive-age category. Adverse effects of thalidomide, such as peripheral neuropathy and cardiovascular side effects, limit its longer use. A prospective single-center study of 25 chronic dialysis patients with UP demonstrated that 6 weeks of treatment with tacrolimus ointment (0.1%) significantly reduced the severity of UP. Tacrolimus was well tolerated in this trial and caused no detectable systemic exposure or side effects.[12] However, a subsequent, smaller vehicle-controlled trial showed equal relief of UP with vehicle and tacrolimus. The risks of long-term topical use of these agents are currently unknown, and their prolonged use is not recommended until more data are available.

5-Hydroxytryptamine Antagonist

Long-Chain Essential Fatty Acids

Ondansetron, a selective 5-HT3 antagonist, was used successfully in a small study in peritoneal dialysis patients. However, a subsequent larger randomized, placebo-controlled study failed to show superiority over placebo in patients on hemodialysis (HD).

Oral administration of γ-linoleic acid (GLA)-rich primrose oil resulted in significant improvement of UP in chronic dialysis patients. Supplementation of GLA-rich primrose oil is thought to augment synthesis of antiinflammatory eicosanoids. Similar effects could be obtained through use of fish oil, olive oil, and safflower oil.

Opioid Receptor Agonists

A κ-opiate receptor agonist, nalfurafine, given intravenously after HD, was tested in two randomized, double-blind, placebocontrolled trials involving 144 patients. Itching intensity, excoriations, and sleep disturbances were significantly reduced in patients receiving the active compound without an excess of drug-related side effects compared with placebo.[5] Oral daily doses of 2.5 to 5

Capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a natural alkaloid found in the pepper plant that depletes the cutaneous type C sensory nerve endings of substance P. Two clinical studies showed that application of 0.025% capsaicin cream significantly alleviated UP in dialysis patients, who exhibited no side effects.

Oral Activated Charcoal

UP symptoms completely disappeared or were significantly reduced in chronic dialysis patients treated with activated charcoal (6 g/day) for 8 weeks. In two different clinical studies, comparable results were obtained with this inexpensive and well-tolerated compound, rendering it a valuable alternative for patients with UP.

Miscellaneous

Various other therapies have been examined for the treatment of UP; some may be effective but are not first-line treatments in chronic HD patients because of undesirable side effects, cumbersome use, or incompatibility with kidney replacement therapy (sauna, cholestyramine, nicergoline). Other therapies that have not reduced UP convincingly in controlled studies include acupuncture, turmeric, low-protein diet, intravenous (IV) lidocaine, melatonin, sertraline, oral montelukast, zinc sulfate, topical vitamin D, and mexiletine.

BULLOUS DERMATOSES

Bullous dermatoses are reported in up to 16% of patients on maintenance dialysis. This skin disease entity mainly includes pseudoporphyrias (e.g., secondary to nonporphyrinogenic drugs and chemicals) and other photodermatoses, whereas true porphyrias (e.g., porphyria cutanea tarda [PCT], variegate porphyria) remain rare.13

Pseudoporphyrias, true porphyrias, and photodermatoses are clinically and histologically similar and are characterized by a blistering photosensitive skin rash. The dorsal hands and the face are the most affected areas (Fig. 91.4).

PCT is caused by abnormalities in the porphyrin-heme biosynthetic pathway, leading to an accumulation of highly carboxylated uroporphyrins in the plasma and skin. Phenotypic expression of the disease also requires one or more of a number of external contributory factors, including alcohol, estrogens, iron overload, and infection with hepatitis B and C viruses. It is important to distinguish PCT from other porphyrias in which patients are at risk for development of potentially fatal neurologic attacks if they are exposed to porphyrinogenic drugs and other precipitants. Therapeutic options include avoidance of environmental triggers, HD with high-flux membranes, repeated smallvolume phlebotomies, and iron chelators.

The term pseudoporphyria was originally used for patients with normal plasma porphyrins who exhibited PCT-like skin lesions secondary to drugs and chemicals. However, some dialysis patients also develop similar skin lesions that spontaneously heal and leave a hypopigmented area; this entity is known as dialysis porphyria; a proportion of these patients have raised plasma porphyrins but without the disturbances in porphyrin metabolism classically found in the porphyrias. In rare patients, an offending medication can be identified. However, in most dialysis patients, protection from sun exposure appears to be the only preventive measure.

Fig. 91.4 Porphyria Cutanea Tarda. Tense bullae, erosions, and crusts of the dorsal hands. (From Kuypers DR, Claes K, Evenepoel P, et al. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus [UP] in patients on chronic dialysis therapy. Nephrol Dial Transplant. 2004;19[7]:1895–1901.)

CALCIFIC UREMIC ARTERIOLOPATHY (CALCIPHYLAXIS)

Definition

CUA, or calciphylaxis, is a devastating and life-threatening ischemic vasculopathy seen primarily among patients with CKD.14 15 The ischemia may be so severe that frank infarction of downstream tissue develops. The most common and most noticeable damage is in the skin and subcutaneous tissues.12 13 CUA should be distinguished from benign nodular calcification (calcinosis cutis), which can develop in patients with very high serum calcium-phosphate product (Fig. 91.5).

Epidemiology, Pathogenesis, and Risk Factors

Although hard epidemiologic data are lacking, it is generally believed that the incidence of CUA is increasing. This might, in part, result from increased physician awareness and the high-risk profile of contemporary dialysis patients.15 The estimated incidence ranges from 1 to 4 per 100 patient-years. The pathogenesis of CUA is complex and incompletely understood.14 16 Recent data suggest that CUA involves a cell-mediated, bone morphogenetic protein-2–driven osteogenic process with extensive subcutaneous extracellular matrix remodeling and deposition of hydroxyapatite.17 A cascade consisting of matrix remodeling, calcification, endothelial damage and thrombus formation, luminal obstruction, and finally full-blown CUA has been postulated.17 Female sex, white ethnicity, obesity, diabetes mellitus, long dialysis vintage, and vitamin K deficiency are established risk factors.15 In a case control study, the incidence of CUA was 10-fold higher in dialysis patients treated with vitamin K antagonists (warfarin or coumarins). Endogenous inhibitors of vascular calcification, such as matrix Gla protein, are dependent on vitamin K for their activation. Patients treated with warfarin or coumarins may thus not be able to appropriately inhibit vascular calcification. CUA prevalence is higher in patients with hyperphosphatemia and/or hypercalcemia. In acute CUA, serum calcium and phosphate levels can be low.

Although data from the Evaluation of Cinacalcet HCl Therapy to

Fig. 91.5 Benign nodular calcification (calcinosis cutis). Firm subcutaneous nodule adjacent to the elbow.

B

C

A

Fig. 91.6 Proximal (A) and distal (B–C) calcific uremic arteriolopathy.

Lower Cardiovascular Events (EVOLVE) trial indicate cinacalcet may reduce the incidence of CUA in HD patients who have moderate to severe secondary hyperparathyroidism,18 registry data fail to confirm a key role for uncontrolled hyperparathyroidism in the pathogenesis of CUA.19 Finally, both low- and high-turnover bone disease have been associated with CUA.

Clinical Manifestations

CUA is typically characterized by areas of zoster-like tenderness and ischemic necrosis of the dermis, subcutaneous fat, and, less often, muscle.14 These ischemic changes lead to livedo reticularis or violaceous, painful, plaque-like subcutaneous nodules on the trunk, buttocks, or proximal extremity—that is, in areas of greatest adiposity (proximal CUA; Fig. 91.6A). The early purpuric plaques and nodules progress to ischemic or necrotic ulcers with eschars that often become infected. Proximal CUA is frequently precipitated by a specific event, such as local skin trauma or a hypotensive episode. CUA also can affect the hands, fingers, and lower extremities, thereby mimicking atherosclerotic peripheral vascular disease (distal CUA; Fig. 91.6B). Peripheral pulses are preserved distal to the area of necrosis. Myopathy, hypotension, fever, dementia, and infarction of the central nervous system, bowel, or myocardium have been described in association with cutaneous necrosis. This condition is termed systemic CUA.

Pathology

Characteristic histologic features of CUA include calcification, fibrointimal hyperplasia, and thrombosis in microvessels in the subcutaneous adipose tissue and dermis, often accompanied by necrosis and adipose tissue, dermal-epidermal separation, panniculitis, proliferation of dermal epithelial cells, and interstitial depositis15 (Fig. 91.7). Calcified lesions consist of hydroxyapatite, typically occupy the entire circumference of the vessel, and are mainly located in the intima.20

Fig. 91.7 Histopathologic Features of Calcific Uremic Arteriolopathy. Medial calcification and intimal hyperplasia of an arteriole at the dermal-subcutaneous junction. Note calcification of interlobular capillaries (arrows) in the subcutaneous tissue. (Van Kossa stain.) (From Kuypers DR, Claes K, Evenepoel P, et al. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus [UP] in patients on chronic dialysis therapy. Nephrol Dial Transplant. 2004;19[7]:1895–1901.)

Diagnosis and Differential Diagnosis

Many clinicians base the diagnosis of CUA on physical examination findings only. Although ulceration is an obvious presentation of CUA, increasing awareness of the condition should allow diagnosis at an earlier, nonulcerative stage when a distinct subcutaneous tenderness can be felt below the early skin lesions. Biopsies are discouraged by most but not all experts because of potential ulceration in the region of the incision and the risk for sampling error. Other potentially useful diagnostic procedures include measurements of transcutaneous oxygen saturation, bone scintigraphy (commonly with Tc-99m-methylene diphosphonate) (Fig. 91.8), and xeroradiography.[21]

The following conditions should be considered in the differential diagnosis: herpes zoster, systemic vasculitis, peripheral vascular disease, pyoderma gangrenosum, atheroemboli, cryoglobulinemia, and systemic oxalosis.[15] Skin biopsy is the standard method for confirmation of clinically suspected calciphylaxis; however, its role in practice is debated, given the risk of provoking new, nonhealing ulcers and infection. A skin biopsy should therefore be performed only when clinical circumstances do not suggest CUA or when clinical and laboratory examinations, including the assessment of coagulation and immunologic parameters, point to an alternative diagnosis.[15]

Natural History

Despite intensive combined treatments, the prognosis of patients with CUA remains poor; the overall 1-year survival is 45% and the 5-year survival is 35%, with a relative risk for death of 8.5 compared with that for other dialysis patients. Patients with ulcerative or proximal CUA have the worst prognosis. Infection accounts for up to 60% of the mortality.[14]

Fig. 91.8 Bone Scintigraphic Abnormalities in Calcific Uremic Arteriolopathy. Calf calcification in a patient with gross ulcerations in both legs from the popliteal fossae to the ankles. (From Nigwekar SU, Thadani R, and Brandenburg V. Calciphylaxis. N Engl J Med. 2018;378:1704–1714.)

Prevention and Treatment

Preventive approaches include controlling bone and mineral metabolism and optimizing nutritional state.[14] Specific therapeutic regimens have been limited to uncontrolled case series (Box 91.1). Intervention should include an aggressive program of wound care and prevention of superinfection, adequate pain control, and correction of underlying abnormalities in serum calcium and phosphorus concentrations. This includes cessation of vitamin D supplementation, intensification of the dialysis regimen, and use of a low-calcium dialysate and non–calciumcontaining phosphate binders. Furthermore, local tissue trauma, including subcutaneous injections, should be avoided. Parathyroidectomy or calcimimetic agents should be reserved for patients with severe hyperparathyroidism. Vitamin K (preferentially vitamin K_1) supplementation is advised, especially in patients with warfarin- or coumarin-associated CUA. Beneficial outcomes have been reported with bisphosphonates in case reports and small series. Sodium thiosulfate has been licensed as an orphan drug for CUA by the European Medicines Agency and is also approved for use in the U.S. It enhances the solubility of calcium deposits22 because exchange of calcium for sodium results in extremely soluble calcium thiosulfate. Besides being a chelator of calcium, sodium thiosulfate is also a potent antioxidant. Sodium thiosulfate is given via IV at the end of every HD session (12.5–25 g over 30–60 minutes). Apart from nausea and vomiting, the therapy is well tolerated. Major side effects of sodium thiosulfate infusion include metabolic acidosis, volume overload, hypocalcemia, and QT-interval prolongation. The optimal duration of treatment and potential effects of long-term treatment on bone are unknown. Efficacy has been suggested by several case-series, but definite proof by a randomized controlled trial is lacking.

Treatment Options in Patients With Calcific Uremic Arteriolopathy

BOX 91.1

1. Reduction of procalcifying factors
- Intensified dialysis (e.g., daily hemodialysis, switch from peritoneal dialysis to hemodialysis, low-calcium dialysate)
- Avoidance of vitamin D and calcium supplements; administration of calcium-free phosphate binders; bisphosphonate administration (caution if adynamic bone disease is suspected)
- Parathyroidectomy (in the case of hyperparathyroidism) or administration of cinacalcet

2. Improving the status of calcification inhibitors
- Halt vitamin K antagonists (warfarin)
- Aggressive treatment of infections or other proinflammatory stimuli to increase fetuin-A levels
- Experimental:
  - Administration of high-dose vitamin K2, and, if unavailable, vitamin K1?
  - Administration of fetuin-A (e.g., by fresh frozen plasma or plasma exchange?)

3. Prevention or reversal of calcium-phosphate precipitation
- Administration of sodium thiosulfate

4. Supportive measures
- Avoidance of additional local tissue trauma by atraumatic wound care with gentle debridement of necrotic tissue and avoidance of subcutaneous injections
- Anticoagulation (heparin and low molecular weight heparin)
- Adequate pain management
- Adequate infection control

Modified from Colboc H, Moguelet P, Bazin D, et al. Localization, morphologic features, and chemical composition of calciphylaxisrelated skin deposits in patients with calcific uremic arteriolopathy. JAMA Dermatol. 2019;155[7]:789-796.

SNF472, an IV formulation of myoinositol hexaphosphate, is currently being investigated in CUA patients (NCT04195906). SNF472 acts through a novel pathway to selectively and directly inhibit the formation and growth of hydroxyapatite crystals, the final common step in the pathophysiology of vascular calcification. SNF472 significantly attenuates the progression of coronary artery calcium and aortic valve calcification in patients with ESKD receiving HD.23

NEPHROGENIC SYSTEMIC FIBROSIS

Definition

NSF, formerly known as nephrogenic fibrosing dermopathy, is a scleroderma-like fibrosing disorder that develops in the setting of kidney failure. The fibrotic process affects the dermis, subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs.24

Pathogenesis

Gadolinium-based contrast (GBC) agents have been identified as the cause of NSF; exposure to gadolinium before the onset of disease was confirmed in more than 95% of reported cases. Free gadolinium ions are highly toxic to tissues. The toxic effects of gadolinium are circumvented by sequestration of the metal by chelates, large organic molecules that form a stable complex with gadolinium and make the ion biochemically inert and nontoxic. Under normal circumstances, GBC agents are eliminated by the kidney through glomerular filtration. Evidence points toward aberrant activation of circulating fibrocytes as a central event in the genesis of NSF. Other investigators have suspected that the strongly profibrotic mediator transforming growth factor-β may be involved in the pathogenesis of NSF.

Epidemiology

NSF is a rare disorder. Since the identification of the first patients with NSF in 1997, the NSF registry (www.icnfdr.org) has confirmed more than 380 patients from medical centers worldwide. NSF equally affects males and females. The risk for development of NSF after GBC agent exposure is related to the degree of kidney failure and stability of the chelate. The incidence of NSF in patients with severe kidney dysfunction (glomerular filtration rate [GFR] < 30) varies from 0.2% to 4%. Gadodiamide (marketed as OmniScan in the United States), the linear nonionic chelate–based formulation, appears to be associated with the highest risk for NSF. Gadopentetate, the linear ionic chelate–based product, probably has a medium risk, less than linear nonionic chelates but more than macrocyclic chelates. Other factors reported to be associated with NSF (without definitive proof) include coagulation abnormalities and deep venous thrombosis, recent surgery (particularly vascular surgery), hyperphosphatemia, and the use of high doses of recombinant erythropoietin. Angiotensin-converting enzyme inhibitors might protect against NSF. After warnings issued by the U.S. Food and Drug Administration (in 2007) and European Medicines Agency regarding the association of linear GBC agents with NSF in individuals with kidney dysfunction, the incidence of NSF declined and in recent years, no new cases of NSF have been reported.[25]

Clinical Manifestations and Natural History

The lesions of NSF are typically symmetric and develop on limbs and trunk. A common location is between the ankles and midthighs and between the wrists and mid-upper arms bilaterally. On occasion, swelling of the hands and feet, sometimes associated with bullae, is noted. The primary lesions are skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with a peau d’orange appearance (Fig. 91.9A). These plaques have been described as having an ameboid advancing edge. Nodules are sometimes also described. Involved skin becomes markedly thickened and woody in texture. Joint contractures may develop rapidly, with patients becoming wheelchairdependent within days to weeks of onset (see Fig. 91.9B). Patients often report pruritus, causalgia, and sharp pains in the affected areas.[24] Although NSF has not been reported as a cause of death, this disorder has led to reduced mobility and/or superinfection that ultimately resulted in a protracted hospital course and death.

Pathology

The histopathologic changes in affected skin include marked proliferation of spindle cells, the presence of numerous dendritic cells, and the accumulation of mucinous material and thick collagen bundles (Fig. 91.10). Most dermal spindle cells in NSF have the immunophenotype of a circulating fibrocyte, a recently characterized circulating cell that expresses markers of both connective tissue cells and circulating leukocytes. Metastatic calcification and NSF may be found in the same lesion.

Diagnosis and Differential Diagnosis

The gold standard of diagnosis is histopathologic examination of skin biopsy specimens from an involved site. Skin lesions also can be visualized by [18F]-fluorodeoxyglucose whole-body positron emission tomography (PET). NSF resembles other fibrosing skin disorders, including scleromyxedema, scleroderma, eosinophilic fasciitis, eosinophilia-myalgia syndrome, and Spanish toxic oil syndrome. The specific distribution of cutaneous involvement, the occurrence in the

Fig. 91.10 Histopathologic Features of Nephrogenic Systemic Fibrosis. Haphazardly arranged dermal collagen bundles with surrounding clefts and a strikingly increased number of similarly arranged spindled and plump fibroblast-like cells.

setting of kidney failure, the history of recent exposure to linear GBC agents, and the unique histopathologic features distinguish NSF from the other fibrotic disorders.

A

B

Fig. 91.9 Nephrogenic Systemic Fibrosis. (A) Peau d’orange appearance. (B) Swelling of the hands, accompanied by palmar erythema, blisters, and contracture of the fingers.

Treatment and Prevention

There is variable evidence for the efficacy of plasma exchange. Other therapeutic modalities that have been used (or are under investigation) include imatinib, oral and topical corticosteroids, selective histamine blockade, calcipotriene ointment, cyclophosphamide, cyclosporine, thalidomide, interferon-α, photopheresis, and psoralen ultraviolet A therapy. Intensive physiotherapy is advised in every patient to prevent or to reverse contractures of the joints. At present, prevention of NSF seems more important than any of the currently available interventions, and widespread clinical awareness of this condition is required.

Avoidance of linear GBC agents in high-risk patients (acute kidney injury and patients with CKD with estimated GFR [eGFR] rate < 30 mL/min/1.73 m^2) is the best measure to prevent this catastrophic complication.[25] According to current guidelines, group II GBC agents, including three macrocyclic agents with 100% kidney excretion (gadoteridol, gadoterate meglumine, and gadobutrol) and one linear ionic agent with approximately 95% kidney and 5% hepatobiliary excretion (gadobenate dimeglumine) can be administered safely independent of preprocedural kidney function screening. Dialysis initiation or alteration is likely unnecessary based on group II or group III GBC administration.[26]

SELF-ASSESSMENT QUESTIONS

1. UP in dialysis patients is:
A. a local skin disorder.
B. a systemic disorder caused by uremia.
C. a neurologic disorder caused by overexpression of opioid skin receptors.
D. an inflammatory systemic disorder caused by dysregulation of the immune system.
E. all of the above.

2. Skin emollients in dialysis patients should be used:
A. only in patients without underlying primary skin diseases.
B. only in patients with proven xerosis.
C. only in patients without skin defects.
D. only in patients with therapy failure.
E. in all patients.

3. Treatment of UP with oral nalfurafine:
A. is limited to patients with proven overexpression of μ receptors in their skin.
B. is limited to patients free from sleeping disturbances.
C. is limited to patients with therapy failure.
D. is limited to patients with baseline normal blood prolactin concentrations.

E. is not limited to any subgroup of patients with UP.

4. Which of the following drugs predisposes to calcific uremic arteriolopathy?
A. Acetylsalicylic acid
B. Heparin
C. β-Blocker
D. Warfarin and coumarins
E. Calcium-free phosphate binders

5. Nephrogenic systemic fibrosis:
A. is a self-limiting disease with benign prognosis.
B. is related to exposure to linear gadolinium chelates.
C. is painless.
D. is especially prevalent in kidney transplant recipients.
E. is related to exposure to iodine radiocontrast agents.

REFERENCES

1. Zucker I, Yosipovitch G, David M, et al. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol. 2003;49(5):842–846.
2. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(8):1410–1419.
3. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus–new perspectives and insights from recent trials. Nephrol Dial Transplant. 2002;17(9):1558–1563.
4. Aramwit P, Keongamaroon O, Siritientong T, et al. Sericin cream reduces pruritus in hemodialysis patients: a randomized, double-blind, placebocontrolled experimental study. BMC Nephrol. 2012;13:119.
5. Wikstrom B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebocontrolled clinical studies. J Am Soc Nephrol. 2005;16(12):3742–3747.
6. Kumagai H, Ebata T, Takamori K, et al. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant. 2010;25(4):1251–1257.
7. Kumagai H, Ebata T, Takamori K, et al. Efficacy and safety of a novel k-agonist for managing intractable pruritus in dialysis patients. Am J Nephrol. 2012;36(2):175–183.
8. Fishbane S, Jamal A, Munera C, et al. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. N Engl J Med. 2020;382(3):222–232.
9. Gunal AI, Ozalp G, Yoldas TK, et al. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004;19(12):3137–3139.
10. Yue J, Jiao S, Xiao Y, et al. Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. Int Urol Nephrol. 2015;47(1):161–167.
11. Foroutan N, Etminan A, Nikvarz N, Shojai Shahrokh AM. Comparison of pregabalin with doxepin in the management of uremic pruritus: a randomized single blind clinical trial. Hemodial Int. 2017;21(1):63–71.
12. Kuypers DR, Claes K, Evenepoel P, et al. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy. Nephrol Dial Transplant. 2004;19(7):1895–1901.

13. Robinson-Bostom L, DiGiovanna JJ. Cutaneous manifestations of endstage renal disease. J Am Acad Dermatol. 2000;43(6):975–986.
14. Nigwekar SU, Thadani R, Brandenburg V. Calciphylaxis. N Engl J Med. 2018;378:1704–1714.
15. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int. 2002;61(6):2210–2217.
16. Brandenburg VM, Evenepoel P, Floege J, et al. Lack of evidence does not justify neglect: how can we address unmet medical needs in calciphylaxis? Nephrol Dial Transplant. 2016;31(8):1211–1219.
17. Kramann R, Brandenburg VM, Schurgers LJ, et al. Novel insights into osteogenesis and matrix remodelling associated with calcific uraemic arteriolopathy. Nephrol Dial Transplant. 2013;28(4):856–868.
18. Floege J, Kubo Y, Floege A, et al. The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. Clin J Am Soc Nephrol. 2015;10(5):800–807.
19. Brandenburg VM, Kramann R, Rothe H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. Nephrol Dial Transplant. 2016.
20. Colboc H, Moguelet P, Bazin D, et al. Localization, morphologic features, and chemical composition of calciphylaxis-related skin deposits in patients with calcific uremic arteriolopathy. JAMA Dermatol. 2019;155(7):789–796.
21. Paul S, Rabito CA, Vedak P, et al. The role of bone scintigraphy in the

diagnosis of calciphylaxis. JAMA Dermatol. 2017;153(1):101–103.
22. Schlieper G, Brandenburg V, Ketteler M, Floege J. Sodium thiosulfate in the treatment of calcific uremic arteriolopathy. Nat Rev Nephrol. 2009;5(9):539–543.
23. Raggi P, Ballasi A, Bushinsky D, et al. Slowing progression of cardiovascular calcification with SNF472 in patients on hemodialysis: results of a randomized phase 2b study. Circulation. 2020;141(9):728–739.
24. Bernstein EJ, Schmidt-Lauber C, Kay J. Nephrogenic systemic fibrosis: a systemic fibrosing disease resulting from gadolinium exposure. Best Pract Res Clin Rheumatol. 2012;26(4):489–503.
25. Lunyera J, Mohottige D, Alexopoulos A, et al. Risk for nephrogenic systemic fibrosis after exposure to newer gadolinium agents: a Systematic Review. Ann Intern Med. 2020;173(2):110–119.
26. Weinreb JC, Rodby RA, Yee J, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: Consensus Statements from the American College of Radiology and the National kidney Foundation. Kidney Med. 2020;3(1):142–150.

92

Acquired Cystic Kidney Disease and Malignant Neoplasms

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DEFINITION

EPIDEMIOLOGY

Acquired cystic kidney disease (ACKD) was first recognized in 1847 by John Simon in patients with chronic Bright disease. He described the development of cystic kidney changes with cysts ranging from “mustard seed to as large as cocoa nuts” and also noted that they “run a slow and insidious progress during life, and often leave in the dead body no such obvious traces as would strike the superficial observer.” ACKD was “rediscovered” by Dunnill and colleagues[1] in 1977 in kidneys from dialysis patients.

ACKD is a specific entity of chronic kidney disease (CKD) of any etiology and has to be differentiated from other types of cystic kidney disease (see Chapters 46 and 47). It is usually defined as more than three macroscopic cysts in each kidney of a patient who does not have a hereditary cause of cystic disease. Some researchers consider ACKD to be preneoplastic.[2,3]

Among adult and pediatric patients starting maintenance dialysis treatment, the prevalence of ACKD ranges from 5% to 20%. In both chronic hemodialysis (HD) and peritoneal dialysis (PD) patients, prevalence then increases at a similar rate and reaches 80% to 100% after 10 years of treatment (Fig. 92.2).[9–11] The rate of progression appears to slow after 10 to 15 years of dialysis.

The frequency of ACKD and kidney tumors in dialysis patients may be underestimated based on imaging alone. Kidney cysts are detectable by ultrasound, with a minimum size of 0.5 cm. Data obtained in native nephrectomy specimens at the time of transplantation identified ACKD in 33%, kidney adenomas in 14%, and RCCs in 4% of the cases.[12] In unselected series of chronic dialysis or transplant patients, the cumulative incidence of RCC complicating ACKD as demonstrated by imaging is less than 1%, although rates up to 7% have been reported in some small studies. These data indicate an up to 40- to 100fold increased risk for RCC in ACKD patients compared with RCC in the general population. Risk factors include male sex (male-to-female ratio, 7:1), Black ethnicity, long duration of dialysis, and severe ACKD with marked organ enlargement.

PATHOGENESIS

The exact mechanisms of tubule transformation into cysts in ACKD are unknown. Responses to acute or chronic kidney injury with parenchymal (nephron) loss are believed to be involved. Progressive nephron loss results in initial tubular hypertrophy followed by hyperplasia and is likely aggravated by tubular distortion and distal tubular outflow obstruction, such as by advanced tubular atrophy, interstitial fibrosis, or calcium oxalate crystals, which are all common in ACKD (Fig. 92.1).[4] ACKD can appear before dialysis is started and does not correlate with dialysis modality or underlying kidney disease. The cysts seem to develop from various tubular segments. Most cysts are lined not only by a single layer of flat to cuboidal epithelial cells but also by cuboidal cells with eosinophilic, foamy, and occasionally also clear cytoplasm, some of which are considered precursor lesions of renal cell carcinomas (RCC).[2,3,5]

With the continuing presence of mitogenic stimuli, the intracystic epithelium becomes multilayered or forms micropapillary proliferates. Further accumulation of mutations, activated protooncogenes, or chromosomal abnormalities, in conjunction with additional factors such as genetic background, environmental chemicals, and sex hormones, most likely accounts for the transition to RCC (see Fig. 92.1).[6] Next-generation sequencing revealed a gain of chromosome 16 and recurrent mutations in the KMT2c and TSC2 genes, which might act as oncogenic drivers in the specific subtype of RCC found in ACKD (i.e., ACKD-associated RCC). So far, these mutations have no implications for therapy, but testing for these mutations in kidney tumors or cysts might in the future be developed into a tool for planning surveillance.[7] ACKD-associated RCC also show a high expression of proximal tubular cell marker genes indicating this segment of the nephron as a potential origin.[8]

CLINICAL MANIFESTATIONS

ACKD can manifest as unilateral or bilateral cysts, which are mostly cortical and variable in size and number. Rarely, severe ACKD can become macroscopically indistinguishable from adult polycystic kidney disease (PKD). In contrast to hereditary cystic diseases, the cysts of ACKD are strictly confined to the kidneys. The disease is usually asymptomatic and discovered accidently during abdominal imaging procedures. Alternatively, it may be manifested by the following potential complications or consequences of ACKD[13]:

- Cystic hemorrhage with or without hematuria; bleeding may occur with cyst rupture with subsequent perinephric hemorrhage or retroperitoneal hemorrhage, which can rarely lead to hypovolemic shock.
- Calcifications in or around cysts and in rare cases stone formation (calcium-containing stones or β2-microglobulin stones).
- Cyst infection, abscess formation, or sepsis.
- Erythrocytosis in advanced cases, similar to the erythrocytosis observed in PKD.
- Malignant transformation.

Acquired Cystic Kidney Disease: Associated Renal Cell Carcinomas

About 85% of RCCs in ACKD are asymptomatic at diagnosis. The remainder mostly manifest with bleeding, usually gross hematuria. In cases in which nephrectomy was done in dialysis patients for intractable

B

C1
C2
C

E

D

F

G

Fig. 92.1 Typical Histomorphologic Appearance of Acquired Cystic Kidney Disease (ACKD) and Commonly Found Renal Cell Carcinoma (RCC) in ACKD. (A) The kidney shows numerous cysts of different sizes and prominent atrophy of kidney parenchyma. (B) At higher magnification global glomerulosclerosis, tubular atrophy with typical focal areas of thyroidization (i.e., intratubular periodic acid–Schiff [PAS]-positive casts), interstitial fibrosis, and arteriosclerosis (PAS-stained section) are noted. (C) Another area of the same kidney specimen as shown in part A, with two cysts. The right cyst is lined by inconspicuous and at this magnification invisible single-layered epithelium (C1). The left cyst (C2) is lined by a thick cell-dense layer (arrows), which at higher magnification (D) is characterized by tubular and papillary proliferation of atypical epithelial cells, characteristic for intracystic ACKD-associated RCC (H&E stained section). (E) Another tumor often found in ACKD is composed of well-differentiated clear cells in a papillary arrangement, characteristic for clear cell papillary RCC. (F) A clear cell RCC, a tumor commonly found in ACKD and the most common kidney tumor in the general population. It is composed of nests and sheets of atypical cells with clear cytoplasm. (G) Papillary RCC, another tumor commonly found in ACKD and the second most common RCC in the general population. It is composed of eosinophilic epithelial cells in a papillary arrangement. In this case the tumor size was 3 cm; therefore the diagnosis of papillary RCC (type 1) was made; if the size were less than 1.5 cm, the same histologic tumor pattern would be classified as papillary adenoma. In the presented cases and typical for ACKD, most clear cell and papillary RCCs in ACKD are well-differentiated, that is, the nuclei show little or no nucleoli and little nuclear pleomorphism. The scale bars in A–D represent 250 µm and in E–G represent 50 µm. The insets in A and C represent areas shown in higher magnification in B and D, respectively.

hematuria, previously undetected RCCs were diagnosed in about onethird of the patients. Compared with sporadic RCCs, ACKD-associated RCCs are characterized by younger age of the patient, male predominance, more frequent multicentric and bilateral manifestation, and less frequent metastases.2

PATHOLOGY

Cystic changes in ACKD are typically bilateral but may vary between kidneys. Most ACKD kidneys are smaller than normal, and all show advanced parenchymal atrophy and chronic injury. An increase in the size of the ACKD kidneys above normal may result from cyst hemorrhage or malignant transformation. The cysts are usually restricted to the kidney cortex. The size of the cysts ranges from microscopic to about 2 cm; about 60% of the cysts are smaller than 0.2 cm.2 Several types of the epithelial lining of cysts can be observed, some of which are likely the earliest precursor lesions of RCCs in ACKD.14

Up to 25% of kidneys with ACKD harbor tumors when examined histologically. About one-quarter to one-third of these are carcinomas. Adenomas are only defined for well-differentiated papillary tumors and compared with RCCs in patients with end-stage kidney disease (ESKD). Tumors are more often multifocal, bilateral, and papillary.16 17 Likely because of the earlier stage at detection, the prognosis of RCCs after kidney transplantation is generally more favorable.

Patients with ACKD (%)

Prevalence of Acquired Cystic Kidney
Disease in Hemodialysis Patients
100
90
80
70
60
50
40
30
20
10
0

Choyke et al. 2000

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Matson et al. 1990
Schillinger 1993

0

1

2

3

4

5

6

7

8

9

>10

ESKD (years)

Fig. 92.2 Prevalence of Acquired Cystic Kidney Disease (ACKD) in Hemodialysis Patients. Summary of reported ACKD prevalence in chronic hemodialysis (HD) patients in relation to the length of HD treatment. ESKD, End-stage kidney disease. (Modified from Choyke PL. Acquired cystic kidney disease. Eur Radiol. 2000;10:1716–1721; Matson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. Medicine (Baltimore). 1990;69:217–226; and Schillinger F. Acquired cystic kidney disease in renal insufficiency: a multicentre study. Group of Nephrologists of the East of France. Eur J

Med. 1993;2:457–460.)

are arbitrarily considered adenomas when less than 1.5 cm, whereas those greater than 1.5 cm are considered carcinomas, given the higher metastatic probability of larger tumors. All other tumors showing typical histology of RCCs regardless of size (e.g., invasive groups of clear cells) are diagnosed as RCCs.

The most common type of RCC that is specific for ACKD is ACKDassociated RCC, which accounts for about 36% of RCCs found in ACKD. The histologic appearance of ACKD-associated RCCs varies from tubular, papillary, acinar, microcystic, to solid. They are mostly composed of eosinophilic tumor cells with prominent nucleoli and frequent intratumoral calcium oxalate crystals (see Fig. 92.1).5 The second most common RCC (24%) that is relatively specific for ACKD (but can be also observed in non-ACKD kidneys) is clear cell papillary RCC, which shows papillary, tubular, or cystic arrangement of relatively well-differentiated clear cells.

Other commonly observed RCCs in ACKD are the same as those in the general population (i.e., papillary [18%], clear cell [10%], and chromophobe RCCs [6%]), with some studies showing that the majority of RCCs in ACKD are clear cell (45%), ACKD-associated (32%), and papillary (13%).15 RCCs arising from ACKD are multicentric in about 50% of cases and bilateral in about 10%. Multiple histologic subtypes may occur in the same kidney. Clear cell RCCs contain cells in solid, tubulocystic, or alveolar arrangements, whereas papillary RCCs show eosinophilic, papillary arranged tumor cells (see Fig. 92.1). In difficult cases with overlapping histologic appearance, immunohistochemistry helps differentiate between these entities. The precise diagnosis is important because ACKD-associated RCCs and clear cell papillary RCCs seem to be more indolent than clear cell RCCs but can also metastasize. All RCCs in ACKD tend to have a better clinical course most likely as a result of early detection given close follow-up of these patients. Compared with other RCCs, ACKD-associated RCCs less frequently showed unfavorable pathologic findings such as sarcomatoid differentiation, lymphovascular invasion, or necrosis, which might be other reasons for a more favorable prognosis.15

RCCs in native kidneys of kidney transplant patients tend to be smaller and exhibit a lower T stage and a lower grade at diagnosis

The diagnostic approach to ACKD usually involves ultrasound (Fig. 92.3).4 9 However, the differentiation between simple cysts and RCCs can be difficult given the echogenicity of end-stage kidney parenchyma and the complexity of cysts in ACKD. Computed tomography (CT) scanning, in particular with early contrast enhancement, is superior to ultrasound in detecting small malignant lesions (see Fig. 92.3).4 9 18 A classification of kidney cysts (Fig. 92.4) based on their appearance in CT scans, introduced by Bosniak,19 20 is now widely accepted and is also applied to ultrasound and magnetic resonance imaging (MRI; see Table 63.6). Criteria that favor the diagnosis of RCC as opposed to a simple cyst include thickened and irregular walls, the presence of septa or kidney tissue within the lesions, contrast enhancement, multilocularity, and large size (≥ 4 cm). MRI scan can be an alternative to contrast-based CT scans. Although the risk for nephrogenic fibrosis after exposure to gadolinium-containing contrast agents is not a concern anymore in early stages of CKD, caution is still recommended in dialysis patients (see Chapter 6). For these cases, a MRI protocol without contrast enhancement has been developed and has been shown in a pilot study in kidney transplant recipients to be superior to kidney ultrasound alone.21 Another small study found that 11C-choline-positron emission tomography (PET)/CT was more sensitive to detect RCC in ACKD compared with fluorodeoxyglucose (FDG)-PET/CT and contrast-enhanced CT, but this method is not broadly available.22

Because of the risk for malignant transformation, testing for ACKD and follow-up imaging when ACKD is detected have both been advocated (Fig. 92.5). However, the cost of testing has to be weighed against the risk-to-benefit ratio of nephrectomy in dialysis patients. A decision analysis23 concluded that testing for ACKD (by either ultrasound or CT scanning) in young patients with a life expectancy of 25 years offers as much as a 1.6-year gain in life expectancy. In contrast, in ACKD patients older than 60 years, no significant gain in life expectancy is achieved by regular testing.24 In a different analysis of 797 dialysis patients who had developed RCCs (90% identified by regular testing), testing provided a mean survival benefit of 3.3 years after adjustment for age and dialysis vintage.24 Testing during transplant evaluation by ultrasound followed by CT in the case of suspicious lesions is recommended based on recent data showing a prevalence of kidney cancer in up to 4% of the patients and concerns about the role of immunosuppression in accelerating tumor growth.25

NATURAL HISTORY

Cystic dilations of kidney tubules may develop at a glomerular filtration rate (GFR) lower than 70 mL/min.26 ACKD thereafter progresses and reaches a prevalence of nearly 100% after more than 10 years of dialysis (see Fig. 92.2). The constant increase in kidney volume seems to reach a plateau after about 20 years of HD, and at least partial regression may occur after very-long-term HD.27 In malignant transformation, tumor growth rates are highly variable. Death is usually associated with widespread metastases and accounts for about 2% of the deaths in kidney transplant patients.

It is not established whether kidney transplantation affects the natural history of RCC complicating ACKD, although immunosuppression has been suggested as a risk factor for RCC in transplant patients

Spleen

Kidney

A

B
C

Fig. 92.3 Imaging Studies in Acquired Cystic Kidney Disease (ACKD). (A) Ultrasound image of the left native kidney of a patient after 16 years of chronic hemodialysis (HD). Multiple cysts are present in the kidney cortex (arrows). (B) Computed tomography (CT) image of a patient after 5 years of chronic HD demonstrating multiple cysts within the right kidney (dashed circle). (C) Contrast-enhanced CT image of a kidney transplant patient who developed a renal cell carcinoma (arrow) originating from the left native kidney with ACKD (dashed circle).

with ACKD.13 A prospective, single-center study in which 561 kidney transplant recipients were imaged with ultrasound identified ACKD in 23%.28 The mean duration of dialysis was 4 to 5 years, and the mean time after transplantation was 9 years. In this cohort, ACKD was slightly less frequent than had been reported in dialysis patients, possibly indicating that kidney transplantation might inhibit the development of ACKD.28 The prevalence of RCCs among all 561 patients was 4.8%. However, among patients with ACKD, RCCs were detected in almost 20%, but in only 0.5% of patients without ACKD.28

TREATMENT

Treatment of ACKD is warranted only when complications such as hemorrhage, cyst infection, or malignant transformation develop. Although the first two complications may be handled conservatively and only rarely require surgery, malignant transformation should raise the question of nephrectomy. Given the perioperative morbidity and mortality of nephrectomy, in particular in multimorbid dialysis or transplant patients, it is not surprising that the threshold for surgical intervention in cases of RCC is still controversial.

Most agree that tumors larger than 3 cm in diameter justify biopsy or surgical treatment (either tumor enucleation or nephrectomy) because, above this size, RCCs in the general population frequently metastasize (for details on urologic evaluation and treatment for kidney masses, refer to Chapter 63).11 However, this strategy is based on an extrapolation from otherwise healthy persons, and a more aggressive approach may be required under certain circumstances.

A Japanese study found that surgically treated RCCs in patients with ESKD seem to have a comparable stage-specific recurrence-free survival, but poorer cancer-specific and overall survival compared with non-ESKD RCC.29

For tumors of less than 3 cm in diameter with no complications, the slow tumor growth may justify observation with repeated imaging studies. Patients with high life expectancy or listed for transplantation should

Testing for Renal Cell Carcinoma in Patients With Acquired Cystic Kidney Disease

Asymptomatic dialysis/kidney transplant patient, poor medical condition with low life expectancy

Asymptomatic dialysis/kidney transplant patient with high life expectancy

Symptomatic dialysis/kidney transplant patient, gross hematuria, lumbar pain, fever, erythrocytosis, etc.

No testing

Ultrasound annually

Ultrasound immediately

No ACKD

Benign cysts (Bosniak I or II)

Moderately complex cysts (Bosniak IIF)

Ultrasound annually or biannually

Ultrasound annually; contrast-enhanced CT scan (patients on KRT) or MRI (kidney transplant patients on progressive lesions)

Ultrasound every 6-12 months; contrastenhanced CT scan (patients on KRT) or MRI (kidney transplant patients on progressive lesions)

Indeterminate cystic mass (Bosniak III)

Clearly malignant cystic mass (Bosniak IV)

Contrast-enhanced CT scan (patients on KRT) or MRI (kidney transplant patients)

Fig. 92.4 Proposed Approach to Testing for Renal Cell Carcinoma in Patients with Acquired Cystic Kidney Disease (ACKD). CT, Computed tomography; MRI, magnetic resonance imaging; KRT, kidney replacement therapy. (Modified from Truong LD, Krishnan B, Cao JT, et al. Renal neoplasm in acquired cystic kidney disease. Am J Kidney Dis. 1995;26:1–12; Sarasin FP, Wong JB, Levey AS, Meyer KB. Screening for acquired cystic kidney disease: a decision analytic perspective. Kidney Int. 1995;48:207–219; and Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. Clin J Am Soc Nephrol. 2007;2:750–756.)

Cancer Risk in Dialysis Patients
Decreased risk
Increased risk
in dialysis patients in dialysis patients
Standardized incidence ratio 0.1

0.5

1

2

10

All cancers, all patients
All cancers, age #34 years
Kidney
Bladder
Prostate
Stomach
Intestine
Lung
Breast

be considered for nephrectomy also in case of tumors with diameters less than 3 cm. In general, tumor enlargement should be used as an indication for nephrectomy if it is permitted by the patient’s status.

In patients with unilateral tumors, prophylactic contralateral nephrectomy is not recommended because of the morbidity associated with the procedure, the worsening of anemia, and the loss of residual kidney function in those who are not considered transplant candidates. A delay of transplantation is not typically required in patients who have had an asymptomatic RCC associated with ACKD in their nephrectomy.

We recommend imaging transplant recipients yearly using ultrasound. In suspicious cases, contrast-enhanced CT scanning or MRI might help differentiate blood-filled cysts from solid tumors. In the case of a suspicious mass or RCC in the native kidneys, a nephrectomy should be performed. However, although immunosuppression is possibly associated with the development of RCC, it does not seem to diminish the likelihood of cure, especially because RCCs in transplant patients tend to be detected at an earlier stage, possibly due to frequent imaging in this population.30

Cervix
Thyroid and other endocrine
Multiple myeloma

Fig. 92.5 Cancer Risk in Dialysis Patients. Relative risk for cancer (plus 95% confidence interval) compared with the general populations in 831,804 dialysis patients from Australia/New Zealand (blue diamonds),

Europe (orange circles), and the United States (purple circles). (Modified from Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet. 1999;354:93–99.)

CANCER IN DIALYSIS PATIENTS

Dialysis patients have a slightly higher cancer risk compared with the general population. Analysis of more than 800,000 dialysis patients in three registries from the United States, Europe, and Australia/New Zealand revealed that most of the increased risk was because of cancers of the kidney, bladder, and endocrine organs (see Fig. 92.5).31 Besides the specific risk associated with malignant transformation of ACKD, some of the increased risk is directly related to the underlying kidney disease or to the immunosuppression that may have been administered to patients with immune-mediated kidney disease. For example, cyclophosphamide may predispose to bladder and ureteral cancer that manifests after patients have been initiated on dialysis. Kidney disease or immunosuppressive therapy may underlie the apparent risk in dialysis patients for the development of multiple myeloma (see Fig. 92.5). In addition, patients with analgesic nephropathy or aristolochic acid nephropathy are at high risk for the development of urothelial carcinoma of the upper urinary tract.32 Other malignancies that are more common in dialysis patients include carcinoma of the cervix, thyroid, and other endocrine neoplasias (see Fig. 92.5), and, at least in the U.S. Renal Data System database, a 1.5- to two fold increase in the risk for non-Hodgkin lymphoma, Hodgkin disease, and leukemias.31

SELF-ASSESSMENT QUESTIONS

1. A 52-year-old White man comes to your clinic with new-onset hematuria. He is receiving chronic hemodialysis (HD) treatment for ESKD because of diabetic nephropathy. Ultrasound of his kidneys reveals four cysts on the left side and five cysts on the right. On the right side, two of the cysts are not echo free and have a thickened wall with multiple calcifications. Which of the following statements is correct?

A. His previous diagnosis of diabetic nephropathy causing ESKD is false. Kidney ultrasound clearly depicts the typical picture of autosomal dominant polycystic kidney disease.
B. ACKD is a common finding in patients on maintenance HD treatment and is a possible cause of hematuria.
C. This patient needs to be carefully evaluated for the presence of RCC because kidney cysts in patients on RRT almost always undergo malignant transformation.
D. Most patients with ACKD have cystic disease outside of the kidneys (liver, pancreas) and need to be screened for cerebral aneurysms.
E. ACKD is associated with exposure to toxic compounds such as benzidine and 2-naphthylamine.

2. A 45-year-old Black woman on maintenance HD for lupus nephritis is asking for your advice. She has heard about an increased risk for malignant tumors in HD patients. Which of the following statements is false?

A. The increase in risk for tumor development in patients on RRT is, in part, related to the underlying kidney disease or to the immunosuppression that may have been administered to patients with immune-mediated kidney disease.
B. Most of the increased risk is because of cancers of the kidney, bladder, and endocrine organs.
C. Cyclophosphamide therapy may predispose to cancer of the bladder.
D. Patients with analgesic nephropathy or Chinese herbs/aristolochic acid nephropathy are at increased risk for development of transitional cell carcinoma (TCC) of the upper urinary tract.
E. Data from large registries reveal a nearly 10-fold increase in the risk for colorectal cancer in patients on HD treatment.

3. A kidney transplant recipient with ESKD secondary to focal segmental glomerulosclerosis presents for a regular checkup. He reports that his primary care physician had ordered an abdominal ultrasound because of recurrent right upper quadrant pain. As an incidental finding, multiple cysts in his native kidneys were noted. Which of the following statements about his condition is false?

A. ACKD is a common finding in patients with ESKD.
B. Up to 25% of kidneys with ACKD harbor tumors, about onethird of which are

carcinomas.

C. ACKD is mostly asymptomatic; however, clinical manifestations include cyst hemorrhage, cyst infection, and malignant transformation.

D. Bilateral nephrectomy is the treatment of choice for asymptomatic ACKD in kidney transplant recipients because malignant transformation occurs in almost 90% of cases.

E. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are the methods of choice to detect small malignant lesions in patients on RRT.

REFERENCES

1. Dunnill MS, Millard PR, Oliver D. Acquired cystic disease of the kidneys: a hazard of long-term intermittent maintenance haemodialysis. J Clin Pathol. 1977;30:868–877.
2. Truong LD, Choi YJ, Shen SS, et al. Renal cystic neoplasms and renal neoplasms associated with cystic renal diseases: pathogenetic and molecular links. Adv Anat Pathol. 2003;10:135–159.
3. Hosseini M, Antic T, Paner GP, et al. Pathologic spectrum of cysts in end-stage kidneys: possible precursors to renal neoplasia. Hum Pathol. 2014;45:1406–1413.
4. Nadasdy T, Laszik Z, Lajoie G, et al. Proliferative activity of cyst epithelium in human renal cystic diseases. J Am Soc Nephrol. 1995;5:1462–1468.
5. Tickoo S, de Peralta-Venturina M, Harik L, et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumorbearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol. 2006;30:141–153.
6. Grantham JJ. Acquired cystic kidney disease. Kidney Int. 1991;40:143–152.
7. Shah A, Lal P, Toorens E, Palmer MB, et al. Acquired cystic kidney disease-associated renal cell carcinoma (ACKD-RCC) harbor recurrent mutations in KMT2C and TSC2 genes. Am J Surg Pathol. 2020;44(11):1479–1486.
8. Ishihara H, Yamashita S, Liu YY, et al. Genetic and epigenetic profiling indicates the proximal tubule origin of renal cancers in end-stage renal disease. Cancer Sci. 2020;111(11):4276–4287.
9. Choyke PL. Acquired cystic kidney disease. Eur Radiol. 2000;10:1716–1721.
10. Matson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. Medicine (Baltim). 1990;69:217–226.
11. Schillinger F. Acquired cystic kidney disease in renal insufficiency: a multicentre study. Group of Nephrologists of the East of France. Eur J Med. 1993;2:457–460.
12. Denton MD, Magee CC, Ovuworie C, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. Kidney Int. 2002;61:2201–2209.
13. Truong LD, Krishnan B, Cao JT, et al. Renal neoplasm in acquired cystic kidney disease. Am J Kidney Dis. 1995;26:1–12.
14. Sun Y, Argani P, Tickoo SK, et al. Renal cell carcinoma (ACKD-RCC)-like cysts. Am J Surg Pathol. 2018;42(10):1396–1401.
15. Kondo T, Sasa N, Yamada H, et al. Acquired cystic disease-associated renal cell carcinoma is the most common subtype in long-term dialyzed patients: central pathology results according to the 2016 WHO classification in a multi-institutional study. Pathol Int. 2018;68(10):543–549.
16. Klatte T, Seitz C, Waldert M, et al. Features and outcomes of renal cell carcinoma of native kidneys in renal transplant recipients. BJU Int. 2009;105:1260–1265.

17. Gigante M, Neuzillet Y, Patard J, et al. Renal cell carcinoma (RCC) arising in native kidneys of dialyzed and transplant patients: are they different entities?. BJU Int. 2012 (epub ahead of print).
18. Takebayashi S, Hidai H, Chiba T, et al. Using helical CT to evaluate renal cell carcinoma in patients undergoing hemodialysis: value of early enhanced images. AJR Am J Roentgenol. 1999;172:429–433.
19. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66:484–488; and modified according to Eknoyan G. A clinical view of simple and complex renal cysts. J Am Soc Nephrol. 2009;20:1874–1876.
20. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66:484–488.
21. Mühlfeld AS, Lange C, Kroll G, et al. Pilot study of non-contrastenhanced MRI vs. ultrasound in renal transplant recipients with acquired cystic kidney disease: a prospective intra-individual comparison. Clin Transplant. 2013;27(6):E694–E701.

22. Kitajima K, Yamamoto S, Kawanaka Y, et al. Imaging of renal cell carcinoma in patients with acquired cystic disease of the kidney: comparison 11 C-choline and FDG PET/CT with dynamic contrastenhanced CT. Jpn J Radiol. 2019;37(2):165–177.
23. Sarasin FP, Wong JB, Levey AS, Meyer KB. Screening for acquired cystic kidney disease: a decision analytic perspective. Kidney Int. 1995;48:207–219.
24. Ishikawa I, Honda R, Yamada Y, Kakuma T. Renal cell carcinoma detected by screening shows better patient survival than that detected following symptoms in dialysis patients. Ther Apher Dial. 2004;8:468–473.
25. Gulanikar AC, Daily PP, Kilambi NK, et al. Prospective pretransplant ultrasound screening in 206 patients for acquired renal cysts and renal cell carcinoma. Transplantation. 1998;66:1669–1672.
26. Liu JS, Ishikawa I, Horiguchi T. Incidence of acquired renal cysts in biopsy specimens. Nephron. 2000;84:142–147.
27. Ishikawa I, Hayama S, Morita K, et al. Long-term natural history of acquired cystic disease of the kidney. Ther Apher Dial. 2010;14:409–416.
28. Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. Clin J Am Soc Nephrol. 2007;2:750–756.
29. Song C, Hong SH, Chung JS, et al. Renal cell carcinoma in end-stage renal disease: multi-institutional comparative analysis of survival. Int J Urol. 2016;23(6):465–471.
30. Tollefson M, Krambeck A, Leibovich B, et al. Surgical treatment of renal cell carcinoma in the immunocompromised transplant patient. Urology. 2010;75:1373–1377.
31. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet. 1999;354:93–99.
32. Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol. 2003;14:197–207.

Section XVii Geriatric and Palliative Nephrology

93

Geriatric Nephrology

Mitchell H. Rosner, Monica Zanella, Kambiz Kalantari

Aging is a natural and progressive process where there is a slow decline in cellular function that ultimately may become manifest as changes in overall organ function. These inevitable changes that occur with aging need to be distinguished from diseases that are more common among older people, such as heart failure, hypertension, and diabetes mellitus (DM), all of which usually have more dramatic effects on organ function. Although it is often hard to distinguish age-related from diseasemediated changes in organ function, it is generally true that they can act synergistically to alter the rate of functional decline of the kidney and to make the kidney more susceptible to injury and less likely to fully recover. In addition, the age-related decline in kidney function has important implications for medication dosing.

Aging-AssociAted chAnges in the Kidney

A8a·9750 c4a832▸

The human kidney reaches a maximum size of approximately 400 g (12 cm in length) in the fourth decade of life. A natural decline of approximately 10% in kidney mass per decade then follows. This natural decline is associated with cortical thinning and a decrease in the number of functional nephrons. An analysis of kidney tissue from healthy living donors examined the changes in nephron number and structure over time.1 The number of nonsclerotic glomeruli was 48% lower in the oldest age groups (70–75 years) compared with those aged 18 to 29 years. In contrast, cortical volume was only 16% lower and the proportion of globally sclerotic glomeruli was only 15% higher. This incomplete representation of nephron loss with aging by either increased glomerulosclerosis or cortical volume decline is consistent with atrophy and reabsorption of globally sclerotic glomeruli and hypertrophy of remaining nephrons.

Other anatomic changes with aging include an increase in simple parenchymal and parapelvic kidney cysts and in angiomyolipomas.2

g6972rÄ6ar c4a832r

Structural glomerular changes with age include basement membrane thickening and development of focal or global glomerulosclerosis, which increases to 10% to 30% and in some studies even exceeds 70% of glomeruli by the eighth decade (Figs. 93.1 [unchanged] and 93.2 [unchanged]).3 The cross-sectional area of the tuft among preserved glomeruli in older people is often larger than average, consistent with glomerular hypertrophy. Neither kidney function nor chronic kidney disease (CKD) risk factors explain the strong association between age and glomerulosclerosis in healthy adults.

tÄbÄ6ar a81 i8·2rr·5·5a6 c4a832r

Tubulointerstitial injury associated with aging is most pronounced in the outer medulla, with tubular dilation and atrophy, mononuclear cell infiltration, and interstitial fibrosis. Some tubules (especially in the distal tubule and collecting duct) may develop small diverticuli; these diverticuli may play a role in the development of upper urinary tract infections (pyelonephritis) by harboring bacteria.4

VaroÄ6ar c4a832r

Arterioles often develop hyalinosis with aging. Thickening of the arterioles with an increase in the ratio of medial thickness to lumen diameter is common with aging but is observed almost exclusively in hypertensive individuals.4 The arcuate arteries become more angulated and irregular with aging, and there is increased tortuosity and spiraling of the interlobar vessels. These changes occur independently of hypertension but are augmented in its presence. With aging, some afferent arterioles, particularly of juxtamedullary glomeruli, develop vascular shunts to the efferent arterioles, thereby bypassing glomeruli, leading to “aglomerular arterioles.”5

n2p4r9ro62r9r5r

Thus, the aging kidney develops some combination of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. In one study, the presence of two or more of these abnormalities was found in 2.7% in young kidney donors and increased to 73% in the oldest group of donors.6

Aging-AssociAted chAnges in Kidney Function

g6972rÄ6ar F56·ra·598 Ra·2

Inulin clearance studies document a progressive fall in glomerular filtration rate (GFR) after the age of 40 years, with a relatively greater decline in males (Fig. 93.3 [unchanged]).7 However, the fall in GFR does not appear to be inevitable; in as many as one-third of patients who remain normotensive, there is no decrease in creatinine clearance with age.2 Studies of potential kidney donors show that the rate of decline of GFR is between 6.3 and 7.5 mL/min per decade.8 Of note, the GFR assesses the function of all nephrons, and the single-nephron GFR assesses the function of individual nephrons. Single-nephron GFR does not vary significantly according to age (among kidney donors <70 years).9 Thus, the fall in GFR is likely because the number of nephrons declines with age.10

F2g. 93.1 Glomerulosclerosis and Tubulointerstitial Fibrosis in an Aging Rat. Similar changes, consisting of focal segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis, occur in humans. (Trichrome stain; original magnification ×400.)

Glomerular filtration rate (mL/min/1.73 m2)

GFR Decreases With Age

5
0

0-9

10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89
Age (years)

F2g. 93.2 The incidence of glomerulosclerosis increases with aging. (Modified from Rule AD, Sasiwimonphan K, Lieske JC, et al. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. Am J Kidney Dis. 2012;59[5]:611–618.)

In addition to the decrease in GFR with aging, there may be a reduction in kidney “reserve.” Although some studies suggest that aging humans show a normal increase in GFR after amino acid infusion, others have shown a marked reduction in increases in kidney plasma flow (KPF) and GFR in response to concurrent infusion of amino acids and dopamine in healthy older individuals.11,12

K5182Ö P6ar7a F69w

KPF also decreases from a mean of 650 mL/min in the fourth decade to 290 mL/min by the ninth decade, with increasing kidney vascular resistance (Fig. 93.4).4 Because KPF decreases relatively more than GFR, filtration fraction (defined as GFR/KPF) increases with age. Studies have demonstrated that there is a true reduction in kidney blood flow when it is factored for kidney mass.13 The decrease in kidney blood flow especially involves the cortex, and blood flow to the medulla is relatively preserved.

A6bÄ758Är5a

The prevalence of albuminuria increases progressively after the age of 40 years. The increased prevalence is most marked in diabetic and hypertensive patients but is also observed in patients lacking these risk factors. However, whether age per se is associated with proteinuria is debatable.14

h27a·Är5a

Malignancies of the urinary tract are more common in older patients, and so the diagnostic workup for hematuria in patients aged 50 years

140
120
100
80
60
30

40

50

60

70

80

90

Age in years
220
Healthy men
200
Glomerular filtration rate (mL/min/1.73 m 2)

Sclerosed glomeruli (%)

10

Healthy women

20

Age-Specific Incidence of
Glomerulosclerosis
15

160

180
160
140
120
100
80
60
40

20

30

40

50

60

70

80

90

Age in years

Fig. 93.3 Glomerular Filtration Rate (GFR) Decreases With Age. GFR (inulin clearance) begins to fall at age 40 years, and the rate of decline is more rapid in males than in females. (Modified from Takazakura E, Sawabu N, Handa A, et al. Intrarenal vascular changes with age and disease. Kidney Int. 1972;2:224–230.)

should include cystoscopy and urinary tract imaging. Renal cell carcinomas (RCCs) are most commonly diagnosed after the fifth decade of life. RCCs may be more aggressive in the elderly, and treatment decisions can be difficult, especially in the setting of significant CKD in which nephrectomy may lead to dialysis dependence.15 However, increased use of biopsy to determine whether a mass lesion is cancer and localized resection of the mass alone or surveillance over time have become more common and preserve kidney function. Other causes of hematuria may need to be considered, as discussed in Chapters 4 and 63.

Urinary Creatinine Excretion
as a Function of Age

Plasma Flow Decreases With Age
800

Creatinine (mg/kg body weight)

Healthy women

Effective renal plasma flow
(mL/min per 1.73 m2)

700
600
500
400
300
200

Males
Females

25
20
15
10
5
0

20–29 30–39 40–49 50–59 60–69 70–79 80–89 90–99
Age (years)

0

10

20

30

40

50

60

70

80

90

Age (years)

Fig. 93.5 Urinary creatinine excretion (adjusted for body weight) decreases with age. (Modified from Denic A, Mathew J, Lerman LO et al. Single-nephron glomerular filtration rate in healthy adults. New Engl J Med. 2017;376[24]:2349–2357.)

the Cockcroft-Gault formula for estimating GFR use age in their calculations (see Chapter 3), neither has been validated in people older than 70 years and both underestimate true GFR in those older than 65 years compared with gold standard techniques. Although the MDRD equation may be more accurate than the Cockcroft-Gault formula,17 serum cystatin C, which is independent of muscle mass, may be superior to both.18 The Berlin Initiative Study equation for estimating GFR was derived from patients who were older than 70 years using iohexol clearance as the gold standard and is particularly accurate for classifying patients whose true GFR is between 30 and 90 mL/min/1.73m2 19 Another equation was recently developed and has improved validity across the full age spectrum, with less bias at the extremes of age and perhaps allowing for better clinical decision making.20
The implementation of routine estimated GFR (eGFR) reporting has led to a higher number of older adults diagnosed with CKD, leading to increased referrals to nephrologists and increased anxiety among patients.9 As discussed later, the clinical significance of this diagnosis (which is largely driven by age in estimation equations) is not clear.

Healthy men

1000
Effective renal plasma flow (mL/min per 1.73 m2)

30

900
800
700
600
500
400

PReVAlence oF chRonic Kidney diseAse in the eldeRly

300
200

0

10

20

30

40

50

60

70

80

90

Age (years)
Fig. 93.4 Renal Plasma Flow (RPF) Decreases With Age. RPF (p aminohippurate clearance) begins to fall rapidly after the age of 50 years, and the rate of decline is more rapid in males than in females. (Modified from Takazakura E, Sawabu N, Handa A, et al. Intrarenal vascular

changes with age and disease. Kidney Int. 1972;2:224–230.)

Assessment oF glomeRulAR FiltRAtion RAte in the eldeRly

Serum creatinine becomes a less reliable indicator of GFR after aging because after the age of 60 years, there is a progressive decrease in urinary creatinine excretion, which largely reflects that muscle mass decreases with aging (Fig. 93.5).16 There is no consensus on the optimal approach to estimation of GFR in elderly people. Although the Modification of Diet in Renal Disease (MDRD) study equation and

According to the U.S. Renal Data System’s Annual Data Report, the prevalence of CKD defined by eGFR is increasing in people aged 65 years and older with nearly 25% of those older than 85 years showing some level of CKD (Fig. 93.6).21 Of note, higher increases in the apparent overall prevalence of CKD occurred around 2005 to 2006 and 2015 to 2016 and are likely attributable to the introduction of stagespecific CKD codes and the shift from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to the ICD-10-CM classification system, respectively.

eGFR is attractive for classifying the severity of CKD because eGFR is an independent predictor of mortality and other adverse events. However, this may not be true in patients older than 65 years of age. For instance, eGFR of 50 to 59 mL/min/1.73 m2 may not be associated with increased mortality among patients age 65 years or older compared with patients with eGFR of more than 60 mL/min/1.73 m2 22

Additionally, cardiovascular mortality begins to increase in those older than 65 years with eGFR less than 45 mL/min/1.73 m2 23 However, other studies have shown that both low eGFR and high albuminuria were independently associated with mortality and end-stage kidney disease (ESKD) regardless of age across a wide range of populations.24

Prevalence of Various Stages of Chronic Kidney Disease
By Age (in years)

30
25
20

Percentage

15
10
5

2006
Stage 1

2009
Stage 2

2012
Stage 3

Stage 4

2015
Stage 5

85+

80-84

75-79

70-74

66-69

85+

80-84

75-79

70-74

66-69

85+

80-84

75-79

70-74

66-69

85+

80-84

75-79

70-74

66-69

85+

80-84

75-79

70-74

66-69

0

2018
Unknown/unspecified

F2g. 93.6 Prevalence of various stages of chronic kidney disease (CKD) in people aged >65 years over 2006 to 2018 demonstrating increases in stage 3 to 5 CKD over time in this population. (Data from U.S. Renal Data System. www.usrds.org.)

The interpretation of small decreases in eGFR in those older than 65 years has led to debate and whether the term chronic kidney disease in such cases should be replaced with age-related reduced kidney function.25

RisK FActoRs FoR chRonic Kidney diseAse in the eldeRly

The variability in the severity of aging-related kidney disease in humans has suggested that other factors besides aging per se may contribute to the loss of GFR that is seen in older populations. A recent study found that in a cohort of patients older than 65 years with stage 3A to 5 CKD, up to 60% of patients showed continued declines in kidney function over 2 years.26 Factors associated with progressive loss of eGFR in prospective and retrospective studies include use of oral analgesics, metabolic syndrome, hyperuricemia, proteinuria, DM, and baseline CKD.26
In another prospective study, increased levels of physical activity correlated with a lower risk for rapid GFR decline (defined as loss > 3 mL/min/1.73 m2 per year, based on cystatin C levels) in a general population of older adults.27

PAthogenesis oF Age-RelAted chRonic Kidney diseAse

A variety of mechanisms have been proposed for the aging-related kidney changes that are reflected in declining GFR, decreased tubular function, progressive fibrosis, and vascular changes (Box 93.1). The kidney is an important source of the antiaging hormone klotho. Klotho is a transmembrane protein and a coreceptor for fibroblast growth factor-23 (FGF-23). Klotho has a role in modulating many aging-related pathways associated with cellular senescence and regeneration, and mice with klotho deficiency recapitulate features of systemic and kidney aging.28
As klotho levels fall during aging, signaling through the Wnt pathway increases, leading to fibrosis and vascular calcification.29 Klotho (and its deficiency) may be a future target for antiaging strategies.

Pr5p5s1d M1oha42sms f5r Ag24g-Ass5o2a61d K2d41y D2s1as1

Box 93.1

H1m5dy4am2o
- Glomerular hypertension and hyperfiltration
- Intrarenal activation of renin-angiotensin system
- Endothelial dysfunction (loss of nitric oxide)
- Kidney ischemia
- Decreased renalase

M16ab5320
- Accumulation of advanced glycation end-products
- Chronic effects of uric acid
- Chronic metabolism of endogenous and exogenous fructose

c13373ar Dysf7406254
- Oxidative stress
- Decreased klotho
- Senescence (with telomere shortening and loss of mitochondria)

Additional mechanisms of kidney aging may involve telomere shortening of chromosomal DNA, declining levels of peroxisome proliferator-activated receptor-γ, loss of mitochondria, and accelerated apoptosis. Aging-associated kidney disease also may be mediated by activation of the renin-angiotensin system, which may lower kidney klotho expression. Other mechanisms may include hyperfiltration injury and glomerular hypertension as well as vascular changes associated with arteriolar stiffening, progressive reduction in nitric oxide production by endothelial cells, progressive capillary loss with ischemia, and accumulation of advanced glycation endproducts.29–35 The possibility that sugar intake and/or fructose metabolism may be involved has also been suggested by the finding that mice lacking the ability to metabolize fructose appear to be protected from ageassociated kidney injury.36

Fluid And electRolytes in Aging

s915Ä7 Ba6a8o2 a81 hÖp2r·28r598

Aging is associated with impaired excretion of a salt load and defective conservation in the setting of sodium restriction.37 Proximal sodium reabsorption is increased in aging, whereas distal sodium reabsorption may be reduced.38 Because the diet of most individuals in wealthier countries contains excess sodium (8–10 g of salt daily), there is a tendency for total body sodium excess among elderly people. This relative defect in sodium excretion and increased total body sodium may be predisposing factors for the development of hypertension, the prevalence of which increases with age. After the age of 60 years, most people are hypertensive (Fig. 93.7).39 Salt sensitivity occurs in more than 85% of aging people, and sodium restriction will result in a significant fall (>10 mm Hg) in mean arterial pressure.40 Populations that ingest lowsodium diets, such as the Yanomami Indians of southern Venezuela, do not show an increase in blood pressure (BP) with age.41 Loss of vascular compliance also may contribute to aging-associated hypertension, as may endothelial dysfunction, perhaps mediated by oxidative stress. Aging-associated kidney and vascular changes may explain why correction of secondary forms of hypertension (e.g., primary aldosteronism, Cushing syndrome, and renovascular hypertension) is less effective at curing hypertension in older patients. In one study, diastolic BP (DBP) fell to less than 90 mm Hg in 24 of 25 patients younger than 40 years after treatment of the mechanism responsible for the secondary hypertension but in only 38 of 61 patients older than 40 years.42 Recent data suggest that treatment of hypertension in the elderly (>75 years) should be similar to that in the younger population because treating to a systolic BP (SBP) target of less than 120 mm Hg (compared with an SBP target of <140 mm Hg) resulted in significantly lower rates of fatal and nonfatal major cardiovascular events.43

Reaching these lower BP goals in the elderly may be more difficult, require more medications, and have risk for orthostatic and diastolic hypotension. Hypotension in the frail elderly patient may be associated with an increased risk of falls and morbidity.

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The most common electrolyte abnormalities in the elderly are the consequence of impaired water handling with aging. Hyponatremia has been found in up to 11% of the ambulatory geriatric population and 5.3% of hospitalized elderly patients.44 Hypernatremia is found in about 1% of patients older than 60 years and admitted to the hospital.44 Both concentration and dilution of the urine are affected by aging and account for part of the susceptibility to dysnatremias.

In the elderly, the maximal urinary osmolality and thirst response to hyperosmolality are reduced, which may predispose to dehydration and hypernatremia. The impairment in urine concentrating ability results from a defect in the concentrating gradient in the medullary region and can lead to nocturia.45 Compounding the risk for hypernatremia is that the ill elderly patient may not have ready access to water.

The elderly also have an impaired ability to dilute the urine and thus have a decreased ability to excrete a water load, leading to an increased predisposition to hyponatremia that is often compounded by the use of medications such as thiazide diuretics and selective serotonin reuptake inhibitors.46 Whether age per se is an independent risk factor for the development of hyponatremia has been questioned, because after adjustment for frailty, the relationship between age and sodium disorders is no longer significant.

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Potassium excretion is impaired in the elderly, and the transtubular potassium gradient is decreased.47 Hyperkalemia occurs more frequently in elderly patients treated with drugs that interfere with potassium excretion (such as potassium-sparing diuretics or agents that block the renin-angiotensin-aldosterone system). Other factors contributing to hyperkalemia in the elderly include decreased GFR, lower basal levels of aldosterone, and tubulointerstitial scarring. Hypokalemia is also common because of kidney (especially with thiazide diuretics) or extrarenal losses.

Most elderly individuals can maintain acid-base balance under normal conditions. However, during conditions of stress when acid production is increased (sepsis or acute kidney injury [AKI]), an inability to excrete an additional acid load may be uncovered. This is supported by a study demonstrating that elderly patients could not increase net acid excretion to the same level as younger adults in response to a protein meal.48 This tendency to metabolic acidosis becomes more manifest in the presence of CKD.

Hypercalcemia occurs in 1% to 3% of elderly patients. Causes include malignancy, hyperparathyroidism, immobilization, and use of thiazide diuretics. Many patients with thiazide-associated

Prevalence of hypertension (%)

Prevalence of Hypertension Increases With Age

80

Men

60
40
20
0

10–29 30–39 40–49 50–59 60–69 70–79

Age (years)

80+

Prevalence of hypertension (%)

1050

80

Women

60
40
20
0

10–29 30–39 40–49 50–59 60–69 70–79

80+

Age (years)

Non-Hispanic Black
Non-Hispanic White
Mexican American

Fig. 93.7 Prevalence of hypertension based on age, sex, and race. (Modified from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension. 1995;25:305–313.)

clinicAl mAniFestAtions

g282ra6 c98r512ra·598r

Aging is associated with declines in kidney function that ultimately limit the ability to defend against destabilizing events. Moderate fluid loss (e.g., an episode of diarrhea) and moderate fluid loading (e.g., inappropriate perioperative intravenous fluids) may be poorly tolerated and lead to hypovolemia and fluid overload, respectively. Hypovolemia in those taking multiple medications with impact on kidney hemodynamics, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs), may lead to AKI. Overzealous administration of water as 5% dextrose or 0.45% saline can result in hyponatremia, especially in patients taking selective serotonin reuptake inhibitors, which may increase levels of antidiuretic hormone. The use of NSAIDs in the elderly is associated with increased risk for hyponatremia, hyperkalemia, hypertension, and impaired kidney function.

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Elderly patients may have treatable kidney diseases identifiable on kidney biopsy.51 In a study of 235 biopsy specimens in patients older than 80 years, 67% of the patients had treatable lesions.52 The pathologic spectrum of glomerular disease seen in elderly people is similar to that in the general population, although the prevalence of various pathologies differs. For example, diabetic kidney disease is seen with increasing frequency in the aging population. Among patients with nephrotic syndrome who are older than 60 years, membranous nephropathy is the most common diagnosis, followed by amyloidosis (typically light chain–derived) and minimal change disease (Fig. 93.8).52 Other important causes of glomerular disease in the elderly include rapidly progressive glomerulonephritis (GN) resulting from pauci-immune (antineutrophil cytoplasmic antibody-associated) GN (accounting for about 30% of elderly patients with AKI who undergo kidney biopsy).51 A recently described entity, immunoglobulin G4 (IgG4)-related kidney disease is seen with a higher frequency in males older than 65 years.53 In contrast, certain glomerular disorders, such as lupus nephritis and IgA nephropathy, are uncommon in

12

<15 years

10

15-65 years
>65 years

8
6
4
2

N
G
PS

N

PG
N
R

PG
M

C
D

-Ig

M

AN

S
G

on
N

FS

M

N

0

AN

Elderly females with eGFR less than 60 mL/min/1.73m2 have lower calcium absorption and lower 1,25-hydroxyvitamin D levels, probably because of diminished conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the aging kidney.50
The kidney removes about 50% of insulin in the peripheral circulation by filtration and proximal tubular uptake and degradation. The decline of kidney function in the elderly leads to a decrease in insulin clearance. This is, in part, offset by diminished glucose tolerance, which may relate to the increasing frequency of obesity observed in aging individuals. However, the risk for hypoglycemia related to insulin use is increased in the elderly.

14

Ig

Epidemiology of Biopsy-Proven
Primary Glomerulonephritis by Age
Incidence (patients/million population)

hypercalcemia have underlying primary hyperparathyroidism.49
Hypocalcemia is less common and is observed mainly in patients with advanced CKD (in association with vitamin D deficiency and hyperphosphatemia), chronic malabsorption, and severe malnutrition. Hypomagnesemia is reported in 7% to 10% of elderly patients admitted to the hospital, most commonly because of malnutrition or laxative or diuretic use. Hypermagnesemia is less common and is found primarily in patients with CKD or who are taking large doses of magnesium-containing antacids. Gout (as well as asymptomatic elevations in serum uric acid levels) is also more common in older people.

Fig. 93.8 Epidemiology of Biopsy-Proven Primary Glomerulonephritis by Age. Children presenting with nephrotic syndrome are often

treated empirically for minimal change disease (MCD); thus diagnosed MCD is likely underrepresented in data derived from biopsy registries. FSGS, Focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MPGN, membranoproliferative glomerulonephritis; non-IgAN, other mesangial proliferative glomerulonephritis; PSGN, poststreptococcal glomerulonephritis; RPGN, rapidly progressive glomerulonephritis. (Modified from Vendemia F, Gesualdo L, Schena FP, D’Amico G. Epidemiology of primary glomerulonephritis in the elderly. Report of the Italian Registry of Renal Biopsy. J Nephrol. 2001;14: 340–352.)

elderly people. Only 2% of patients with lupus nephritis present after the age of 60 years.52

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There is an increased frequency of renovascular and atheroembolic disease with aging. In several case series, AKI resulting from atheroembolic disease accounted for 4% to 7% of cases.54 Atherosclerotic renal artery stenosis is estimated to be present in about 7% of patients older than 65 years and is a major cause of secondary hypertension, ischemic nephropathy, and CKD in the elderly.54 In elderly people with hypertension, elevated serum creatinine, and a history of vascular disease, testing for renovascular disease with magnetic resonance angiography or renal artery duplex scanning may be considered (see Chapter 43). Percutaneous transluminal renal angioplasty and renal artery stenting are of variable value in the elderly because many patients have significant arteriosclerosis, which may limit the benefits of intervention.54 Thus, an individualized approach to therapy is warranted that weights the likelihood of improvement in GFR and BP against the potential risks of the procedure.

d5ab2·50 K5182Ö d5r2ar2

Diabetic kidney disease (DKD) is a common disease in the elderly; more than half of all diabetic individuals in the United States are older than 60 years. In type 2 diabetic patients, the prevalence of both eGFR decline and albuminuria increases with age.55 In patients older than 65 years with type 2 DM, 44.3% had eGFR less than 60 mL/min/1.73 m2 and 38.7% had albuminuria, with 17.8% having both findings.55 Relatively healthy older adults with no major comorbidities may benefit from more intense glucose control (target hemoglobin [Hb] A1c < 7%), whereas more lenient targets may be more appropriate for elderly with major comorbidities, established diabetic end-organ damage, or limited life expectancy. The doses of oral hypoglycemic agents and insulin may need to be decreased as the kidney function declines, especially in the elderly, to avoid hypoglycemia and other side effects.56 Generally, specific guidelines for the treatment of DM in older people address in a very limited manner the use of more recent therapies, such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), which may have important benefits for older people, such as a low risk of hypoglycemia and reduction of cardiovascular and kidney disease risk. The use of SGLT2i in the elderly must take into account the use of other hypoglycemic medications and drugs such as loop diuretics that may negatively impact volume status.57 Kidney function should be monitored closely when introducing these agents.

AoÄ·2 K5182Ö i8jÄrÖ

Polypharmacy associated with aging greatly increases susceptibility to the development of AKI as a result of drug toxicity.58 Although the causes of AKI in the elderly patient encompass the same spectrum of prerenal, renal, and postrenal causes that are seen in other age groups, the elderly patient has a higher relative risk for developing AKI from obstructive uropathy or sepsis and associated with cancer and antineoplastic therapies. Decision making about renal replacement therapy (RRT) in elderly patients with AKI and multisystem organ failure will be influenced by comorbidity and the expected likelihood of a good clinical outcome. These discussions require a multidisciplinary approach.

n2p4r9·9x5o5·Ö a81 drÄ3 d9ra32

Elderly patients are prone to increased nephrotoxicity because they are often administered medicines on the assumption that normal or nearly normal serum creatinine concentration is consistent with normal kidney function. Thus, eGFR or perhaps creatinine clearance (but not serum creatinine) should be used to determine drug doses. In addition, elderly patients with CKD usually are prescribed multiple medications, and this creates a great risk for drug-drug interactions that can be exacerbated when GFR is low.

e81-s·a32 K5182Ö d5r2ar2 a81 K5182Ö R2p6ao2728· t42rapÖ

The mean age for a patient to initiate RRT is currently over 60 years in the United States and Europe. The mean age of patients receiving maintenance dialysis in most low- and middle-income countries is much lower (32–42 years) than that in high-income countries. In the United States there has been a slight decline in the incidence of ESKD in patients older than 65 years, with a continued higher but stable incidence in those older than 75 years.59 However, the prevalence of RRT continues to rise in patients older than 65 years (Fig. 93.9). Despite the frequency of CKD among elderly patients, kidney replacement therapy is far less common as an outcome than events associated with cardiovascular morbidity or mortality. For example, older patients with CKD stage 3 are more likely to die of cardiovascular disease and less likely to receive RRT than their younger counterparts.60

The decision to offer RRT should not be based solely on the age of the individual. It is important to recognize that such a decision involving an elderly patient is more complex and fraught with more challenges than in younger patients and requires a multidisciplinary approach that involves family members. Nonmedical barriers, such as limited transportation, family support, and cost, may be particularly important in the elderly. Of note, nursing home patients who began dialysis experienced sharp and sustained declines in their ability to perform basic daily activities.61 A year after beginning dialysis, 58% of the patients had died and only 13% still functioned at the same level as they had before beginning dialysis. Thus, although dialysis may extend life, it does not necessarily lead to improvements in functional status in older patients. In fact, the increased longevity associated with institution of dialysis may be entirely accounted for by increased days in the hospital without improvements in quality of life (QOL).62

As with other populations, the survival of arteriovenous fistulas (AVFs) in elderly patients is significantly greater than that of arteriovenous grafts.63

Adjusted Prevalence of End-Stage Kidney Disease by Age
By Age (Years)

6000

4000

2000

Year
0-17
18-44
45-64
65-74
75+

Fig. 93.9 Adjusted Prevalence of End-Stage Kidney Disease (ESKD) by Age. Adjusted ESKD prevalence increased with advancing age, with 7401 cases per million people aged 65 to 74 years and 7233 cases per million people age 75 years or older. (Data from U.S. Renal Data System. www.usrds.org.)

2018

2017

2016

2015

2014

2013

2012

2011

2010

2009

2008

2007

2006

2005

2004

2003

2002

2001

0
2000

Cases per million people

8000

In fact, successful use of an AVF in the elderly has results similar to those in younger people, with prolonged patency and low incidence of infections and thromboses, and thus age alone should not preclude AVF creation. Similarly, use of tunneled hemodialysis (HD) catheters is also associated with increased mortality in older HD patients.63 However, the high prevalence of comorbidities, particularly DM, peripheral vascular disease, and congestive heart failure, usually make vascular access creation more difficult in the elderly. Furthermore, many of these patients may have an insufficient vasculature for fistula maturation. Finally, many fistulas may never be used because of the competing risk for death before dialysis initiation. In these cases, an arteriovenous graft or a central venous catheter becomes a valid alternative form of vascular access.

Additional limitations of HD in the elderly may include sensitivity to fluid shifts and the presence of significant cardiac dysfunction, leading to poor tolerance of HD sessions; hence peritoneal dialysis (PD) may theoretically offer some advantage by offering a slow, sustained degree of ultrafiltration that leads to greater hemodynamic stability. Unfortunately, inherent functional limitations may provide impediments to broader use of PD in the elderly, especially in those without social support.64 Studies have demonstrated similar outcomes in elderly patients undergoing HD versus PD.64 Comprehensive care programs have been designed to support elderly patients to perform PD in their community or at nursing facilities and may offer options to increase the choices that patients have regarding treatment options.65

Transplantation should be considered in the management of elderly patients with ESKD because selected elderly transplant recipients have significantly lower mortality compared with otherwise comparable patients who are wait-listed for transplantation.66 This survival benefit is most striking for patients with kidney failure caused by DM or hypertension,

but it declines with longer projected waiting times. Even when expandedcriteria donor kidneys are used, a 25% mortality reduction has been shown in those who undergo transplantation compared with those who are waitlisted.66 Overall graft survival for the elderly transplant patient is similar to that in younger patients.66 It has been argued that lower doses of immunosuppression are sufficient in elderly kidney transplant recipients. However, the Eurotransplant Senior Program, allocating kidneys from donors 65 years or older to recipients 65 years or older regardless of human leukocyte antigen (HLA) matching, found 5% to 10% increased rejection rates in this “old to old” group compared with two better HLA-matched groups, the “old to any” and the “any to old,” within the Eurotransplant Kidney Allocation System.67 In a subanalysis of the Efficacy Limiting Toxicity Elimination (ELiTE)-Symphony study, a large prospective randomized trial comparing immunosuppressive regimens in kidney transplant patients, equal rates of rejection in elderly (≥60 years) versus younger (<60 years) recipients were demonstrated.68 Furthermore, this subanalysis suggested that older recipients who receive a marginal kidney from an older or expanded-criteria donor may fare worse than younger recipients, with an increased likelihood of death, delayed graft function, graft loss, treatment failure, and reduced graft function.

For those who decide not to pursue RRT, symptomatic therapy (supportive management and palliative care) is an option. This concept underscores the importance of individualizing patient goals with a focus on QOL. For those with severe functional or cognitive impairment or for whom complications of dialysis have negatively affected their QOL, dialysis discontinuation is an important consideration. Hospice services remain underused for ESKD patients but may provide an important support mechanism for patients and their families who wish to discontinue dialysis.

SelF-ASSeSSMent QueStionS

1. An 82-year-old man has a sudden onset of severe lower extremity edema and weight gain (6 kg in 10 days). He has been taking allopurinol for gout prophylaxis, celecoxib for pain associated with osteoarthritis, losartan for hypertension, and metformin for type 2 diabetes. He has smoked half a pack of cigarettes daily for the past 60 years. His BP is 160/90 mm Hg. Other than the pitting lower extremity edema, the physical examination findings, including findings from a retinal examination, are within normal limits.
Chest radiograph shows mild emphysematous changes and small bilateral pleural effusions. A urinalysis reveals 4+ protein and 1+ blood. Serum creatinine is 3.6 mg/dL, and serum albumin is 2.1 g/dL. The erythrocyte sedimentation rate is 90 mm/h (Westergren). Blood glucose is 140 mg/dL (nonfasting). Electrolytes show sodium of 132 mEq/L, potassium of 5.5 mEq/L, bicarbonate of 20 mEq/L, and chloride of 98 mEq/L. A kidney biopsy is performed. Complete blood count is within normal limits. Which one of the following lesions is most likely to be present in the kidney biopsy?
A. Minimal change disease (MCD) with interstitial nephritis
B. Amyloidosis
C. Crescentic glomerulonephritis
D. Membranous nephropathy
E. Immunoglobulin A nephropathy

2. An 87-year-old woman with hypertensive nephrosclerosis was started on HD 3 months ago. Before dialysis initiation, she had significant weight loss and anorexia, with a serum albumin of 2.8 g/dL. Most recently, her appetite has improved and with this her albumin has improved to 3.2 g/dL, with a serum phosphorus of 5.4 mg/dL and a serum calcium of 9.6 mg/dL. She is currently living in a nursing facility and unable to ambulate without assistance. She appears depressed and apathetic and reports that she has little energy and motivation to participate in any exercise. The family has asked you to meet with them to tell them what they can expect for their mother’s health in the future. Which statement is correct?
A. Dialysis will likely continue to improve her energy level and appetite; the family should expect continued improvement over the next few months.
B. Her inability to ambulate, frailty, and depression will likely not improve with dialysis, and her condition is likely to continue to deteriorate over time.
C. Home HD should be considered because this modality is associated with improved outcomes in this age group.
D. Assisted PD should be considered as a way to keep the patient at home; this modality is associated with increased survival over in-center HD.

3. A 79-year-old patient who recently started HD for ESKD secondary to drug-induced interstitial nephritis approaches you to discuss his potential for kidney transplantation. His clinical history includes hypertension, mild angina-like symptoms, and hyperlipidemia.
He does not smoke and is very active. In your region, the average time for patients with his blood type to be on the wait list is 5 years before transplantation. Which of the following statements would most accurately inform the patient with regard to his candidacy for kidney transplantation?
A. He is unlikely to gain any benefit from transplantation because there is a high risk for death in the first year postoperatively in patients older than 75 years.
B. He would likely benefit from transplantation, and he should consider living donation as the best option.
C. He should seek transplant listing but not seek a living donor.
D. He should be advised to avoid going on the extended-criteria donor waiting list.

94

Palliative Nephrology

Edwina A. Brown, Fliss E. Murtagh

Palliative care is defined by the World Health Organization as “an approach that improves the health-related quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.”[1] The term supportive care is usually preferred by patients and families and is the term used by the Kidney Disease: Improving Global Outcomes (KDIGO) summary document on supportive care in kidney disease[2] and likewise in this chapter. As shown in Fig. 94.1, supportive care should begin at the time of diagnosis of advanced kidney disease. Fig. 94.2 shows how the different components can be used at different times.

PROGNOSIS

Informing patients accurately about prognosis is key to individualizing dialysis and associated supportive care. Patients with advanced kidney disease often have other comorbidities and complications of treatment; these and increasing age are causes of a high burden of morbidity affecting quality of life (QOL) and shortening length of life. Physicians, however, often are not good at estimating prognosis, with quotes in recent literature such as, “If you’re on dialysis you could last 10, 15, 20 years (male, 76 years old)” or “You will probably have 6 years on dialysis (male, 82 years old).”[3] Patients often want to have conversations about life expectancy,[4] and failure to have these discussions can result in high expectations and increased desire for aggressive treatment.[5] Being aware of prognosis is a key part of shared decision making.[6] At the individual level, the surprise question of “Would you be surprised if the patient died in the next 6 or 12 months?” has been shown to enhance prognostic prediction,[7] although it has the limitation of being subjective and depending on clinician perception.

Prognostic tools have therefore been developed to enable clinicians to estimate the prognosis of patients. Factors that can be used to develop tools are summarized in Box 94.1; more detailed information can be found in an overview by Couchoud et al.[6]

Prognostic tools, however, have limitations because they provide an estimate of average survival for a population of similar risk but not for the individual. Before using a particular tool, it is important to know whether the patient concerned is similar to those used for the development of the tool in terms of things such as age, ethnicity, kidney replacement therapy (KRT), and clinical data available. The tool that is most readily accessible is the Analyzing Data, Recognizing Excellence and Optimizing Outcomes (ARO) score, which is based on simple clinical and laboratory data for prevalent European patients on hemodialysis[7]; it can be easily calculated on the ARO Risk Score website.[8] For patients who have not begun KRT, a risk score for mortality in the first 90 days of dialysis has been developed for patients older than 75 years from the French Renal Epidemiology and Information Network (REIN) registry.[9] In routine clinical practice, these tools can inform discussions with patients and families.

The prognostic tools discussed herein are all specific for kidney disease and mostly for patients on dialysis. Clinical tools useful as prognostic indicators in the general population are also applicable in the presence of kidney disease. The concept of frailty is rapidly becoming one of the useful prognostic indicators for hospitalization, complications of procedures, and mortality in the general population.[10]

Clinically, frailty manifests as a composite of poor physical function, exhaustion, low physical activity, and weight loss and is associated with an increased risk for falls, cognitive impairment, hospitalization, and death. Frailty is more common in the chronic kidney disease (CKD) population and, not surprisingly, is a strong predictor of mortality.11 There are various methods of assessing frailty, but the easiest to use clinically is the Clinical Frailty Scale (Table 94.1), which correlates with more complex assessment methods and predicts hospitalization and mortality.12 Using this scale, prior work has shown that it is frailty, not dialysis modality (assisted peritoneal dialysis [PD] and hemodialysis [HD]), that is associated with symptom score, physical functioning, and better QOL.13 Routinely determining a frailty score in older patients approaching or on dialysis enhances prognostication both of survival and QOL. Frailty therefore is another factor that should inform discussions with patients and families.

COMMUNICATION AND SHARED DECISION MAKING

Good communication is key to enabling people to optimize QOL and achieve their goals at all stages of a long-term condition. Conversations must include awareness of prognosis and wishes for end-of-life planning. These latter conversations are commonly referred to as “advance care planning,” but conversations about prognosis and realistic outcomes of potential treatments and their limitations should ideally be routinely conducted with people at all stages of advanced kidney disease. Treatment decisions should be made with and not for the patient, using shared decision making. This is a process in which patients, when faced with an important choice about their health care, can review all the treatment options available to them and participate actively with their healthcare professional in making that decision,14 thereby respecting patient autonomy.15 Shared decision making is embedded in the U.S. Renal Physicians Association guidelines on dialysis initiation and withdrawal,16 which state that “clinicians, family members, and others have an ethical duty to accept the decisions regarding medically indicated treatment made by competent patients and, in the absence of competence, to formulate decisions that would respect patients’ wishes, or if wishes are unknown, advance the best interest of their patients.” To make these decisions, patients and families must be given evidence-based information about what is happening regarding disease process, what is likely to

Supportive Care in Patients With
Advanced Kidney Disease
Time
Transplant

Access
creation

Surgery

Aggressive treatment
Supportive care

Antibiotics

Bereavement

Dialysis

Pain control, symptom control, psychosocial support
Communication and shared decision making around
prognosis, patient goals, and concerns

Fig. 94.1 Schematic diagram of how supportive care fits into patient pathway with advanced kidney disease.

Supportive Care at Different Time Points in Patients
With Advanced Chronic Kidney Disease
Medical care

Supportive care

Diagnosis

Comorbidities?
Symptoms?
Treatment choices?

- Prognosis
- Patient concerns and goals
- Shared decision making for treatment choices, including conservative care
- Symptom control

Maintenance

Comorbidities?
Symptoms?
Dialysis/transplant
Avoiding complications

- Prognosis
- Patient concerns and goals
- Shared decision making for treatment choices
- Symptom control
- Psychosocial support

Acute event

Diagnosis, investigation
and management of acute
event—antibiotics,
surgery, etc.

- Reassess prognosis
- Patient concerns and goals
- Shared decision making for treatment choices of acute event, including ceilings of care
- Symptom control
- Psychosocial support

Increasing
frailty

Diagnosis and management
of reversible features
Continuing management
of dialysis, medications

- Reassess prognosis
- Symptom control
- Shared-decision making around patient concerns and goals to determine ceilings of care, place of care, potential treatment withdrawal
- Psychosocial support

Fig. 94.2 Use of supportive care at different time points in life with advanced kidney disease.

BOX 94.1

Factors Used to Develop Prognostic Tools

BOX 94.2

Clinical Data
- Age
- Assistance with activities of daily living
- Sex
- Congestive heart failure
- Peripheral vascular disease
- Dysrhythmia
- Active malignancy
- Mobility
- Diabetes
- Body mass index
- Behavioral disorders
- Frequency of hospitalization

- As part of kidney replacement therapy planning, particularly if transplant ineligibility or conservative care is discussed.
- Starting or within first few months of starting dialysis.
- Not eligible for transplant and patient does not want dialysis or is anticipated to have poor outcomes on dialysis.
- Not responding to peritoneal dialysis (PD) and patient does not want hemodialysis (HD) or is anticipated to have poor outcomes on HD and transplantation is not feasible.
- Recurrent vascular access problems in HD patient who does not want or cannot transfer to PD, and transplantation is not feasible.
- Patient wants to withdraw from dialysis.
- After intercurrent event that results in worsening of prognosis, such as stroke, fall and bone fracture, worsening cognitive function, or new malignancy.
- Development of intercurrent event needing major surgical intervention, such as coronary artery bypass surgery or major abdominal surgery.
- Increasing frailty and/or cognitive decline.
- Answer of “no” to surprise question: “Would you be surprised if patient died in the next 12 months?”

Dialysis Related
- Use of central vein dialysis catheter
- Early nephrology referral

Laboratory Values
- Plasma albumin
- Plasma creatinine
- C-reactive protein

Time Points for Advance Care Planning Discussions

Questions and Statements to Use in Advance Care Planning

BOX 94.3

TABLE 94.1

Clinical Frailty Scale

Score	Definition
1	Very fit: Robust, active, energetic, well-motivated and fit
2	Well: No active disease but less fit than people in category 1
3	Well, with treated comorbid disease: Disease symptoms are well controlled compared with category 4
4	Apparently vulnerable: Although not frankly dependent, commonly complain of being “slowed up”
5	Mildly frail: With limited dependence on others for instrumental activities of daily living
6	Moderately frail: Help is needed with both instrumental and noninstrumental activities of daily living
7	Severely frail: Completely dependent on others for the activities of daily living or terminally ill

From Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet 2013;381:752–762.

happen regarding prognosis, what treatment options are available, and what the realistic outcomes are from these treatments. Healthcare professionals should seek to understand the patient’s concerns and lifestyle priorities and then use these to guide the patient through decision making about, for example, wishes regarding specific treatments, ceilings/limits of care if they are no longer able to make decisions, and place of care at end of life. A summary of when such conversations could and should take place is shown in Box 94.2

There are challenges to having advance care planning discussions, such as time needed, cultural and linguistic challenges,[17] and overcoming the inhibitions of healthcare professionals to have difficult conversations, particularly when the prognostic future is uncertain.[18] Some useful questions to help with overcoming these challenges are shown in Box 94.3

Conversations about prognosis and advance care planning should be embedded in nephrologic practice. The timing and frequency of discussions can have a huge influence on patient outcomes. Fig. 94.3

- How is your health now compared with a few months ago?
- Would you be surprised if I told you that things are not going well?
- It is always hard to predict the future, but it would not be a surprise if some major acute event occurred or your health deteriorated significantly in the next few months (or other applicable time scale). We should therefore discuss what your wishes would be should this occur.
- It is a good idea to talk about what we can do and how to get help if you proceed to become more unwell.
- Different people make decisions in different ways. Do you make decisions on your own, do you involve your family, or does someone from your family make important decisions for you?
- Do you have a faith or spiritual beliefs that help you in difficult times?
- Have you ever thought how much treatment you would want if you are very ill, unable to communicate to make your own decisions, and unlikely to leave hospital and be independent?
- You know you have a choice about where you would like your end-of-life

care to take place. Would you like to talk through the options?

- Some people decide to stop dialysis when their health has deteriorated and they feel that dialysis has become a burden and is no longer of benefit. We do not need to mention that any further now, but it is something you may want to discuss later.

gives the example of a woman who has had a major stroke 5 years after starting dialysis at age 70 years and who has had progressive cognitive impairment in the last 2 years. In the absence of any previous discussions, the family would be unaware of the high probability of stroke and, in all likelihood, would not have had discussions about extent of treatment in such an event; there would then be a high probability of them expecting intensive investigations and management. In reality, for this particular patient, there had been a number of discussions after the onset of cognitive impairment and the patient had made it clear that she did not want continuing active management if she was not going to be independent; this made the final decision making by the family much easier. This has been confirmed by randomized controlled

Scenario 1: First Discussion With Family at Time of Major Stroke 5 Years After Starting Dialysis
First discussion
Mrs M starts PD age 70
Good quality of life
CAPD 5 days/week
Boat at weekends
with partner, Dick

↓ Urine
Changes to APD
Parathyroidectomy

Family unware of possible stroke and never discussed ceilings of care
- Transfer to high dependency
- CT scans, EEG, antiepileptic drugs, physiotherapy, extended stay
- Eventual possible discharge—but question level of dependency and cognitive function

Cognitive impairment
More help from Dick
Family concern
Stroke – right hemiplegia
2 days later:
3 seizures; very confused
0

1

2

3
Years

4

5

Scenario 2: Discussions Throughout Timespan on Dialysis
Discussions from onset of cognitive impairment
Mrs M starts PD age 70
Good quality of life
CAPD 5 days/week
Boat at weekends
with partner, Dick

↓ Urine
Changes to APD
Parathyroidectomy

Family aware of potential stroke and had discussed ceilings of care with Mrs M; she did not want continued treatment if no longer independent
- Supportive care—symptom control, no investigations
- No improvement after a week
- PD discontinued

- Died peacefully at home surrounded by family

Cognitive impairment
More help from Dick
Family concern
Stroke – right hemiplegia
2 days later:
3 seizures; very confused
0

1

2

3
4
5
Years

Fig. 94.3 How Communication and Aadvance Care Planning Can Influence Patient Outcomes. Scenario 1: First discussion with family at time of major stroke 5 years after starting dialysis. Scenario 2: Discussions throughout time span on dialysis. APD, Ambulatory peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CT, computed tomography; EEG, electroencephalogram; PD, peritoneal dialysis.

studies in elderly and dialysis populations showing better QOL at end of life and improved certainty about decision making by close family members when these conversations have occurred.19 20

CONSERVATIVE CARE

Conservative (nondialytic) kidney care has been defined (Box 94.4), using the term comprehensive conservative care and encompassing all the components required for effective comprehensive care.
It has also been proposed that globally there are three distinct groups within the conservative care population (Box 94.5); this reflects limited availability of KRT, the consequent (lack of) options for choice

in low-income and middle-income countries, and constraints on diagnosis of stage 5 CKD in resource-poor settings.
Rates of conservative management vary considerably among and within countries, and it is likely that individual nephrology practice is a factor in this variation.21 It is important therefore to consider all available evidence on survival of those managed conservatively and to contrast this to evidence on survival with dialysis. However, this is challenging, because those who are more fit usually opt for dialysis, and others are advised to follow conservative nondialytic management because of comorbidity or other factors that adversely influence survival. This selection bias makes it hard to meaningfully compare survival between those with dialysis and those managed conservatively.

BOX 94.4

Definition of Comprehensive Conservative Care

BOX 94.6

Comprehensive conservative care is planned, holistic, patient-centered care for patients with stage 5 (glomerular filtration rate category 5) chronic kidney disease that includes:

- Interventions to delay progression of kidney disease and minimize risk for adverse events or complications
- Shared decision making
- Active symptom management
- Detailed communication, including advance care planning
- Psychological support
- Social and family support
- Cultural and spiritual domains of care

Comprehensive conservative care does not include dialysis.

- Patients with decision-making capacity who, being fully informed and making voluntary choices, refuse dialysis or request that dialysis be discontinued
- Patients who no longer possess decision-making capacity
- Those who have previously indicated refusal of dialysis
- Those whose legal agents/surrogates request that it be discontinued
- Patients with irreversible, profound neurologic impairment such that they lack signs of thought, sensation, purposeful behavior, and awareness of self and environment

From Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: Developing a roadmap to improving quality care. Kidney Int. 2015;88:447–459.

BOX 94.5

Populations

Distinct Conservative Care

Comprehensive conservative care: Conservative care that is chosen or medically advised.

Choice-restricted conservative care: Conservative care for patients in whom resource constraints prevent or limit access to kidney replacement therapy; therefore a choice for conservative care cannot be recognized.

Unrecognized stage 5 chronic kidney disease: Chronic kidney disease is present but has not been recognized or diagnosed; therefore a choice for conservative care cannot be recognized.

From Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: Developing a roadmap to improving quality care. Kidney Int. 2015;88:447–459.

The summary of the evidence by O’Connor and Kumar[22] provides a good overview of current evidence, although further comparative studies[23–27] have since been published. This collected evidence shows that there is a substantial survival advantage with dialysis; however, for older people with end-stage kidney disease (ESKD; >75–80 years) with comorbidity, much of this survival advantage is lost. When time in hospital and receiving dialysis is also considered, there is little or no survival advantage to be gained from dialysis for these older patients with comorbidities. However, there are two notes of caution in interpreting and applying this evidence; first, the evidence from those receiving conservative care remains very limited, and second, the conservative care population is heterogeneous. This makes it much harder to relate to individual circumstances, yet decisions for conservative care always need to be individually tailored.

It is important to also consider symptoms, QOL, illness experience, and survival. There is robust evidence that patients rarely prioritize survival above all else; QOL is equally important and often takes precedence.28 The systematic review cited previously29 shows that patients managed conservatively (as do those receiving dialysis) report significant symptom burden, with an average of 9 to 17 symptoms. QOL is generally similar between patients on dialysis and patients receiving conservative care, although there may be some decrease in life satisfaction in relation to dialysis adjustment.30 Of note, with good supportive care, many of the conservatively managed patients have stable or improved symptoms and QOL.31

Situations Where Dialysis Withdrawal Is Appropriate

From Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: Developing a roadmap to improving quality care. Kidney Int. 2015;88:447–459.

DIALYSIS WITHDRAWAL

As already demonstrated in the case discussed in Fig. 94.3, patients may decide to stop dialysis. The median time to death after stopping dialysis is 8 to 9 days32 but can be considerably longer if there is significant residual kidney function. There is information for patients and caregivers about stopping dialysis on both U.K. and U.S. patient support websites.33 34 The situations in which dialysis withdrawal is appropriate are shown in Box 94.6

Studies suggest that the rate of dialysis withdrawal has increased over the years, but this needs to be interpreted with caution because there is no well-accepted definition of dialysis withdrawal.35 A recent report published from the Scottish Renal Registry36 has defined death resulting from withdrawal as patients refusing further treatment, therapy ceased for other reasons, and dialysis withdrawn for medical reasons. In this study, dialysis withdrawal was the primary cause of death in 19% of all deaths (a rate of 41 in 1000 patient-years) over a 7-year period; in a further 17% of patients, withdrawal from dialysis was considered to have contributed to death but not to have been the main cause. Using this definition, deaths attributed to dialysis withdrawal accounted for around one-third of deaths; this did not change over the 7 years of the study but did vary significantly across the different kidney centers with dialysis withdrawal accounting for 3.3% to 55.8% of all deaths per center.36 This variation also has been found on a larger scale between different European countries, with higher reports of dialysis withdrawal if respondents in the survey worked in a public center, if stopping life-supporting treatments was perceived as allowed, if withdrawal decisions were considered shared between patients and doctors, and if palliative care was reimbursed by payers.37 The patient factors associated with dialysis withdrawal vary in individual studies, but many of the following have been consistently identified: older age, female sex, higher comorbidity burden (particularly cerebrovascular disease), being on HD, early initiation of dialysis, and late referral to nephrologist.36 38 39 Cultural differences also play an important role in dialysis withdrawal with lower rates of dialysis discontinuation in racial and ethnic minorities reported in studies in English-speaking countries.38 39 40

Withdrawal from dialysis is ethically and clinically acceptable only after a process of shared decision making with the patient (and close persons if the patient is no longer able to make decisions). These discussions need to be attuned to the culture (ethnic and religious) of the individual.17 It is also incumbent on all providers caring for a patient who is contemplating stopping dialysis to address potentially remedial factors contributing to the decision, such as depression, or other symptoms, such as pain and potentially reversible social factors.2 It is essential to ensure access to appropriate supportive and/or hospice care as an integral part of care after any decision to withdraw dialysis.2 Details of this are discussed in the following section.

SYMPTOM CONTROL AND MANAGEMENT OF LAST DAYS

Symptoms are as common in those managed conservatively as among those on dialysis, with 3 in 4 reporting weakness and pruritus; 1 in 3 reporting drowsiness, breathlessness, and edema; and more than 1 in 2 patients with ESKD reporting pain.41 These symptoms are not mild; a high proportion (more than two-thirds) of those with pain, for instance, have moderate or severe pain, often related to comorbid conditions rather than to kidney disease. In addition, symptoms often accumulate, with an average of 12 symptoms experienced by each patient that impair QOL and need optimal management.

Evidence on management of symptoms is often extrapolated from other populations or based on best understanding of the

pharmacodynamics and pharmacokinetics in severe kidney impairment. This evidence is limited but is well summarized in a recent series of articles.42

In the last days of life, additional symptoms may arise from uremia (nausea, vomiting, drowsiness, myoclonus, pruritus), fluid overload (breathlessness and edema), and immobility and poor tissue perfusion (pain, muscle soreness, pressure sores). It is best practice to prescribe “as required” doses of an analgesic, an antiemetic, a sedative, and an antisecretory agent for all patients with ESKD as they enter the last few days of life, to anticipate any distressing symptoms and ensure they can be rapidly addressed. The actual drugs used will vary between different centers and countries. What is important is involvement with local palliative care team support in determining which drugs to prescribe for the individual patient.

As end of life approaches, both patient and family often need much more information and explanation than is provided by health professionals. Encouragement to ask questions, straightforward but sensitively judged responses, and frequent opportunities for professionals to check on concerns and anxieties can go a long way to provide support to the patient and family at a difficult and challenging time.

SELF-ASSESSMENT QUESTIONS

1. Which of the following factors have been shown to be associated with a poor survival prognosis in an 80-year-old man who has been on dialysis for 2 years?
A. Being on peritoneal dialysis
B. Peripheral vascular disease
C. Use of central venous catheter
D. Requiring assistance to get dressed
E. Low plasma albumin
2. Advance care planning should include which of the following?
A. Legal process resulting in advance decision
B. Informing the patient that they will not be resuscitated
C. Discussion about prognosis
D. Identification of patient concerns
E. Opportunity for patient to record future wishes
3. Which of the following statements can be made about dialysis withdrawal?
A. Approximately 20% of deaths of dialysis patients are stated to be because of dialysis withdrawal.

B. Death invariably occurs within 3 days of stopping dialysis.

C. Dialysis withdrawal can be viewed as euthanasia.
D. Shortness of breath is the main symptom after withdrawing dialysis.
E. Dialysis can be stopped in patients lacking decision-making capacity who have made a previous decision to this effect.
4. Which of the following statements can be made about conservative care?
A. Survival rates of multimorbid patients older than 80 years are similar on dialysis and conservative care.
B. Survival of functionally independent patients 70 to 75 years old are the same on dialysis and conservative care.
C. Patients choosing conservative care should be persuaded to start dialysis if they deteriorate acutely.
D. Anemia management with erythropoietin is appropriate for patients choosing conservative care.
E. Conservative care is not “rationing” because patients choose not to have dialysis themselves.

REFERENCES

1. WHO Definition of Palliative Care. World Health Organization. http://www.who.int/cancer/palliative/definition/en/.
2. Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on supportive care in chronic kidney disease: developing a roadmap to improving quality care. Kidney Int. 2015;88:447–459.
3. Tonkin-Crine S, Okamoto I, Laydon GM, et al. Understanding by older patients of dialysis and conservative management for chronic kidney failure. Am J Kid Dis. 2015;65:443–450.
4. Davison SN. End-of-life care preferences and needs: perceptions of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5:195–204.
5. Wachterman MW, Marcantonio ER, Davis RB, et al. Relationship between the prognostic expectations of seriously ill patients undergoing hemodialysis and their nephrologists. JAMA Intern Med. 2013;173:1206–1214.
6. Couchoud C, Hemmelgam B, Kotanko P, et al. Supportive Care: time to change our prognostic tools and their use in CKD. Clin J Am Soc Nephrol. 2016. https://doi.org/10.2215/CJN.12631115.
7. Floege J, Gillespie IA, Kronenberg F, et al. Development and validation of a predictive mortality risk score from a European hemodialysis cohort. Kidney Int. 2015;87:996–1008.
8. Risk ARO Score Calculators. http://aro-score.askimed.com/.
9. Couchoud CG, Beuscart J-P, Aldigier J-C, et al. On behalf of the REIN registry. Development of a risk stratification algorithm to improve patient-centered care and decision making for incident elderly patients with end-stage renal disease. Kidney Int. 2015;88:1178–1186.
10. Clegg A, Young J, Iliff S, et al. Frailty in elderly people. Lancet. 2013;381:752–762.
11. Alfaadhel TA, Soroka SD, Kiberd BA, et al. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. Clin J Am Soc Nephrol. 2015;10:832–840.
12. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. Can Med Assoc J. 2005;173:489–495.
13. Iyasere OU, Brown EA, Johansson L, et al. Quality of life and physical function in older patients on dialysis: a comparison of assisted peritoneal dialysis with hemodialysis. Clin J Am Soc Nephrol. 2016;11:423–430.
14. NHS England. Shared decision making. https://www.england.nhs.uk/ourwork/pe/sdm/#.
15. Muthalagappan S, Johansson L, Kong WM, Brown EA. Dialysis or conservative care for frail older patients: ethics of shared-decision making. Nephrol Dial Transplant. 2013;28:2717–2722.
16. Renal Physicians Association. Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis (Clinical Practice Guideline). 2nd ed. Rockville: MD; 2010.
17. Brown EA, Bekker HL, Davison SN, et al. Supportive care: communication strategies to improve cultural competence in shared decision making. Clin J Am Soc Nephrol. 2016;11(10):1902–1908.
18. Kimbell B, Murray SA, Macpherson S, Boyd K. Embracing inherent uncertainty in advanced illness. BMJ. 2016;354:i3802.
19. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ. 2010;340:c1345.
20. Song M-KS, Ward SE, Fine JP, et al. Advanced care planning and end-oflife decision making in dialysis: a randomised controlled trial targeting patients and their surrogates. Am J Kid Dis. 2015;66:813–822.
21. Kee F, Patterson CC, Wilson EA, et al. Stewardship or clinical freedom? variations in dialysis decision making. Nephrol Dial Transplant. 2000;15(10):1647–1657.
22. O’Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. J Pall Med. 2012;15(2):228–235.

23. Hussain JA, Mooney A, Russon L. Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. Pall Med. 2013;27(9):829–839.
24. Da Silva-Gane M, Wellsted D, Greenshields H, et al. Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. Clin J Am Soc Nephrol: CJASN. 2012;7(12):2002–2009.
25. Kwok WH, Yong SP, Kwok OL. Outcomes in elderly patients with end-stage renal disease: comparison of renal replacement therapy and conservative management. Hong Kong J Nephrol. 2016;19:42–56.
26. Martínez Echevers Y, Toapanta Gaibor NG, Nava Pérez N, et al. Survival of patients ≥70 years with advanced chronic kidney disease: dialysis vs. conservative care. Nefrologia. 2016;36(3):283–291.
27. Chandna SM, Carpenter L, Da Silva-Gane M, et al. Rate of decline of kidney function, modality choice, and survival in elderly patients with advanced kidney disease. Nephron. 2016;134(2):64–72.
28. Higginson IJ, Gomes B, Calanzani N, et al. Priorities for treatment, care and information if faced with serious illness: a comparative populationbased survey in seven European countries. Palliat Med. 2014;28(2):101–110.
29. O’Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. J Pall Med. 2012;15(2):228–235.
30. Da Silva-Gane M, Wellsted D, Greenshields H, et al. Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. Clin J Am Soc Nephrol: CJASN. 2012;7(12):2002–2009.
31. Brown MA, Collett GK, Josland EA, et al. CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. Clin J Am Soc Nephrol. 2015;10(2):260–268.
32. Cohen LM, McCue JD, Germain MJ, Kjellstrand CM. Dialysis discontinuation: a ‘good’ death? Arch Int Med. 1995;155:42–47.
33. Kidney Care UK Saying no to dialysis. https://www.kidneycareuk.org/about-kidney-health/order-or-download-booklets/.
34. DaVita. What happens if someone stops dialysis? https://www.davita.com/kidney-disease/dialysis/treatment/what-happens-if-someone-stopsdialysis?/e/1521.
35. Murphy E, Germain MJ, Cairns H, et al. International variation in classification of dialysis withdrawal: a systematic review. Nephrol Dial Transplant. 2014;29:625–635.
36. Findlay MD, Donaldson K, Doyle A, et al. On behalf of the Scottish Renal Registry (SRR). Factors influencing withdrawal from dialysis: a national registry study. Nephrol Dial Transplant. 2016;31:2041–2048.
37. van Biesen W, van de Luijtgaarden MWM, Brown EA, et al. Nephrologists’ perceptions regarding dialysis withdrawal and palliative care in Europe: lessons from a European Renal Best Practice survey. Nephrol Dial Transplant. 2015;30:1951–1958.
38. Ellwood AD, Jassal SV, Suri RS, et al. Early dialysis initiation and rates and timing of withdrawal from dialysis in Canada. Clin J Am Soc Nephrol. 2013;8:265–270.
39. Chan HW, Clayton PA, McDonald SP, et al. Risk factors for dialysis withdrawal: an analysis of the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, 1999-2008. Clin J Am Soc Nephrol. 2012;7:775–781.
40. Agunbiade A, Dasgupta A, Ward Michael M. Racial/ethnic differences in dialysis discontinuation and survival after hospitalization for serious conditions among patients on maintenance dialysis. J Am Soc Nephrol. 2020;31:149–160.
41. Murtagh FE, Addington-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. J Palliat Med. 2007;10(6):1266–1276.
42. Davison SN, Tupala B, Wasylynuk BA, Siu V, Sinnarajah A, Triscott J. Recommendations for the care of patients receiving conservative kidney management: focus on management of CKD and symptoms. Clin J Am Soc Nephrol. 2019;14:626–634.

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Approach to Kidney Replacement Therapy

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Individuals with advanced chronic kidney disease (CKD) will have one of three fates: stable CKD, progressive loss of kidney function to kidney failure, or death prior to developing kidney failure. The options for treatment for people who progress to kidney failure include kidney replacement therapy (KRT), consisting of transplantation or dialysis, and supportive (nondialysis) care (see Chapter 94).

Broadly there are two types of dialysis: peritoneal dialysis (PD) and hemodialysis (HD).

The number of people starting dialysis for KRT each year varies enormously around the globe (Fig. 95.1).[1] The incidence per million population in most countries has risen steadily over the past decade (Fig. 95.2), although some have seen a decline in recent years (Fig. 95.3). The incidence of dialysis for KRT is influenced by multiple factors: the incidence and prevalence of diseases that may lead to kidney failure, especially diabetes; the ability of health care systems to identify CKD and to slow progression to kidney failure[2,3]; the level of kidney function at which KRT is begun; and the availability of resources to provide dialysis.

Dialysis is costly and time-consuming; once started, it may continue for many years. All individuals likely to reach kidney failure, their families, and their caregivers require physical and psychological preparation, including education about future treatment options, given in a form that they find accessible.

PREDICTION OF KIDNEY FAILURE

Preparation for kidney failure treatment requires two things: identification of those individuals who are at high risk for reaching kidney failure and prediction of the likely time when KRT may be needed.[4]

Diabetes, heavy proteinuria, declining estimated glomerular filtration rate (eGFR), and previous episodes of acute kidney injury make it more likely that an individual will progress to kidney failure. A variety of risk prediction tools can be used. The Kidney Failure Risk Equation (KFRE) performs reasonably well over 2 years and has been extensively studied and validated in a variety of populations (Fig. 95.4).[5] Models making predictions at 5 years or more considerably overestimate the risk of kidney failure because of the competing risk of death.[6] The Grams model, which accounts for this, is suitable for predictions over 4 years.[7]

Predicting when someone may need KRT is made easier by a graphical display of eGFR. The trajectory of the eGFR accurately reflects changes in the true GFR over time[8] and is easier to understand than columns of figures. The graph should be shared with patients to help

them understand how their disease is progressing. If individuals with a declining trend in eGFR are systematically identified,[9] the number starting KRT without adequate preparation may be reduced and the rising trend in KRT incidence slowed.[2]

MULTIDISCIPLINARY CARE IN ADVANCED CHRONIC KIDNEY DISEASE

Advanced CKD care aims to address several issues: preservation of remaining kidney function; prevention or treatment of complications of CKD; involvement of the individual, their family, and caregivers in making an informed choice in regard to PD, HD, and conservative kidney management; creation of dialysis access in good time; and, in appropriate individuals, preparation for kidney transplantation ideally before dialysis is started. People who receive consistent predialysis care have better outcomes[10] and incur lower health care costs.

People need time (often months) to understand and make decisions about dialysis and its implications. The best approach is to transfer the care of individuals with a high risk of kidney failure to a multidisciplinary team at least 12 months before dialysis is started. One method of determining who should be referred to multidisciplinary care is to use a risk-based assessment such as the Kidney Failure Risk Equation described earlier. A risk of kidney failure of more than 10% over 2 years has been suggested as a trigger for referral. Alternatively, one can estimate the start date for KRT by extrapolating a trendline of the eGFR forward until it reaches 10 mL/min/1.73 m^2.[11] Using the 12-month prediction rather than an arbitrary value of eGFR to prompt referral avoids older individuals with slowly declining GFR being referred for dialysis preparation unnecessarily.

The trajectory of the eGFR graph may not be linear; intercurrent illness in individuals at stage 5 CKD can cause a sudden drop in GFR and precipitate urgent dialysis. It is therefore prudent to refer all individuals with CKD for multidisciplinary care once the eGFR reaches 15 mL/min/1.73 m^2.

Predialysis Education Programs

Conventional office consultations with a nephrologist may not enable people with advanced CKD to gain sufficient knowledge and understanding to make good decisions about KRT.[12] Individuals receiving additional care from a predialysis multidisciplinary team have better biochemical results, are more likely to start dialysis in a planned way with less hospitalization, and may even have improved survival rates once they have started dialysis. As well as being good clinical practice, Global Incidence of Treated Kidney Failure, Based on Individual Country Data

>200.2 pmp
144.1-200.2 pmp
103.1-144.0 pmp
<103.1 pmp
Data not reported

Fig. 95.1 Geographic Variation in the Incidence of Treated Kidney Failure per Million Population (pmp), by Country, 2019. Data presented only for countries from which relevant information was available. All rates are unadjusted. (From Bello AK, Levin A, Lunney M, et al. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. BMJ. 2019;367:l5873.)

Countries or Regions With the Largest Percentage Increase in Incidence of ESKD, 2009–2010 vs 2017–2018

500
400
300
200
100

2018

2017

2016

2015

2014

2013

2012

2011

2010

0
2009

ESKD incidence (per million population)

600

Year
Bangladesh
Thailand
Hungary
Rep. of Korea
Indonesia
Brazil
Singapore
Malaysia

Saudi Arabia
Jalisco (Mexico)
United States

Fig. 95.2 Ten Countries Having the Highest Percentage Increase in the Incidence of End-Stage Kidney Disease (ESKD) From 2009 to 2018. All data are unadjusted. Data for United States are shown for comparison purposes. (From US Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.)

these programs may make good financial sense because the savings in inpatient costs can exceed those required to run the clinics.13 Although clinicians are expert in the technical aspects of dialysis and transplantation, people living with CKD know best about their own needs and preferences and should be encouraged to share in making decisions.

Education should follow the principles of adult learning: first, assess the individual’s existing level of knowledge and understanding; second, build on this knowledge by delivering appropriate information in an appropriate form; and third, establish that they have understood and accepted the information given. Education can be delivered both

Country/region

Average Yearly Change in ESKD Incidence Data, 2009–2018
Hungary
Thailand
Rep. of Korea
Singapore
Taiwan
Brazil
Malaysia
Jalisco (Mexico)
Greece
Indonesia
Saudi Arabia
Canada
Bangladesh
United States
Hong Kong
Uruguay
France
Qatar
Finland
United Kingdom
Argentina
Japan
Portugal
Iceland
Israel
Norway
Sweden
Italy
Bosnia and Herzegovina
Colombia
Chile
Turkey

_15

_10

_5

0

5

10

15

20

25

30

35

40

Average yearly change in ESKD incidence (per million population)

Fig. 95.3 Average Yearly Change in End-Stage Kidney Disease (ESKD) Incidence Data From 2009 to 2018. All data are unadjusted. (From US Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.)

Predicting the Probability of Kidney Failure

Variables	Patient A	Patient B
Age	70 years old	50 years old
Sex	Male	Male
Estimated glomerular filtration rate	30 mL/min/1.73 m2	30 mL/min/1.73 m2
Urine albumin to creatinine ratio	200 mg/g	50 mg/g
Albumin	3.5 g/dL	4.0 g/dL
Bicarbonate	21 mEq/L	26 mEq/L
Calcium	9.0 mg/dL	9.8 mg/dL
Phosphorus	4.5 mg/dL	3.8 mg/dL

Kidney failure risk

9.2% (2 years)
27.0% (5 years)

3.6% (2 years)
11.3% (5 years)

Fig. 95.4 Predicted Probability of Kidney Failure for Two Patient Profiles Using the 8-Variable Kidney Failure Risk Equation. The Kidney Failure Risk Equation uses eight common variables to estimate the 2- and 5-year risk of kidney failure.

individually and in groups. In a group education session, individuals living with CKD may learn more from fellow participants than from the group's facilitator. Furthermore, support groups help individuals and their relatives appreciate that they are not alone in facing the demands of kidney failure.

The multidisciplinary team may include a dietician, nurse educator, pharmacist, physical therapist, occupational therapist, social worker, and sometimes a trained peer-support volunteer. There is no ideal team composition, and it will vary depending on the local context.14 A controlled trial in California studied the value of social worker input to the predialysis program in reducing unemployment.15 In the intervention group, individuals and their relatives met regularly with a licensed social worker both before and after starting dialysis to explore strategies for continuing their current employment. Blue-collar workers in the intervention group were 2.8 times more likely to continue working. People in employment had a better quality of life, greater self-esteem, and a more positive attitude toward work. Because it is difficult for individuals treated with dialysis to regain jobs once they are lost, this result is particularly valuable for long-term rehabilitation.

Individuals living with CKD should be directed to the wide range of educational materials available. Many national organizations, such as Kidney Care UK (https://www.kidneycareuk.org/),16 provide webbased information and produce printed and audiovisual material.

Decision aids can help people think through their options and choose the treatment that suits them best. A good online example is My Kidneys, My Choice (http://mychoice.kidney.org.au).17 Each consultation should be followed by a letter or report, ideally written directly to the patient18 and copied to their family doctor.

Education About Transplantation

For many, transplantation offers the best prospect for improved survival and quality of life, especially in younger people. Even in older people with greater comorbidity, transplantation can improve survival and be cost-effective.19

The options of transplanting kidneys from a deceased or living donor should be discussed, as well as combined kidney and pancreas transplants for some people with diabetes. Although outcome data from the local transplant center should be made available, published data can be used, such as from the US Scientific Registry of Transplant Recipients20 or NHS Blood and Transplant in the United Kingdom (https://www.odt.nhs.uk).

The ideal time for the transplant to be performed is before dialysis has begun (preemptive transplantation). This avoids the need for access surgery, and in most studies, survival, graft survival, and acute rejection rates are better.21

WHEN SHOULD DIALYSIS BE STARTED?

There is no single measure that can be used to determine the right time to start dialysis. A low eGFR, rising serum phosphate, and falling serum bicarbonate may indicate kidney failure, but these levels are also affected by muscle mass and protein intake. Falling serum albumin may indicate inflammation rather than malnutrition secondary to uremia.

The mean eGFR at the start of dialysis varies across countries. In the United Kingdom, the mean eGFR at dialysis initiation was 7.4 mL/min/1.73 m2 in 2018. Registry data from USRDS shows 10.6% of individuals starting dialysis with eGFR greater than 15 mL/min/1.73 m2 and 27.3% with eGFR 10 to 14 mL/min/1.73 m2.20 In Canada, 7.9% started dialysis with eGFR greater than 15 mL/min/1.73 m2 and 19.4% with eGFR 10.5 to 15 mL/min/1.73 m2.22 The median eGFR at dialysis initiation in Australia was 7.4 mL/min/1.73 m2 and 5.6 mL/min/1.73 m2 in New Zealand.23

In the United States, dialysis was started at a consistently lower eGFR within the Department of Veterans Affairs, a non–fee-for-service health system, than with other providers.24

Limitations of a Purely Clinical Approach to the Initiation of Dialysis

Waiting for uremic symptoms to develop before starting KRT carries the risk that the individual will be malnourished when they start dialysis, with an increased risk for mortality. The chronic nature of progressive kidney disease means that people may remain unaware of the severity of their illness. Protein intake may fall spontaneously so that symptoms of uremia do not develop, at the expense of a loss of lean body mass. Similarly, people may gradually reduce their activities as their exercise tolerance declines. Many individuals only appreciate how ill they have become once they have rehabilitated on a dialysis program. Lack of awareness can be avoided by seeking insidious symptoms of uremia. For example, people should be asked to compare their current eating habits and level of activity with those 6 to 12 months previously. Close friends and relatives may provide a useful third-party view of their well-being. A validated patient-reported outcome measure (PROM) may help identify changing symptoms as CKD advances.25

Limitations of a Purely Laboratory Results–Based Approach to the Initiation of Dialysis

Starting dialysis early must have proven benefits to justify the additional inconvenience, risk of dialysis-related complications, and cost. Dialysis treatment has a finite life, either from loss of peritoneal function or failure of HD access; thus, starting treatment earlier will bring forward the time when further procedures or a change of modality are needed. Moreover, there is likely to be resistance from many individuals to the suggestion that they should start dialysis if they have no symptoms of uremia. Starting dialysis is the first step in a lifelong commitment to KRT, and people treated with dialysis will be asked to comply with a wide variety of inconvenient and sometimes unpleasant treatments. A high level of compliance is required for a successful outcome. Missed dialysis treatments are associated with increased risk of mortality and health care interventions.26,27

A randomized trial comparing individuals who started dialysis at eGFR of 9.0 mL/min/1.73 m2 with those who started 6 months later at eGFR of 7.2 mL/min/1.73 m2 showed no difference in survival or quality of life (Fig. 95.5).28 Starting dialysis earlier was not associated with better quality of life and incurred higher health care costs.29 The one advantage in the earlier-start group was that a higher proportion of those who had previously chosen PD actually started dialysis with PD (80% vs. 70%, P = .01).

Some clinicians advocate an incremental start to hemodialysis. Incremental hemodialysis is the delivery of less than the conventional thrice-weekly sessions of dialysis with adjustments of dialysis prescription informed by changes in residual kidney function.30 Prescription changes can include frequency of dialysis sessions, session duration, fluid volumes, needle size, dialyzer surface area, blood flow rate, dialysate flow rate. Additionally, dietary intervention can be modified.

People with preserved residual kidney function (>500 mL/day), limited weight gain between dialysis sessions (<2.5 kg), and the ability to maintain metabolic parameters in an acceptable range with shorter or fewer sessions would be good candidates for consideration of incremental dialysis. Close monitoring of residual kidney function, interdialytic weight gain, and metabolic parameters are needed to ensure that continuing incremental dialysis is still appropriate. In low-income countries, less frequent dialysis may be all that is available.31

CHOICE BETWEEN PERITONEAL DIALYSIS AND HEMODIALYSIS

Atlas, only 32% of low-income countries report that PD is available[32] compared with greater than 90% of upper-middle- and high-income countries. Some countries such as Hong Kong and New Zealand have consistently high incidence and prevalence rates of PD.[33,34] In Hong Kong, PD comprises approximately 75% of prevalent dialysis[33] and since 1985 has been provided as first-choice KRT unless absolute medical contraindications to PD are present.[35]

Globally, higher expenditure of gross domestic product (GDP) on health care, a larger proportion of private health-care expenditure, and lack of local production of PD consumables and high duty imports on PD supplies are associated with higher costs of PD relative to HD.[36] However, in Hong Kong PD has been shown to be more cost-effective than HD.[37]

Most people with kidney failure are suitable for treatment with either PD or HD. How should we choose between the two? Ideally, we would apply evidence from a randomized clinical trial (RCT) of PD versus HD, but executing such a trial would be difficult. One attempted RCT, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), had to be stopped because of low recruitment.

Retrospective and prospective nonrandomized comparative studies have failed to indicate a consistent survival advantage for either modality.[38] Previous evidence suggested that PD may be inferior to HD over the longer term in individuals with coronary heart disease and congestive heart failure.[39] More recent evidence suggests that this may not be the case,[40] and PD is associated with superior healthrelated quality of life.[41]

PD technique failure can be due to infection, mechanical problems, inadequate dialysis, and social reasons. Late technique failure is associated mainly with social factors.[42] Technique failure due to infection and social reasons are associated with a higher short-term risk of death,[43] most frequently because of cardiac mortality when technique failure is due to infection, and dialysis withdrawal due to social reasons.

The mix of PD and HD in the dialysis population varies considerably across countries (Fig. 95.6). In the most recent Global Kidney Health

Mortality of Patients Started on Dialysis Early or Late

60

Early-start group

Late-start group

50

Mortality (%)

40

30

20

10

Hazard ratio, 1.04 (95% Cl, 0.83 1.30)

P = .75

0
0

1

2

6
7
4
5
Year

Fig. 95.5 Mortality of Individuals Started on Dialysis Early or Late. Kaplan-Meier curves for the time to death. (From Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2019;36[7]:609–619.)

3

Country/region

Dialysis Modality in Patients With ESKD, 2018
Hong Kong
Jalisco (Mexico)
Aguascalientes (Mexico)
Colombia
Norway
Canada
Sweden
Qatar
Finland
Hungary
Singapore
United Kingdom
Italy
United States
Malaysia
Uruguay
Rep. of Korea
Israel
Brazil
Argentina
France
Greece
Chile
Turkey
Czech Republic
Lithuania
Albania
Bangladesh
Japan

0

10

20

30

40

50

60

70

80

Percentage of patients
CAPD/APD/IPD

Home HD

In-Center HD

Fig. 95.6 Distribution of the Percentage of Prevalent Patients Using In-Center Hemodialysis (HD), Home HD, or Peritoneal Dialysis (PD), 2018. Denominator is calculated as the sum of patients receiving HD, PD, or home HD; does not include patients with other/unknown modality. APD, Automated peritoneal dialysis; CAPD, Continuous ambulatory peritoneal dialysis; IPD, Intermittent peritoneal dialysis. (From US Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.)

90

100

Contraindications to Peritoneal Dialysis

There are a few situations in which PD is contraindicated (Box 95.1). Relative contraindications to PD include those discussed in the following section.

Fresh Intraabdominal Foreign Body

Individuals with prosthetic aortic grafts have been successfully treated with PD. HD is usually used for up to 16 weeks to allow the graft to be covered with epithelium and so avoid the risk for graft infection via peritoneal dialysate. However, this risk must be balanced against that of bacterial seeding from the HD access.

Body Size Limitations and Intolerance of Intraabdominal Fluid Volume

Both very large and very small body size can be challenging for people treated with PD. Small individuals may be intolerant of the volume of dialysate needed to achieve adequate dialysis, particularly if they have negligible residual kidney function. Alternative methods of fluid exchange, such as automated PD, can be used to overcome this limitation. Larger dwell volumes or automated PD are required to achieve adequate solute clearance and ultrafiltration in people with a body mass index greater than 35 kg/m2. Discomfort as a result of increased intraabdominal volume can be significant in those with chronic respiratory disease, low-back pain, or large polycystic kidneys. In general, it is hard to predict someone’s tolerance of intraabdominal fluid, and so these limitations usually appear after PD has been started.

Bowel Disease and Other Sources of Infection

The presence of ischemic bowel disease, inflammatory bowel disease, or diverticulitis is likely to increase the incidence of peritonitis caused by organisms passing through the bowel wall into the peritoneum. Abdominal wall infection may lead to peritonitis via the exit site and catheter tunnel.

Testing for methicillin-resistant Staphylococcus aureus (MRSA) before all elective surgical procedures is good practice. Clearance of nasal S. aureus with topical mupirocin cream reduces the risk for staphylococcal infection at the exit site.

Severe Malnutrition or Severe Obesity

Severe malnutrition may lead to poor wound healing and leakage from the catheter tunnel. In addition, peritoneal protein losses during dialysis may exacerbate hypoalbuminemia. At the other end of the spectrum, it may prove difficult to satisfactorily place a peritoneal catheter through the abdominal wall in people with severe obesity, and the risk for infection is greater. Thereafter, absorption of glucose from the dialysate, which may average as much as 800 calories per day, may contribute to further weight gain.

Contraindications to Hemodialysis

Contraindications to HD are few (see Box 95.1). As discussed in Chapter 96, access to the circulation usually can be obtained, even in people with extensive vascular disease or previous surgery. An aversion to needle puncture of the atrioventricular fistula (AVF) is common in the early stages but usually can be overcome by careful use of local anesthetic and nursing encouragement. Severe coagulopathy may make management of anticoagulation in the extracorporeal circuit difficult.

HOME HEMODIALYSIS

In the 1960s, maintenance dialysis was mostly done by the patient and the family at home. Because in-center HD programs were established

BOX 95.1

Contraindications to Dialysis

Peritoneal Dialysis

Absolute
- Lack of housing/lodging
- Loss of peritoneal function producing inadequate clearance
- Adhesions blocking dialysate flow
- Surgically uncorrectable abdominal hernia
- Abdominal wall stoma
- Diaphragmatic fluid leak
- Inability to perform exchanges in absence of suitable assistant

Relative
- Recent abdominal aortic graft
- Ventriculoperitoneal shunt
- Intolerance of intraabdominal fluid
- Large muscle mass
- Extreme obesity
- Severe malnutrition
- Skin infection
- Bowel disease

Hemodialysis

Absolute
- No vascular access possible

Relative
- Difficult vascular access
- Needle phobia
- Cardiac failure
- Coagulopathy

Modified from Peritoneal Dialysis Adequacy Work Group. Clinical practice guidelines for peritoneal dialysis adequacy. Am J Kidney Dis. 2006;48(suppl 1):S91–S97.

and then PD became available, people could choose not to have HD at home. This removed the burden of dialysis from the individual and family and avoided the cost of installing a dialysis machine with its associated water treatment. In the United Kingdom the percentage of the adult dialysis population having home HD fell from 35% in 1984 to 1% in 2006.[44]

Home-based HD offers similar clinical outcomes compared with facility-based HD and provides significant benefits: it removes the inconvenience of traveling to and from the dialysis facility, gives individuals the freedom to dialyze at a time that suits them, reduces the cost of nursing and support staff, and gives the individual more opportunities to take part in home and work activities.[45]

People who dialyze at home often perform more than three treatments per week, and some dialyze overnight. More frequent dialysis significantly reduces the time taken to recover after each treatment, reduces dietary restrictions and antihypertensive medications, and leads to improved quality of life and reduced mortality.[46]

In recent years there has been increasing recognition of the benefits of home HD, and this, along with better technology, has increased nephrologists’ enthusiasm for it.[47] In 2018, the proportion of individuals treated with KRT (including transplant) receiving home HD was 2.0% in the United Kingdom,[44] 2.1% in the United States,[20] and 2.6% in Canada; the highest proportion in Europe was 3.45% in Denmark.[48] Some countries achieve higher uptake: the proportion in Australia was 4.2% and in New Zealand 8.1%.[19,22]

Hemodialysis or Hemodiafiltration

for dialysis can start PD urgently,[53] and if they do start hemodialysis, they still should have access to an education program about their options for long-term treatment.

Frail individuals can be assisted to have PD at home by a spouse, family member, or trained assistant. This can avoid them having the burden of in-center HD and improve their quality of life,[54] and they may progress to independent PD after a month or two of assistance.[55]

The major differences in dialysis modality across countries (see Fig. 95.6) suggest that the type of dialysis individuals receive is more often determined by physicians and organizational factors than by their preferences.

Hemodiafiltration (HDF) is increasingly used throughout Europe and elsewhere but is not available in the United States because of regulatory restrictions. HDF adds the removal of fluid containing larger molecules by convection to the clearance of smaller molecules by diffusion. For example, β_2-microglobulin levels are lower in individuals treated by HDF than by HD. In this way, HDF theoretically mimics glomerular filtration more closely and potentially may benefit people with little or no residual kidney function.

A number of trials comparing outcomes with HD and HDF have been conducted, yielding conflicting results. Evidence suggests that high convection volumes (>30 L/wk/m^2) need to be used to deliver better outcomes if HDF is selected as the dialysis modality.[49]

IMPORTANCE OF DIALYSIS ACCESS

CHOICE OF HEMODIALYSIS OR PERITONEAL DIALYSIS

Before starting dialysis, every patient would ideally have made an informed choice between PD and HD after weeks or months of counseling and preparation, and those choosing HD would have a functioning AVF. Unfortunately, dialysis is frequently started in less than ideal circumstances. The percentage of individuals presenting shortly before starting dialysis varies between dialysis units and countries (Fig. 95.7). This is a particular issue in the United States, where in 2015 only 31% of individuals beginning KRT had received 12 months of nephrology care before KRT.[56]

People presenting to a nephrologist shortly before starting dialysis have a longer initial hospital stay and a higher incidence of major complications and death.[10] Late presentation is one reason why HD is started using a catheter rather than an AVF (Fig. 95.8), and increased catheter use is associated with increased mortality.

The timing of AVF placement is complex.[57] If an AVF is created many months before the individual is predicted to reach kidney failure, then the chances that a catheter is used are reduced. However,

Ideally, everyone with advanced CKD would be given “modalityneutral” counseling and allowed to select their preferred mode of treatment. When provided with modality education, people are more likely to select and be treated with PD.[50] Independent predictors for choosing PD include being married, being counseled before the start of dialysis, and increasing distance from the base unit; predictors for choosing HD are increasing age, comorbidity, and male sex. However, although 45% of patients may choose PD, not all of them start dialysis on this modality. Individuals who require urgent dialysis often receive HD rather than PD, although PD can be started urgently if the necessary resources are available.51 Once started on HD, only a small proportion transfer to PD, even if this was their original preference. Individuals who do transfer from HD to PD are more likely to have technique failure in the following 12 months.52 Patients presenting late

Timing of First Nephrology Care Before Initiation of Hemodialysis by Country, 2012-2014

Timing of first nephrology care before HD

DOPPS 5 (2012-2014)

6 months

4-6 months

2-3 months

0-1 month

Not at all

100

90

26

80

% of patients

70

60

83

80

72

68

68

66

63

62

59

53

40

3

30

20

0

11

11

50

10

43

3
8
3

4
10

3
14

7
8
10
7

13
19

9

10
24

14
7

10

10
5

14
10

17

8
8

26

34

23
12
11

17
13

Swe Spa
Ger
Can
UK
Jpn
Ita
Bel
US
Rus GCC Chi
Fig. 95.7 Global Differences in Timing of First Nephrologist Care Before

Starting Dialysis Among Individuals Enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Within 60 Days of Starting Dialysis (2012–2014). Data were calculated among individuals on dialysis for fewer than 60 days at the time of enrollment in the study. Bel, Belgium; Can, Canada; Chi, China; Ger, Germany; GCC, Gulf Cooperation Council countries; HD, hemodialysis; Ita, Italy; Jpn, Japan; Rus, Russia; Spa, Spain; Swe, Sweden.

(From Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in US vascular access use, patient preferences, and related practices: an update from the US DOPPS Practice Monitor with international comparisons. Am J Kidney Dis. 2015;65[6]:905–915.)

Type of Vascular Access in Use Among Incident Hemodialysis
Patients by Country, 2012-2014
Vascular access use incident patients
DOPPS 5 (2012-2014)
Other
100
90

Catheter

AV-Fistula
7

11
5

80

34

42

42

47

70
% of patients

AV-Graft

49

50

42
55

50

67

68

60

30

81

10

50
40

71

84
66

58

56

20

53

51

10

50

48

45

5

4

28

28

44

6
23

19

0
Jpn
Tur
Ita
Ger UK Spa Rus Swe A/NZ Chi
US Can Bel GCC

Fig. 95.8 Country Differences in Timing of First Nephrologist Care Before Starting Dialysis Among Individuals Enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Within 60 Days of Starting Dialysis (2012–2014). Data were calculated among individuals on dialysis for fewer than 60 days at the time of enrollment in the study. AV, Arteriovenous; Bel, Belgium; Can, Canada; Chi, China; Ger, Germany; GCC, Gulf Cooperation Council countries; Ita, Italy; Jpn, Japan; Rus, Russia; Spa, Spain; Swe, Sweden. (From Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in US vascular access use, patient preferences, and related practices: an update from the US DOPPS Practice Monitor with international comparisons. Am J Kidney Dis. 2015;65[6]:905–915.)

elderly individuals may die without the AVF ever being used.58 AVF placement after dialysis has started is associated with a lower chance of long-term fistula use.59 International data from the Dialysis Outcomes and Practice Patterns Study show that the risk for death is higher for individuals dialyzing in units that use central venous catheters in a high proportion of patients.60 The risk is also increased if arteriovenous grafts are commonly used. Catheters can cause complications such as infection, pulmonary embolism, and central venous stenosis.

There is wide variation across countries in the time required for permanent access to be created and used. If a fistula can be created swiftly and used as soon as it is mature, perhaps after only 2 weeks, the need for a catheter may be avoided. Details of HD access surgery are discussed in Chapter 96 and PD catheter placement in Chapter 101

DECISION WHETHER TO OFFER KIDNEY REPLACEMENT THERAPY

Availability of Dialysis Facilities

Because of its high cost, KRT is not available to most people with kidney failure worldwide. The practice of rationing dialysis has been candidly documented in a report from a South African center,61 in which more than half the people with kidney failure assessed between 1988 and 2003 were not offered dialysis. Socioeconomic factors such as age, race, employment, and marital status outweighed medical factors in the decision to begin treatment.

The phenomenon of “supply-sensitive care” applies to dialysis as it does to health care in general.62 KRT incidence is independently associated with a country’s GDP, the percentage of GDP spent on health care, and the reimbursement rate relative to GDP for HD

dialysis facilities. In more developed countries, those with a greater proportion of private for-profit facilities have a higher incidence of dialysis.63

Selection by Physicians and Nephrologists

Although incidence rates of KRT in most countries have increased in recent decades (see Fig. 95.2), not all of this is due to increases in the incidence of kidney failure.63 64 In other words, physicians have become more willing over time to offer dialysis to people with kidney failure. The practice of starting dialysis in people who are very elderly and dependent on others for their care or who have multiple comorbid conditions varies significantly across countries and among nephrologists within those countries.65 In the UK only 19% of individuals on hemodialysis were fully independent. In Japan in 2010, 13% of individuals treated with hemodialysis had dementia, and 54% of these individuals spent more than half the day in bed.66

Uncertainty about prognosis, lack of palliative care services and training, and financial incentives toward providing dialysis may persuade nephrologists to offer dialysis.67

Rationing Versus Rational Dialysis Treatment

How dialysis should be used has raised a range of bioethical issues over the years.68 In the 1960s, committees would meet to decide who should be offered dialysis, on the grounds that the greatest good should be derived from the limited resources available. Individuals who were expected to survive for only a few months would not be offered dialysis. As resources became more widespread, a rationing approach became unacceptable and was replaced by decisions based on the balance of benefit and harm gained from dialysis for each individual.

Predictive Factors

Are there objective criteria that can be applied to identify individuals for whom the harms of dialysis will outweigh the benefits? One criterion to be dismissed is age. Although advanced age was used as a simple exclusion criterion in the early days of dialysis, the elderly are now the most rapidly growing section of the dialysis population.

There are several mortality risk prediction scores that estimate 6-month mortality for individuals starting dialysis.69 For older individuals, a high Ramipril Efficacy in Nephrology (REIN) score predicts 6-month mortality with high sensitivity and specificity.70

ADVISING ABOUT PROGNOSIS ON DIALYSIS

Despite these uncertainties, individuals should be given an estimate of their likely future on dialysis. The Renal Physicians Association (RPA) has suggested the following criteria to help identify those over 75 years of age who have a poor prognosis on dialysis71: (1) clinicians' response of "No, I would not be surprised if my patient died in the next 6 months"; (2) high comorbidity score; (3) significantly impaired functional status (e.g., Karnofsky Performance Status score <40); and (4) severe chronic malnutrition (i.e., serum albumin <2.5 g/dL using the bromocresol green method). Quality of life is also strongly predictive of mortality, even after statistical correction for these comorbid factors.

For individuals whose prognosis is particularly uncertain, or where there is disagreement between the views of the individual and the dialysis team, a time-limited trial of dialysis may be offered. This may give the individual and their family a better understanding of what life on dialysis entails and allow time for further discussion between all parties. The duration of the trial should be judged for each person, and clinical and biochemical parameters such as serum albumin reviewed regularly.

The RPA in the United States has issued guidelines for decisions to not initiate or to discontinue dialysis (Fig. 95.9) and provides a comprehensive toolkit to support shared decision-making.71

CONSERVATIVE KIDNEY CARE

Conservative kidney care can be defined as planned, holistic, patientcentered care for individuals with stage 5 CKD including a full range of treatment and support but not dialysis.72 This modality is increasingly adopted for a subset of individuals with kidney failure and multiple comorbidities.73 To date, evidence to inform discussions about conservative care as an alternative to dialysis has come from observational studies of varied quality.74 A meta-analysis found that at 1-year survival was similar for individuals managed with dialysis (73%) and conservative care (71%), but that at 2 years survival diverged to 62% for the dialysis group and 44% for the conservative care group. The Prepare for Kidney Care trial has been undertaken to address this evidence gap.75 It is an RCT comparing preparing for either dialysis or conservative care in frail, multimorbid older individuals with advanced CKD.

When asked in a survey about their priority between quality of life or extending the length of life if they were faced with a serious illness, Europeans strongly favored quality of life, with only a few expressing a preference for extending life.76 Individuals who are likely to have an unacceptable quality of life should not be subjected to the discomfort of dialysis. Individuals choosing conservative kidney management are spared surgical procedures and the inconvenience and discomfort of traveling to the HD unit or performing PD. Depending on age and the number of comorbidities, survival with dialysis may be no longer, and much of any additional time is made up of days having or recovering from dialysis treatments.77 Quality of life is likely to be better without dialysis, and patients are more likely to die at home.

Making a Decision to Not Initiate or to Discontinue Dialysis

Consider forgoing dialysis for AKI or ESKD patients who have a very poor prognosis
or for whom dialysis cannot be provided safely. This includes:

Patients unable to cooperate
(e.g., advanced dementia patient who
pulls out dialysis needles)

Patients who have a terminal illness from
nonrenal causes (acknowledging that
some in this condition may
perceive benefit from and choose
to undergo dialysis)

Patients older than age 75 years with two or more of the following criteria:
- Clinicians’ response of “No” to the question “Would you be surprised if the patient died within the next 6 months?”
- High comorbidity score
- Significantly impaired functional status (e.g., Karnofsky Performance Status score less than 40)
- Severe chronic malnutrition (i.e., serum albumin <2.5 g/dL)

Medical management incorporating palliative care is an integral part of the decision to forego dialysis in AKI, CKD, or ESRD
Attention should be given to patient comfort and quality of life while dying
Management may include palliative care consultation and referral to a hospice program
Fig. 95.9 Making a decision to not initiate or to discontinue dialysis. AKI, Acute kidney injury; CKD, chronic
kidney disease; ESKD, end-stage kidney disease.

Many of the symptoms and complications of kidney failure, such as anemia, acidosis, itching, insomnia, depression, fluid overload, and hypertension, can be treated with medication and diet. Individuals may not report symptoms such as pain or itching that they do not associate with kidney failure and so should be asked specifically about them.78 Symptom management tools and other resources for individuals who chose conservative care and their care providers are available at https://www.ckmcare.com/

Family physicians can be supported to deliver conservative care along with a specialist CKD multidisciplinary team and palliative care specialists.

INDIVIDUALS WHO DO NOT WANT DIALYSIS

Nephrologists may be presented with the dilemma of someone who has decision-making capacity and whom they would normally treat but who does not wish to have dialysis. From an ethical viewpoint, an individual's decision not to start dialysis or to discontinue it is justified on the principle of individual autonomy. Legally, in the United Kingdom this is based on the individual's common law right to selfdetermination and in the United States on the constitutional right of liberty. Where the individual is able to express a clear wish, the physician is obliged to respect this, because to treat them against their will constitutes an assault.

The physician must nonetheless ensure that all reversible factors have been addressed, such as unfounded fears about what dialysis will entail or a depressive illness affecting the patient's judgment, and ideally request a psychiatric evaluation. It is not uncommon for individuals to express a strong desire not to have dialysis, particularly if they are relatively asymptomatic, only to change their mind when they become more symptomatic. At this late stage, the basic “will to survive” comes to the fore. An advance directive not to have dialysis should never be held as a reason against a change of mind.

DISAGREEMENT ABOUT A DECISION TO DIALYZE

There will inevitably be differences of opinion about the harms and benefits of dialysis to individuals. Dialysis nurses may disagree with the nephrologist's decision to treat someone. If the dialysis nurses and doctors are functioning well as a team, they should feel able to express these reservations and have the issue adequately discussed. It is demoralizing for staff to feel pressured into giving treatment they believe to be inappropriate.

The nephrologist may remain reluctant to offer dialysis despite the insistence of either the individual or, more often, their family or caregivers, the legal agent, or another doctor (see Fig. 95.9). Dialysis must never be given if it is against the individual's clearly expressed wishes, despite the insistence of others. However, if they insist on treatment against the nephrologist's advice, dialysis usually should be given while a resolution is reached.

Extensive discussions and explanations of the treatment options and prognosis may be needed to gain a better understanding of the reasons behind the differing views. Helpful advice may be obtained from another physician, particularly the individual's family doctor, who will have a broader understanding of their circumstances. It may be appropriate to involve a psychologist, social worker, or religious counselor.

It may be necessary to refer the case to a formal ethics committee, if one exists locally, to clarify the issues of disagreement and enable a resolution. A physician cannot be compelled to offer treatment against his or her professional judgment, but the physician is ethically and legally obliged to attempt to transfer the care of the individual to another physician. Only as a last resort, if no alternative dialysis unit can be found and after adequate notice has been given, should dialysis be withdrawn. The RPA Clinical Practice Guideline Toolkit provides a systematic approach to conflict resolution if there is disagreement regarding the benefits of dialysis71 (Fig. 95.10).

MANAGEMENT OF DISRUPTIVE INDIVIDUALS ON DIALYSIS

Most nephrologists have had experience of treating a small number of individuals who, for one reason or another, will not comply with the discipline required for maintenance dialysis and who become disruptive to the staff and others. This behavior can range from nonadherence with treatment, which harms the individual but is merely inconvenient to the staff, to verbal or even physical aggression toward the staff and others in the unit. The impact of this small number of individuals can be very great.

The strategy for dealing with this situation must be tailored to the individual, particularly their decision-making capacity. Useful suggestions for resolving conflict have been provided by the RPA (Box 95.2). They emphasize the importance of understanding, information, patience, and persistence. However, the bottom line for individuals who have capacity and are aggressive toward staff on the dialysis unit must be that they are taken off dialysis and sent home.

RESUSCITATION AND WITHDRAWAL OF DIALYSIS

Cardiopulmonary Resuscitation

If people are to be fully involved in making decisions about their treatment, two sensitive issues need to be discussed: cardiopulmonary resuscitation (CPR) and the possibility of withdrawal of dialysis. The two are not necessarily linked; individuals may wish to continue with dialysis but express a desire that resuscitation not be attempted should they have a cardiac arrest. The outcome of CPR in patients treated with dialysis is worse than in the general population, the odds ratio for mortality being 1.24 (95% confidence interval, 1.11–1.3; $P < .001$). In 2011 survival after CPR in the United States was 31%, but a greater proportion of people with kidney failure who survived a cardiac arrest were discharged to skilled nursing facilities.79 In Taiwan in 2012, 18.8% of individuals suffering an in-hospital cardiac arrest were discharged from hospital, with a median survival of 6.8 months.80 For a witnessed cardiac arrest in an outpatient dialysis unit, fewer than half survive and are admitted to hospital, and only 26% survive to discharge from hospital.81

A decision not to attempt CPR must be documented in the individual’s medical and nursing records, and all nursing staff must be made aware of it. It is important to be clear what is meant by “cardiac arrest” and for there to be agreement on how the nursing staff should respond to a hypotensive “crash” while on dialysis. These notes may form part of an advance directive, as discussed later.

Withdrawal of Dialysis

It is not possible to predict accurately which individuals will gain prolonged benefit from dialysis; thus, many nephrologists offer dialysis to all individuals with kidney failure who wish to have it. This policy ensures that no one is denied dialysis but has the inevitable consequence that some people are started on dialysis who subsequently have an unacceptable quality of life. The possibility of withdrawing dialysis needs to be addressed if these individuals are not to suffer unreasonably.

Rates of withdrawal vary widely between countries and cultures. Withdrawal rates are much higher in Australia, New Zealand, and

Suggested Steps for Resolving Conflict in the Shared Decision About Starting Dialysis

Questions to be asked:

- Does the patient or legal agent understand the diagnosis, prognosis, and treatment alternatives?
- Does the nephrologist understand the patient’s or legal agent’s reasons for requesting dialysis and their psychosocial, cultural, or spiritual concerns and values?
- Has a psychologist, social worker, or chaplain been consulted for assistance?
- Do other physicians agree with the attending physician’s recommendations?

Consultation with an ethics committee or ethics consultants may be required to clarify issues of disagreement and to negotiate a resolution.

The physician and ethics consultants should document their assessment of the patient’s diagnosis and prognosis, their recommendations, and the reasons behind them in the chart.

If reconciliation is not achieved and the physician, in good conscience, cannot agree to the patient or legal agent’s request, the physician is ethically and legally obliged to attempt to transfer the care of the patient to another physician.

Another physician and/or institution may not be willing to accept the patient under the terms of the family’s request. Physicians and institutions that refuse to accept the patient and their reasons should also be documented in the medical record. In these circumstances, consider consultation with a mediator, extramural ethics committee, or the ESKD network in the region.

Fig. 95.10 Suggested steps for resolving conflict in the shared decision about starting dialysis. ESKD, Endstage kidney disease. (Modified from Shen JI, Mitani AA, Saxena AB, Goldstein BA, Winkelmayer WC. Determinants of peritoneal dialysis technique failure in incident US patients. Perit Dial Int. 2013;33[2]:155–166.)

Suggested Steps for Dealing With Disruptive Individuals

BOX 95.2

Identify and document problem behaviors and discuss them with the individual.

- Seek to understand their perspective.
- Identify their goals for treatment.
- Share control and responsibility for treatment with them.
- Educate them so they can make informed decisions.
- Involve them in the treatment as much as possible.
- Negotiate a behavioral contract with them.
- Consult a psychiatrist, psychologist, or social worker for assistance in clinical management or determination of decision-making capacity.
- Be patient and persistent; try not to be adversarial.
- Allow the individual to vent concerns but do not tolerate verbal abuse or threats to staff or others.
- Contact law enforcement officials if physical abuse is threatened or occurs.
- If satisfactory resolution has not occurred with these strategies, contact the local ESKD Network to discuss the situation and ensure due process.
- As a last resort, consider transferring the individual to another facility or

discharging them.

- Obtain legal advice before proceeding with plans for discharge, and do not discharge without advance notice and a full explanation of future treatment options.

Modified from Butler CR, Mehrotra R, Tonelli MR, Lam DY. The evolving ethics of dialysis in the United States: a principlist bioethics approach. Clin J Am Soc Nephrol. 2016;11(4):704–709.

Canada than in Japan and Italy.82 For the countries where withdrawal is more common, the rates are much higher in the 4 months after the start of dialysis. Individuals who withdraw from dialysis are more likely to be older and female, require assistance for transferring and eating, reside in an institution, and have multimorbidity. Rates of dialysis withdrawal are higher in units where conservative care is always or usually discussed, which suggests that individuals' wishes are not always fully included in these decisions.

People may be reticent to express a wish to withdraw from dialysis. Many see it as their duty as a patient to go along with the treatment recommended by their physician and do not wish to appear ungrateful for the efforts that are being made to keep them alive. Their physician may be the last member of the team to learn about their views, and it is very important that good communication exists within the multidisciplinary team so that any clues that the individual gives are acted upon. Staff should adopt a proactive approach and raise the issue of withdrawal of dialysis with individuals who are not thriving.

People's willingness to discuss planning for the end of their life will be affected by factors such as age, ethnicity, cultural background, and religious beliefs, as well as the circumstances of their daily lives. Qualitative research suggests that, when done sensitively, raising the subject of death does not destroy hope for the future. Early discussion of these issues can lead to a more satisfactory outcome for patients, relatives, and staff when the individual eventually dies. In the United States, formal advance directives play an important part in these discussions, and helpful guidance on how to conduct sensitive interviews has been published.83

In the United Kingdom, dialysis teams may enter individuals on an "at risk" register so they can receive appropriate assessment and care. The dialysis unit should have close links with palliative care specialists so there is a smooth transition from maintenance to palliative dialysis, where priority is given to symptoms and person-centered outcomes. Palliative care for people with kidney disease is discussed further in Chapter 94. Individuals who take a long time to recover after a dialysis treatment may benefit from reducing the number of treatments per week.84

When someone is no longer competent to make a decision, an advance directive can provide a clear legal basis for the decision to stop dialysis. Indeed, some US states (e.g., Missouri and New York) insist that dialysis must be continued in the absence of such clear and convincing written evidence. In other US states and the United Kingdom, the physician is given the task of deciding on the individual's behalf. Helpful advice for dialysis staff and individuals wishing to complete an advance directive is available in the RPA Clinical Practice Guideline Toolkit (see Fig. 95.9).71

Once someone has expressed a wish for dialysis to be withdrawn, or his or her relatives have raised the issue, the first priority must be to identify any reversible factors that may improve their health sufficiently for the decision to be reversed. In particular, any depression must be identified and treated. Once all these factors have been ruled out, the process of withdrawing dialysis should be managed according to some key principles (Box 95.3).

Key Principles Underlying the Process of Withdrawal of Dialysis

BOX 95.3

- The ultimate responsibility for the decision rests with the physician, not the relatives or caregivers.
- The individual's interests and dignity should be protected at all times.
- The process should not be rushed. If there is any doubt about the correctness of the decision, treatment should continue.
- There should be an open discussion among the multidisciplinary team to avoid any damaging disagreements.
- The psychological needs of the health care team should not be overlooked.
- Palliative care must be given in the most appropriate environment (e.g., a hospice or, ideally, the individual's own home).

Withdrawing dialysis should not be seen as an admission of failure but as a final stage in the process of KRT. The opportunity provided by dialysis to complete unfinished emotional and financial business can make the subsequent bereavement period much less traumatic. Managing this terminal phase can be uniquely rewarding, particularly if it allows an individual and their family and caregivers to prepare themselves for the end of their life.

SELF-ASSESSMENT QUESTIONS

1. Which of the following provides the best outcomes in someone with advanced CKD?
A. Deceased donor transplant
B. Preemptive living donor transplant
C. Home hemodialysis
D. Peritoneal dialysis
2. Early initiation of dialysis is associated with:
A. improved survival
B. improved quality of life
C. decreased morbidity
D. higher health care costs
3. Dialysis should be started in someone with advanced CKD when:

A. eGFR is less than 15 mL/min/1.73 m2 (CKD stage 5)
B. Urine output is decreased
C. Clinical and biochemical features of azotemia develop
D. Serum bicarbonate is less than 20 mEq/L
4. A decision to transfer someone to multidisciplinary renal care should be made when:

A.
B.
C.
D.

symptoms of kidney failure begin
the eGFR reaches 10 mL/min/1.73 m2
the individual is in CKD stage 4 with stable eGFR
the trajectory of eGFR indicates a likely need to start kidney replacement therapy within the next 12 months
5. The nephrologist may withhold dialysis from someone with endstage kidney disease:
A. if they have verbally expressed a wish not to have dialysis.
B. if it is against the judgment of the nephrologist.
C. if the individual is disruptive on dialysis.
D. if the dialysis nurses do not wish to continue dialysis.
6. Which of the following is not predictive of a poor prognosis on dialysis?
A. Karnofsky performance status score less than 40
B. Severe chronic malnutrition
C. Age older than 75 years
D. Physician would not be surprised if the individual died within the next 6 months

REFERENCES

1. Bello AK, Levin A, Lunney M, et al. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. BMJ. 2019;367:l5873.
2. Rayner HC, Baharani J, Dasgupta I, et al. Does community-wide chronic kidney disease management improve patient outcomes? Nephrol Dial Transplant. 2014;29(3):644–649.
3. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709–733.
4. Tamura MK, Li S, Chen S-C., et al. Educational programs improve the preparation for dialysis and survival of patients with chronic kidney disease. Kidney Int. 2014;85(3):686–692.
5. Ramspek CL, de Jong Y, Dekker FW, van Diepen M. Towards the best kidney failure prediction tool: a systematic review and selection aid. Nephrol Dial Transplant. 2019;35(9):1527–1538.
6. Ramspek C.L., Evans M., Wanner C., et al. Kidney failure prediction models: a comprehensive external validation study in patients with advanced CKD. J Am Soc Nephrol. Published online March 8, 2021
7. Nelson RG, Grams ME, Ballew SH, et al. Development of risk prediction equations for incident chronic kidney disease. JAMA. 2019;322(21):2104.
8. Padala S, Tighiouart H, Inker LA, et al. Accuracy of a GFR estimating equation over time in people with a wide range of kidney function. Am J Kidney Dis. 2012;60(2):217–224.
9. Thomas N, Nation M, Woolnough L, Gallagher H. Quality improvement at scale: evaluation of the drivers and barriers to adoption and sustainability of an intervention to reduce late referral in chronic kidney disease. BMJ Open Qual. 2020;9(4):e001045.
10. Singhal R, Hux JE, Alibhai SMH, Oliver MJ. Inadequate predialysis care and mortality after initiation of renal replacement therapy. Kidney Int. 2014;86(2):399–406.
11. Rayner H. Understanding Kidney Diseases. Springer; 2021.
12. Manns BJ, Taub K, VanderStraeten C, et al. The impact of education on chronic kidney disease patients’ plans to initiate dialysis with self-care dialysis: a randomized trial. Kidney Int. 2005;68(4):1777–1783.
13. Chen Y-R., Yang Y, Wang S-C., et al. Multidisciplinary care improves clinical outcome and reduces medical costs for pre-end-stage renal disease in Taiwan. Nephrology. 2014;19(11):699–707.
14. Collister D, Pyne L, Cunningham J, et al. Multidisciplinary chronic kidney disease clinic practices: a scoping review. Can J Kidney Health Dis. 2019;6. 2054358119882667.
15. Rasgon S, Schwankovsky L, James-Rogers A, Widrow L, Glick J, Butts E. An intervention for employment maintenance among blue-collar workers with end-stage renal disease. Am J Kidney Dis. 1993;22(3):403–412.
16. Kidney Care UK. https://www.kidneycareuk.org/.
17. My Kidneys, My Choice. http://mychoice.kidney.org.au/#/.
18. Rayner H, Hickey M, Logan I, Mathers N, Rees P, Shah R. Writing outpatient letters to patients. BMJ. 2020;368:m24.
19. Wong G, Howard K, Chapman JR, et al. Comparative survival and economic benefits of deceased donor kidney transplantation and dialysis in people with varying ages and Co-morbidities. PLoS One. 2012;7(1).
20. Unites States Renal Data System Annual Data Report. 2020. https://adr.usrds.org/.
21. Abramowicz D, Hazzan M, Maggiore U, et al. Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP. Nephrol Dial Transplant. 2016;31(5):691–697.
22. Canadian Institute for Health Information. Organ Replacement in Canada: CORR Annual Statistics; 2021. https://www.cihi.ca/en/organ-replacementin-canada-corr-annual-statistics/.
23. Australia and New Zealand Dialysis and Transplant Registry. ANZDATA 43rd Annual Report 2020 (data to 2019). Chapter 2: Prevalence of RRT in

ESKD. https://www.anzdata.org.au/report/anzdata-43rd-annual-report2020-data-to-2019/.

24. Yu MK, O'Hare AM, Batten A, et al. Trends in timing of dialysis initiation within versus outside the Department of Veterans Affairs. Clin J Am Soc Nephrol CJASN. 2015;10(8):1418–1427.
25. Kyte D, Anderson N, Auti R, et al. Development of an electronic patientreported outcome measure (ePROM) system to aid the management of patients with advanced chronic kidney disease. J Patient-Rep Outcomes. 2020;4(1):55.
26. Chan KE, Thadhani RI, Maddux FW. Adherence barriers to chronic dialysis in the United States. J Am Soc Nephrol. 2014;25(11):2642–2648.
27. Salmi IA, Larkina M, Wang M, et al. Missed hemodialysis treatments: international variation, predictors, and outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2018;72(5):634–643.
28. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010;363(7):609–619.
29. Harris A, Cooper BA, Li JJ, et al. Cost-Effectiveness of initiating dialysis early: a randomized controlled trial. Am J Kidney Dis. 2011;57(5):707–715.
30. Murea M, Moossavi S, Garneata L, Kalantar-Zadeh K. Narrative review of incremental hemodialysis. Kidney Int Rep. 2019;5(2):135–148.
31. Htay H, Bello AK, Levin A, et al. Hemodialysis use and practice patterns: an international survey study. Am J Kidney Dis. 2021;77(3). 326–335.e1.
32. Cho Y, Bello AK, Levin A, et al. Peritoneal dialysis use and practice patterns: an international survey study. Am J Kidney Dis Off J Natl Kidney Found. 2021;77(3):315–325.
33. Li PK-T., Rosenberg ME. Foreign perspective on achieving a successful peritoneal dialysis-first program. Kidney360. 2020;1(7):680–684.
34. Australia and New Zealand Dialysis and Transplant Registry. ANZDATA 43 rd Annual Report 2020 (data to 2019). Chapter 5: Peritoneal Dialysis. https://www.anzdata.org.au/report/anzdata-43rd-annual-report-2020-data-to-2019/.
35. Liu FX, Gao X, Inglese G, Chuengsaman P, Pecoits-Filho R, Yu A. A global overview of the impact of peritoneal dialysis first or favored policies: an opinion. Perit Dial Int J Int Soc Perit Dial. 2015;35(4):406–420.
36. Nayak Karopadi A, Mason G, Rettore E, Ronco C. The role of economies of scale in the cost of dialysis across the world: a macroeconomic perspective. Nephrol Dial Transplant. 2014;29(4):885–892.
37. Wong CKH, Chen J, Fung SKS, et al. Lifetime cost-effectiveness analysis of first-line dialysis modalities for patients with end-stage renal disease under peritoneal dialysis first policy. BMC Nephrol. 2020;21(1). 42. 0.
38. Elsayed ME, Morris AD, Li X, Browne LD, Stack AG. Propensity score matched mortality comparisons of peritoneal and in-centre haemodialysis: systematic review and meta-analysis. Nephrol Dial Transplant. 2020;35(12):2172–2182.
39. Sens F, Schott-Pethelaz A-M., Labeeuw M, Colin C, Villar E. Survival advantage of hemodialysis relative to peritoneal dialysis in patients with end-stage renal disease and congestive heart failure. Kidney Int. 2011;80(9):970–977.
40. Molnar AO, Bota SE, Garg AX, et al. Dialysis modality and mortality in heart failure: a retrospective study of incident dialysis patients. Cardiorenal Med. 2020;10(6):452–461.
41. Chuasuwan A, Pooripussarakul S, Thakkinstian A, Ingsathit A, Pattanaprateep O. Comparisons of quality of life between patients underwent peritoneal dialysis and hemodialysis: a systematic review and meta-analysis. Health Qual Life Outcomes. 2020;18(1):191.
42. Shen JI, Mitani AA, Saxena AB, Goldstein BA, Winkelmayer WC. Determinants of peritoneal dialysis technique failure in incident us patients. Perit Dial Int. 2013;33(2):155–166.
43. Chen JHC, Johnson DW, Hawley C, Boudville N, Lim WH. Association between causes of peritoneal dialysis technique failure and all-cause mortality. Sci Rep. 2018;8(1):3980.
44. UK Kidney Association. 22nd Annual Report: data to 31/12/2018. https://renal.org/audit-research/annual-report/22nd-annual-reportdata-31122018/.

45. Dialysis CADTH. Modalities for the treatment of end-stage kidney disease. Health Technol Assess. 2017:292. https://www.cadth.ca/sites/default/files/pdf/OP0526_Dialysis_Modalities_Science_Report.pdf.
46. Chertow GM, Levin NW, Beck GJ, et al. Long-term effects of frequent in–center hemodialysis. J Am Soc Nephrol. 2016;27(6):1830–1836.

47. Castledine CI, Gilg JA, Rogers C, Ben-Shlomo Y, Caskey FJ. Renal centre characteristics and physician practice patterns associated with home dialysis use. Nephrol Dial Transplant. 2013;28(8):2169–2180.
48. European Renal Association. ERA-EDTA Registry Annual Report; 2018:152. https://www.era-online.org/registry/AnnRep2018.pdf/.
49. Canaud B, Barbieri C, Marcelli D, et al. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. Kidney Int. 2015;88(5):1108–1116.
50. Devoe DJ, Wong B, James MT, et al. Patient education and peritoneal dialysis modality selection: a systematic review and meta-analysis. Am J Kidney Dis. 2016;68(3):422–433.
51. Ghaffari A, Kumar V, Guest S. Infrastructure requirements for an urgentstart peritoneal dialysis program. Perit Dial Int. 2013;33(6):611–617.
52. Nessim SJ, Bargman JM, Jassal SV, Oliver MJ, Na Y, Perl J. The impact of transfer from hemodialysis on peritoneal dialysis technique survival. Perit Dial Int. 2015;35(3):297–305.
53. Bittencourt Dias D, Mendes ML, Alves CA, Caramori JT, Ponce D. Peritoneal dialysis as an urgent-start option for incident patients on chronic renal replacement therapy: world experience and review of literature. Blood Purif. 2020;49(6):652–657.
54. Brown EA, Wilkie M. Assisted peritoneal dialysis as an alternative to incenter hemodialysis. Clin J Am Soc Nephrol. 2016;11(9):1522–1524.
55. Farragher JF, Oliver MJ, Jain AK, Flanagan S, Koyle K, Jassal SV. PD assistance and relationship to Co-existing geriatric syndromes in incident peritoneal dialysis therapy patients. Perit Dial Int. 2019;39(4):375–381.
56. Purnell TS, Bae S, Luo X, et al. National trends in the association of race and ethnicity with predialysis nephrology care in the United States from 2005 to 2015. JAMA Netw Open. 2020;3(8):e2015003.
57. Woo K, Lok CE. New Insights into dialysis vascular access: what is the optimal vascular access type and timing of access creation in CKD and dialysis patients? Clin J Am Soc Nephrol. 2016;11(8):1487–1494.
58. Oliver MJ, Quinn RR, Garg AX, Kim SJ, Wald R, Paterson JM. Likelihood of starting dialysis after incident fistula creation. Clin J Am Soc Nephrol. 2012;7(3):466–471.
59. Clarke A, Ravani P, Oliver MJ, et al. Timing of fistula creation and the probability of catheter-free use: a cohort study. Can J Kidney Health Dis. 2019;6. 2054358119843139.
60. Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. Am J Kidney Dis. 2009;53(3):475–491.
61. Moosa MR, Kidd M. The dangers of rationing dialysis treatment: the dilemma facing a developing country. Kidney Int. 2006;70(6):1107–1114.
62. Wennberg J. Tracking Medicine: A Researcher’s Quest to Understand Health Care. Oxford University Press; 2010.
63. Pecoits-Filho R, Okpechi IG, Donner J-A., et al. Capturing and monitoring global differences in untreated and treated end-stage kidney disease, kidney replacement therapy modality, and outcomes. Kidney Int Suppl. 2020;10(1):e3–e9.
64. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709–733.
65. Jassal SV, Karaboyas A, Comment LA, et al. Functional dependence and mortality in the international Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2016;67(2):283–292.
66. Nakai S, Iseki K, Itami N, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2010). Ther Apher Dial. 2012;16(6):483–521.
67. Grubbs V, Tuot DS, Powe NR, O’Donoghue D, Chesla CA. System-level barriers and facilitators for foregoing or withdrawing dialysis: a qualitative

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70.

71.

72.

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74.

75.

76.

77.

78.

79.

80.

81.

82.

83.
84.

study of nephrologists in the United States and England. Am J Kidney Dis. 2017;70(5):602–610.
Butler CR, Mehrotra R, Tonelli MR, Lam DY. The evolving ethics of dialysis in the United States: a principlist bioethics approach. Clin J Am Soc Nephrol. 2016;11(4):704–709.
Anderson RT, Cleek H, Pajouhi AS, et al. Prediction of risk of death for patients starting dialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2019;14(8):1213–1227.
Couchoud C, Labeeuw M, Moranne O, et al. A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. Nephrol Dial Transplant. 2009;24(5):1553–1561.
Renal Physicians Association. Shared Decision Making in the Appropriate Initiation of and Withdrawal from Dialysis; 2010. https://www.renalmd.org/store/viewproduct.aspx?ID=7014408.
Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on supportive care in chronic kidney disease: developing a roadmap to improving quality care. Kidney Int. 2015;88(3):447–459.
Parvez S, Abdel-Kader K, Pankratz VS, Song M-K., Unruh M. Provider knowledge, attitudes, and practices surrounding conservative management for patients with advanced CKD. Clin J Am Soc Nephrol. 2016;11(5):812–820.
Foote C, Kotwal S, Gallagher M, Cass A, Brown M, Jardine M. Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: a systematic review and meta-analysis. Nephrol Carlton Vic. 2016;21(3):241–253.
Caskey F, Gibson A, Burns A, et al. Prepare for Kidney Care: a randomised controlled trial of preparing for responsive management versus preparing for renal dialysis in advanced kidney disease. https://www.journalslibrary.nihr.ac.uk/programmes/hta/155739/#/.
Higginson IJ, Gomes B, Calanzani N, et al. Priorities for treatment, care and information if faced with serious illness: a comparative population-based

survey in seven European countries. Palliat Med. 2014;28(2):101–110.
Verberne WR, Geers ABMT, Jellema WT, Vincent HH, Delden JJM van, Bos WJW. Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. Clin J Am Soc Nephrol. 2016;11(4):633–640.
Aresi G, Rayner HC, Hassan L, et al. Reasons for underreporting of uremic pruritus in people with chronic kidney disease: a qualitative study. J Pain Symptom Manage. 2019;58(4). 578–586.e2.
Saeed F, Adil MM, Malik AA, Schold JD, Holley JL. Outcomes of inhospital cardiopulmonary resuscitation in maintenance dialysis patients. J Am Soc Nephrol. 2015;26(12):3093–3101.
Yang C-H., Chen J-J., Yeh J-K., et al. The incidence and survival after in-hospital cardiopulmonary cerebral resuscitation in end-stage kidney disease patients: a nationwide population-based study. PLoS One. 2020;15(8):e0238029.
Pun PH, Dupre ME, Starks MA, et al. Outcomes for hemodialysis patients given cardiopulmonary resuscitation for cardiac arrest at outpatient dialysis clinics. J Am Soc Nephrol. 2019;30(3):461–470.
Jassal SV, Larkina M, Jager KJ, et al. International variation in dialysis discontinuation in patients with advanced kidney disease. CMAJ. 2020;192(35):E995–E1002.
Davison SN, Torgunrud C. The creation of an advance care planning process for patients with ESRD. Am J Kidney Dis. 2007;49(1):27–36.
Rayner HC, Zepel L, Fuller DS, et al. Recovery time, quality of life, and mortality in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2014;64(1):86–94.

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Vascular Access for Hemodialysis

Jan H.M. Tordoir, Charmaine E. Lok

Functional vascular access is needed for all extracorporeal dialytic therapies and is the lifeline for patients treated with chronic hemodialysis (HD). The three main forms of vascular access are the arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC). Arteriovenous (AV) access refers to either an arteriovenous fistula or graft. The ideal AV access should have a suitable superficial conduit (autogenous or synthetic) that allows for two-needle cannulation that delivers blood flow for effective dialysis (Qb), with intraaccess flows (Qa) usually in the range of 400 to 1500 mL/min. A well-planned vascular access should be functional when needed for dialysis, have good primary patency, have few complications, and align with the patient’s end-stage kidney disease (ESKD) Life-Plan.1 Previously, it had been taught that the ideal access should be an AVF placed peripherally at the wrist. However, because upper arm and lower limb access sites or CVCs are increasingly used due to the patient’s limiting anatomy or circumstances (e.g., frail elderly with multiple comorbidities, exhaustion of access sites, future transplant), a more comprehensive approach to vascular access choice was developed that considers the patient’s ESKD Life-Plan.

ESKD LIFE-PLAN

The ESKD Life-Plan is an individualized map of kidney replacement modalities (hemodialysis [HD], peritoneal dialysis, transplantation) required during the patient’s life with chronic kidney disease (CKD). All patients with progressive CKD and/or with estimated glomerular filtration rate (eGFR) of 15 to 20 mL/min/1.73 m2 or already on kidney replacement therapy should have a Life-Plan. The Life-Plan is regularly reviewed and revised after considering the patient’s unique medical and life circumstances and their informed preferences. The appropriate dialysis access is then chosen to align with and support the patient’s ESKD Life-Plan; if done correctly, each patient would then have an individualized PLAN: patient life-plan and their access needs.1 Within “access needs,” there are three main components: (1) insertion/creation plan, (2) contingency plan (a plan to manage complications), and (3) succession plan. Concurrently, there must always be a vessel preservation plan to ensure viability for future access as required. Therefore, each vascular access must include four plans: vessel preservation plan, insertion/creation plan, contingency plan, and succession plan.1

Vascular access should be created in a timely manner by a surgeon or interventionalist experienced in vascular access creation to avoid unnecessary CVC use and its associated complications.1 However, vascular access complications are almost inevitable and may require management by endovascular procedures or surgical revision. A multidisciplinary approach to access creation and maintenance (involving nephrologists, interventional radiologists, access surgeons, and dialysis nurses) helps optimize HD access–related outcomes and minimize costs.

EVALUATION OF THE PATIENT FOR VASCULAR ACCESS

CKD patients should be considered for vascular access if they have progressive decline in kidney function and referred when eGFR is 15 to 20 mL/min/1.73 m2. Earlier referral should occur in patients with unstable and/or rapid rates of GFR decline (e.g., >10 mL/min/1.73 m2/yr).1

Patients with a failing kidney transplant or who are not responding to peritoneal dialysis should be assessed for vascular access in a timely manner to avoid CVC use when transitioning to HD. If an AV access is deemed appropriate based on the ESKD Life-Plan, the type and site of the vascular access will be based on the following:

✓•✓ Physical examination, with careful inspection and palpation of arterial pulses and venous vasculature. Particular attention is paid to the venous filling capacity, with use of a blood pressure cuff and variable pressures, and to the presence of venous collaterals and swelling. The nondominant arm is not necessarily the preferred side, and the decision should be based on the quality of the vessels and future access needs.

✓•✓ Vascular mapping is usually done with Duplex ultrasound and provides information about the venous vasculature (particularly in obese patients and in the upper arm) and the diameter of the brachial, radial, and ulnar arteries; detects vascular calcifications; and reveals the blood flow volume in the brachial artery. The resistance index (a measure of arterial compliance) can be calculated from the differences between the high-resistance triphasic Doppler signal with clenched fist and the low-resistance biphasic waveform after the fist is released. A preoperative resistance index of 0.7 or higher in the feeding artery indicates insufficient arterial compliance (often associated with arterial calcification), warning of lower success with AVF creation. Guidelines support vessel mapping in most patients (Table 96.1).

✓•✓ Additional angiography and/or phlebography is needed only in very difficult cases or in patients with previous ipsilateral CVCs to rule out central vein stenosis or obstruction; the use of radiocontrast media should be minimized in patients with residual kidney function.

Preservation of vessels is crucial for the success of vascular access. Patients should be instructed to protect their veins, restricting blood sampling and intravenous cannulas to the dorsum of the hand whenever possible. Physicians that may access radial arteries for interventional procedures (e.g., cardiac investigations) should be alerted to consider alternate access for these procedures.

VASCULAR ACCESS TYPES

Autogenous Access

Distal Forearm Fistulas

Radiocephalic arteriovenous fistula. A well-functioning distal radiocephalic AVF in the nondominant arm is the ideal permanent

TABLE 96.1
Risk Factors for Which Vessel Mapping May Be Beneficial

Clinical Problem	Risk Factors
Fistula failure	Elderly age; female sex; comorbidities (e.g., peripheral vascular disease; coronary artery disease)
Peripheral vessel damage	PICC insertion; iatrogenic vein damage; radial artery harvesting for coronary artery bypass grafting
Central venous stenosis	Multiple CVC; prolonged CVC duration; cardiac implantable electronic device; PICC; surgery or trauma to neck, chest or upper extremity
Limitations to physical examination	Severe obesity; suboptimal conditions (dehydration or vasoconstriction); poor skin integrity

CVC, Central venous catheter; PICC, peripheral inserted central catheter.

access for HD. This usually gives adequate blood flow and a long length of superficial vein for needling. It also leaves proximal sites for further procedures in the event of failure. Although this distal radiocephalic AVF is the aim for incident patients, its creation and success may be compromised if the cephalic and antecubital fossa veins are damaged because of thrombophlebitis and/or thrombosis from previous intravenous cannulas or venipunctures.

A radiocephalic AVF is usually created at the wrist but can be created more proximally in the forearm if distal vessels are inadequate (Fig. 96.1). On occasion, three or four radiocephalic AVFs can be created at progressively more proximal sites in the forearm before a brachiocephalic AVF is created. The radiocephalic AVF at the wrist was initially described as a side-to-side anastomosis, but an end-to-side configuration is preferred to reduce the risk of venous hypertension in the radial aspect of the hand.

The patency of radiocephalic fistulas varies from center to center and from surgeon to surgeon. Reported primary failure rates vary from 5% to 60%, and 1-year patency rates vary from 52% to 71% (Table 96.2),[2-8] primarily due to early thrombosis and AVF nonmaturation. Risk factors for early failure include diminished radial artery or cephalic vein size or quality, female sex, older age, greater and complex comorbidity, and center effect.[9,10] Patients deemed at high risk for distal radiocephalic fistula primary failure should be considered for a proximal elbow or upper arm AVF or forearm graft, depending on the patient’s ESKD Life-Plan.

Proximal Forearm and Upper Arm Fistulas

Although a radiocephalic AVF is preferable, the first created vascular access is increasingly an upper arm AVF with use of an autogenous superficially located arm vein,[11] especially in patients with comorbidities such as diabetes mellitus, coronary heart disease, and peripheral vascular disease.[12,13]

The upper limb is preferred to the lower limb for vascular access because of the ease of cannulation, comfort for the patient, and considerably lower incidence of complications. Similarly, autogenous conduits are preferable to the use of prosthetic grafts because of better patency and lower risk of infection.

Forearm cephalic and basilic vein transposition. Vein transposition or elevation increases the possibilities for creating a forearm fistula. The cephalic vein is preferred, but if it is unsuitable, the more deeply located basilic vein can be transposed from the ulnar to the

Standard Radiocephalic
AV Fistula at the Wrist
Cephalic vein

Radial artery

Fig. 96.1 Standard Radiocephalic Arteriovenous (AV) Fistula at the Wrist. Anastomosis of end of vein to side of artery.

radial side along a straight subcutaneous course from the elbow to the radial artery. Alternatively, an anastomosis from the basilic vein to the ulnar artery can be performed with additional volar transposition to facilitate needling for dialysis.

Different surgical techniques (with or without vein transposition) have been advocated according to the forearm artery and vein location, with the possibility of achieving 91% fistula maturation[14]; for example, in one study 15% of participants had a straightforward AVF, 33% required vein transposition from dorsal to volar, and 52% required superficial forearm vein transposition before arterial anastomosis. Primary patency rates were 84% at 1 year and 69% at 2 years.

Cannulation of radiocephalic and/or brachiocephalic AVFs may be difficult, particularly in obese patients. Preplanned vein elevation or transposition techniques in such patients can be effective and should be considered; the primary failure rate has been reported to be 15%, with a 1-year patency rate of 84%. Alternatively, surgical lipectomy or liposuction can be performed to facilitate cannulation of deeply located AVF.[15]

Elbow and upper arm cephalic vein arteriovenous fistula. The brachiocephalic and antecubital configurations can be used for AV anastomoses in the elbow region. If possible, the anastomosis can be created between the cephalic, cubital, or perforating vein and the brachial artery, typically 2 cm distal to the elbow, which optimizes opportunities for cannulation along the cephalic vein in the upper arm (Fig. 96.2). The outcome of a brachiocephalic AVF is usually good, with high primary function and good long-term patency; studies show a 10% early failure rate caused by nonmaturation and an 80% 1-year patency rate.[16,17] Twoyear primary, assisted primary, and cumulative patency rates were 40%, 59%, and 67%, respectively. Primary patency means that the access is functioning without any intervention; assisted primary patency means that the access is functioning but required a preemptive intervention for flow decline. Cumulative or secondary patency refers to accesses that are functioning after intervention for thrombosis. The term cumulative patency is preferred to reduce confusion and improve standardization for communication about vascular access.[1,18] The early failure and 1-year patency rates of brachiocephalic AVFs are shown in Table 96.3[16,17,19-21]

Newer endovascular options for creation of antecubital AVF, typically between the perforating vein and ulnar or radial arteries, have recently been described. Early data are promising, demonstrating both technical success and 6-month patencies each greater than 88%.[22-24]

Upper arm basilic vein arteriovenous fistula. The upper arm basilic vein is usually inaccessible or painful for dialysis cannulation because of its medial and deep position. Therefore, the basilic vein needs to be superficialized and transposed to an anterolateral position. In the

TABLE 96.2

Early Failure and 1-Year Patency Rates of Radiocephalic Arteriovenous Fistulas

Study	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Ravani et al., 2002	197	5	71
Rooijens et al., 2005	86	41	52
Korten et al., 2007	148	11	57
Biuckians et al., 2008	80	37	63
Al-Jaishi et al., 2014	890	28	55
Goh et al., 2016	204	12	66
Wilmink et al., 2016	689	26	70

Options for the Creation of Elbow AV Fistulas

Median
cubital
vein

Accessory
cephalic
vein

Basilic
vein
Perforating
vein

Cephalic

vein

B

Brachial
artery

C

A

Fig. 96.2 Options for the Creation of Elbow Arteriovenous (AV) Fistulas. (A) Anatomy of arterial and venous vessels in the elbow. (B) Brachio-perforating vein AV fistula with ligation of proximal cubital vein. (C) Brachiocephalic AV fistula.

TABLE 96.3

Early Failure and 1-Year Patency Rates of Brachiocephalic Arteriovenous Fistulas

Study	Number of Fistulas	Early Failure (%)	1-Year Patency (%)
Zeebregts et al., 2005	100	11	79
Lok et al., 2005	186	9	78
Woo et al., 2007	71	12	66
Koksoy et al., 2009	50	10	87
Ayez et al., 2012	87	8	83

two-step approach to creating a brachiobasilic AVF, the anastomosis is first constructed, followed by a second operation, usually 6 weeks later, whereby the arterialized vein is mobilized into a subcutaneous position to enable needling (Fig. 96.3). Alternatively, in the one-step approach to creating the brachiobasilic AVF, the vein is elevated and transposed into position at the time of anastomosis creation. Primary failure rates are 2% to 26%, with 1-year cumulative patencies varying from 69% to 86%.25

Brachiobasilic AVF have several advantages over forearm or upper arm AV grafts, such as less infection and thrombosis. A meta-analysis found that brachiobasilic AVFs have superior primary and cumulative patency compared with AV grafts26 and should be preferentially considered in difficult access cases and when suitable according to the PLAN.1

Lower limb vascular access. The main indications for lower limb vascular access are bilateral central venous or caval obstruction,

Transposed Brachiobasilic AV Fistula

Basilic vein

A

Median cubital
vein
Basilic vein

B

Brachial artery

Fig. 96.3 Transposed Brachiobasilic Arteriovenous (AV) Fistula. (A) Dissection of the basilic vein. (B) Anterolateral transposition and brachial artery anastomosis.

which endangers the outflow of upper limb AVFs. Saphenous and superficial femoral vein transposition is a primary option for thigh AVFs, although this carries a relatively high risk for distal ischemia. If clinical evaluation indicates incipient ischemia, primary flow reduction by tapering of the anastomosis is indicated to prevent complications. Synthetic AV graft implantation in the thigh bears a high risk for infection and septicemia.27

NONAUTOGENOUS SYNTHETIC VASCULAR ACCESS

Arteriovenous Grafts

An AV access (referring to AVF or AV graft) is preferable to a CVC, whenever feasible. When autogenous AVF creation is impossible, an AV graft should be considered. Xenografts such as the ovine (sheep) graft are an alternative access conduit with acceptable patency and low infection rates. However, the most frequently used synthetic grafts are made of expanded polytetrafluoroethylene (ePTFE) and, less commonly, polyurethane. These prosthetic grafts can be implanted in a wide variety of locations and configurations in the upper and lower limbs (Fig. 96.4). At present, early cannulation of AV grafts (within 24 hours of surgery) is feasible because of newer graft compositions. In randomized controlled trials (RCTs), they have been shown to be catheter sparing and have equivalent patencies to standard AV grafts.28 29

The primary patency rates of AV grafts vary from 60% to 80% at 1 year and from 30% to 40% at 2 years of follow-up. Secondary patency ranges from 70% to 90% and from 50% to 70% at 1 and 2 years, respectively.30-33 The new KDOQI Vascular Access Guidelines 2019 have helpful algorithms for the appropriate use of early cannulation and standard AV grafts.1

CENTRAL VENOUS CATHETER ACCESS

CVCs are widely used to initiate HD despite recommendations for AV access use.1 34 35 Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)36 indicate that 15% of HD patients in the United States are dialyzed with catheters; in other countries, CVC use is even more common (Canada, 45%; Belgium, 38%; United Kingdom, 16%). Two types of CVC are used: nontunneled CVC for short-term use, and tunneled cuffed CVC, which can be used for several weeks to months or as permanent access in patients without AV access options. Nontunneled CVCs are associated with higher infectious complications and should be limited to less than 2 weeks duration of use. Box 96.1 provides indications for short- and long-term use of CVCs. Although the physical

CVC characteristics (i.e., design and geometry) theoretically influence the performance (blood flow rate, recirculation, and resistance) and affect the overall efficiency of the HD therapy and morbidity risk

Nonautogenous Prosthetic Graft Vascular Access

Brachial
vein

Brachial
artery

Cephalic
vein

Axillary
artery
PTFE

Axillary
vein

PTFE
Axillary
artery

Radial
artery

PTFE

PTFE

Ulnar
artery

Fig. 96.4 Nonautogenous Prosthetic Graft (Polytetrafluoroethylene [PTFE]) Vascular Access. Straight and loop configuration in upper limb.

Indications for Short and LongTerm Use of Central Venous Catheters

BOX 96.1

- Temporary switch from another modality (PD-related complications; transplant acute rejection)
- Awaiting live-donor kidney transplant with established surgical date
- Short-term use of nontunneled CVC awaiting placement of tunneled CVC
- Temporary use if established AV access is temporarily unusable (e.g., maturing fistula); AV access requiring cannulation-free time due to complication (e.g., significant infiltration injury)
- Limited life expectancy (<6 months)
- Clinical conditions that worsen with AV access (heart failure with ejection fraction <15%; nontreatable skin lesions where cannulation increases infection or rupture risk)
- All other AV access options have been exhausted
- Patient choice after proper informed consent

AV, Arteriovenous; CVC, central venous catheter; PD, peritoneal dialysis.

(infection, thrombosis), no CVC type has been proven consistently superior to another.1 37

Nontunneled Catheters

Single- or double-lumen CVCs are usually made of polymers (polyethylene, polyurethane), which enable easy insertion. The length of the CVC must be appropriately chosen to consider the anatomic insertion site. The femoral route requires catheters of 27 to 35 cm in length for the distal tip to be located in the inferior vena cava. The internal jugular vein route needs shorter catheters of 19 to 25 cm in length, with tip location at the mid–right atrium. The ideal CVC diameter is 12 to 14 Fr to allow sufficient blood flow to achieve adequate dialysis.

Tunneled Catheters

Tunneled CVCs have two lumens, each having a length of 40 cm, 10 cm of which is tunneled under the skin; the cannulae are made of synthetic polymer with a large internal lumen and, typically, a Dacron cuff to ensure subcutaneous anchoring. The CVC characteristics rely on the type of polymer, design, and geometry (e.g., double-lumen CVC, dual CVC, split CVC). The use of tunneled CVCs is associated with reduced morbidity and consistently better performance compared with noncuffed, nontunneled CVC.38

Both tunneled and nontunneled CVC are inserted percutaneously by the Seldinger technique with ultrasound guidance and fluoroscopy. The internal jugular vein and femoral vein routes are preferred because of ease of insertion and lower risk of some complications, such as central vein stenosis, compared with subclavian vein insertion (Fig. 96.5). Radiologic placement of tunneled translumbar HD catheters (TLDC) is a safe and technically successful procedure in those with exhausted conventional CVC access. Compared with traditional CVCs, TLDCs have higher complication rates, exchanges, and removals (>30% of patients), usually due to poor blood flow and infection. These catheters function well in the short term but are typically considered a last resort.

VASCULAR ACCESS COMPLICATIONS

Primary Arteriovenous Fistula Problem: Nonmaturation

The AVF needs time to mature, allowing the vein to enlarge and toughen so that it can be needled for dialysis. Depending on the practice pattern and dialysis prescription, typically 6 to 12 weeks for maturation is required. AVF may be successfully cannulated by 2 weeks but can take as long as 9 months.35 39 Nonmaturation rates vary from 7% to 60%. The essential components of a successful AVF are a sufficient vein diameter of 4 to 5 mm for needling and Qa greater than 500 to 600 mL/min, for a typical dialysis prescription with a Qb of 300 to 400 mL/min, in order to prevent recirculation and achieve dialysis adequacy in a 4-hour time frame. Although these criteria have been used in research studies, clinical practice has informed that usability of AVF for cannulation is best judged by an experienced dialysis nurse with or without ultrasound vein diameter and access flow measurements.

The statement of successful cannulators, such as “It’s the feel of the integrity and ‘toughness’ of the fistula, not just the size that determines

Tunneled Cuffed Double-Lumen Central
Venous Catheter Inserted in the
Right Internal Jugular Vein

Fig. 96.5 Tunneled cuffed double-lumen central venous catheter inserted in the right internal jugular vein.

successful usability," highlights that objective measurement should support, and not replace, cannulation experience.

Fistulas that fail immediately do so as a consequence of poor selection of vessels, poor surgical technique, or postoperative hemodynamic instability. New AVFs should be assessed by the operator within 2 weeks of creation with 4 to 6 weeks follow-up by the team if there is suspected nonmaturation. Almost all early, non–process-related AVF failures involve vascular abnormalities. Therefore, duplex ultrasound investigation can detect poor flow, stenosis, and accessory branches, guiding the interventional radiologist and surgeon to the appropriate treatment. More than half of the stenoses detected are in the perianastomotic area. Arterial inflow stenoses of more than 50% reduction in vessel diameter are seen in less than 10% of nonmaturing fistulas, but if identified, they should undergo angioplasty. Anastomotic and swing segment (in which the vein has been mobilized and swung over to the artery) stenosis may be treated percutaneously or surgically, depending on local expertise.

Percutaneous intervention includes angioplasty (± drug coated balloons) of stenotic lesions, coil embolization, or ligation of accessory or collateral veins. In patients with residual kidney function (either predialysis or on HD), the risk of further loss of kidney function as a result of radiocontrast load can be mitigated by use of CO_2 angiography or by performance of ultrasound-guided angioplasty of the nonmatured fistula.[1,40] Percutaneous transluminal balloon angioplasty (PTA) is further discussed in Chapter 97

When a surgical approach is selected, nonmatured AVFs should be reconstructed, usually under regional or local anesthesia. The anastomosis is exposed and ligated; the vein then can be divided, mobilized proximally, and reanastomosed to the proximal radial artery.

Limiting or preventing early failure is difficult, as the physiologic, functional, pathologic, and process of care factors that contribute to AVF failure or nonmaturation remain elusive.[9,41,42] An RCT that compared brachial plexus block (BPB) with local anesthesia for AVF creation showed superiority of BPB, with significant improvement in the primary outcome of patency at 3 months.

Consideration may be given to using BPB for AVF creation.[43] Hand and finger exercise may improve maturation and can be considered 2 weeks post AVF creation.[1] The use of far infrared therapy appears promising, but its availability and generalizability is limited.[1,44,45] To date, there are no consistent medical therapies found to improve maturation.

Primary Arteriovenous Graft Problem: Reduced Patency

Numerous studies have evaluated the influence of AV graft material and design on AV graft patency. Theoretically, modulating the distensibility (e.g., polyurethane grafts) or geometry of the arterial inlet or venous outlet of the AV graft may have a beneficial effect on intimal hyperplasia. However, clinical studies of polyurethane grafts and those using tapered (at the arterial side of the graft) AV grafts did not improve patency rates, nor did cuff implantation at the venous anastomosis. Cuff-shaped prosthesis (e.g., Venaflo) may be beneficial.[46,47]

Because ePTFE AVGs are prone to thrombosis, infection, and intimal hyperplasia at the venous anastomosis, tissue-engineered vascular grafts have been developed as a potential solution to these limitations. Preliminary results of human studies suggest these biologic grafts are safe and functional; further phase III studies are underway.48 Both Aggrenox and fish oil have been found to improve primary patency of AV grafts.49 50 Fish oil has also been shown to reduce the rate of thrombosis and interventions. Given its low cost and safety, fish oil can be considered in patients who need AV graft access.1

General Arteriovenous Access Problem: Stenosis and Thrombosis

Vessel stenosis is common in both autogenous AVFs and prosthetic AVGs. Intimal hyperplasia, with smooth muscle cell migration, proliferation, and matrix deposition, is the major cause of stenosis formation and thrombosis. The cause of the intimal hyperplasia is multifactorial, with uncertain contributing factors. They range from the uremic environment, the impact of surgery, the high wall shear stress caused by the access flow itself, and the downstream effect of the denuded endothelial cell layer, resulting in platelet adhesion and initiation of a cascade of proteins that stimulate the smooth muscle cells to proliferate and to migrate.51 52 Progressive stenosis leads to access flow deterioration and subsequently thrombotic occlusion. Prophylactic repair of access stenoses may prevent thrombosis and prolong access patency.

Autogenous Arteriovenous Fistula Stenosis or Thrombosis

AVF stenosis should be suspected if the vessel diameter is reduced by more than 50% and is accompanied by clinical indicators such as difficulties with cannulation or prolonged bleeding time after decannulation (indicating high intraaccess pressure caused by outflow vein stenosis). Box 96.2 discusses clinical indicators. In AVFs, 55% to 75% of the stenoses are close to the AV anastomosis, 25% in the venous outflow tract, and 15% in the arterial inflow. In brachiocephalic and brachiobasilic AVFs, stenosis is typically located (other than the anastomosis) at the junction of the cephalic with the subclavian vein (cephalic arch) and the basilic with the axillary vein (junctional stenosis). Initial evaluation of suspected access stenosis is by ultrasound; angiography is used subsequently when intervention is planned. Endovascular treatment by PTA is the first option for arterial inflow and venous outflow stenoses and junctional stenoses, with the option of stent or stent-graft placement.53 These techniques are discussed further in Chapter 97. Use of stents or stent grafts should avoid cannulation segments.1 Some stenoses may not be sufficiently dilated by conventional balloons (12–16 atm), and in these accesses, cutting balloons or ultra-high-pressure balloons (up to 36 atm) may be applied. Drug-eluting balloons have shown to be beneficial in preventing restenosis; however, data are conflicting.54 55 Surgical revision may be appropriate, depending on the nature and location of the lesion; for

Clinical Indicators of Vascular Access Stenosis

BOX 96.2

Physical Examination
- Ipsilateral extremity edema
- Alterations in pulse, with a weak or resistant pulse, difficult to compress in the area of the stenosis
- Abnormal thrill (weak and/or discontinuous) with only a systolic component in the region of the stenosis
- Abnormal bruit (high pitched with a systolic component in the area of stenosis)
- Failure of the fistula to collapse when the arm is elevated (outflow stenosis) and lack of pulse augmentation (inflow stenosis)
- Excessive collapse of the venous segment upon arm elevation

Dialysis
- New difficulty with cannulation when previously not a problem
- Aspiration of clots
- Inability to achieve the target dialysis blood flow without any other cause
- Prolonged bleeding beyond usual for that patient from the needle puncture sites for three consecutive dialysis sessions
- Unexplained decrease in the delivered dialysis dose (Kt/V) on a constant dialysis prescription without prolongation of dialysis duration, and other variables excluded

example, a more proximal reanastomosis for swing segment stenosis is indicated after failed PTA of a radiocephalic AVF.

Fistula thrombosis should be treated as soon as possible because timely declotting allows immediate use of the AVF without the need for a CVC. Fistula intervention is ideal within 6 hours, and success is greatly reduced after 72 hours (grafts should be intervened on within 72 hours but can be salvaged up to 5–7 days). The duration and site of AV access thrombosis, as well as the type of AV access, are important determinants of treatment outcome. Thrombi become progressively fixed to the vein wall, which makes surgical removal more difficult. When the clot is localized at the anastomosis in radiocephalic and brachiocephalic AVFs, the outflow vein may remain patent because of continuing flow in its tributaries, making it possible to create a new proximal anastomosis.[56]

Thrombolysis can be performed mechanically or pharmacomechanically. Whereas the immediate success rate is higher in AVGs than in AVFs (99% vs. 93% in forearm AVFs), the primary patency rate of the forearm AVF at 1 year is much higher (49% vs. 14%). One-year secondary patency rates are 80% in forearm and 50% in upper arm AVFs.[57]

Nonautogenous Arteriovenous Graft Stenosis or Thrombosis

The most common cause of AV graft dysfunction and thrombosis is venous anastomotic stenosis. Because AV grafts are typically created in patients with exhausted peripheral veins, vein-saving procedures such as PTA or patch angioplasty are preferred to AV graft extensions to more central venous segments. When a stent or a patch fails, AV graft extension is still possible. Clinical monitoring of an AV graft is recommended (see Box 96.2) and can be supplemented with surveillance, such as access flow (Qa) measurement[1]; ultrasound detection of stenoses with preemptive endovascular treatment may diminish AV graft thrombosis but does not extend AV graft patency.

Intragraft (or midgraft) stenoses are found in the cannulation segment of AV grafts. They result from excessive ingrowth of fibrous tissue through puncture holes. These stenoses can be treated by PTA, AV graft curettage, or segmental AV graft replacement. When only a part

of the cannulation segment is replaced, the access can be used immediately for HD without the need for a CVC. When restenosis occurs in a nonexchanged part of the AV graft, this can be replaced after healing of the new segment.

AV graft thrombosis can be treated with various percutaneous techniques and tools, including combinations of thromboaspiration, thrombolytic agents such as urokinase, tissue plasminogen activator (tPA), and mechanical thrombectomy. An initial success rate of 73% and primary patency rates of 32% and 26% at 1 and 3 months, respectively, are reported.57 It is ideal to perform thrombolysis as soon as possible to avoid CVC use and as an outpatient procedure for best clinical outcomes and cost containment. Postprocedural angiography to detect and correct inflow, intraaccess, or venous outflow stenosis is mandatory.

When endovascular treatment fails or is not possible, surgical thrombectomy may be performed with a Fogarty catheter after venotomy, with correction of the underlying obstruction. On-table angiography should be performed after completion of thrombectomy of both the arterial and venous limbs of the graft.

Central Venous Obstruction

In the majority of patients, central vein obstruction is a result of previously inserted CVCs or pacemaker wires. In 40% of patients with subclavian vein catheters and in at least 20% with jugular vein catheters, central venous stenosis or occlusion will develop. Chronic swelling of the access arm is the most obvious sign, usually with prominent superficial collateral veins around the shoulder. The indications for intervention by PTA and stent placement are severe and disabling arm swelling, pain, finger ulceration, and inadequate HD. Contrast angiography of the access and complete venous outflow tract must be performed; ultrasound is not suitable for examining the central veins because of their retroclavicular location.

The benefits and risks of AVF, AVG, and CVCs are listed in Table 96.4

Interventions to Manage Patency Complications

Endovascular intervention. Endovascular intervention is the first treatment option for central venous obstruction. PTA alone results in patency rates of only 10% or less at 1 year, and numerous restenoses may develop. Primary or additional stent implantation is associated with a better outcome, with 1-year patency rates up to 56% or higher.58 Reinterventions are usually required to maintain patency and achieve long-term clinical success.

Stent placement should avoid overlapping the ostium of the internal jugular vein because this vein is essential for future placement of CVCs. Similarly, a stent placed in the innominate vein should not overlap the ostium of the contralateral vein; otherwise, contralateral stenosis may occur and preclude future creation of a contralateral AV access.

A percutaneous approach to bypass central venous obstruction with the “inside out” technique using the Surfacer System Inside-Out Access Catheter System is a novel and daring method for gaining central venous access.59

Surgical intervention. When endovascular treatment of central venous obstruction fails, surgical revision with bypass grafting is indicated. Surgical bypass to the ipsilateral jugular vein or contralateral subclavian or jugular vein is the first option in these patients. Alternative surgical approaches for upper limb vascular accesses with compromised venous outflow are axillary vein to femoral, saphenous, or popliteal vein and right atrial bypasses.60 In case of bilateral obstruction of the mediastinal veins, including the superior vena cava, it will not be possible to sustain upper limb access, and lower limb access will be required.

TABLE 96.4

General Benefits and Risks of AV Fistula, AV Graft, and CVC

AV Fistula	AV Graft	CVC
high maturation failure	low maturation failure	no maturation needed
difficult cannulation	easy cannulation	easy connection to dialysis machine
low-moderate infection rate	low-moderate infection rate	moderate-high infection rate
low-moderate revision rate	moderate-high revision rate	high revision rate
good long-term patency if maturation with few facilitative interventions	moderate long-term patency	short long-term patency
low thrombosis rate	moderate thrombosis rate	high thrombosis rate

AV, Arteriovenous; CVC, central venous catheter.

Ultimately, ligation of the upper limb access can be considered, which will relieve local symptoms but sacrifices a valuable dialysis access.

Pharmacologic approaches for access patency. Based on clinical trials, there is insufficient evidence to determine whether medical treatments such as ticlopidine, aspirin, fish oil, clopidogrel, dipyridamole, warfarin, and sulfinpyrazone improve the patency of AV accesses compared with placebo treatment; the quality of the evidence is low because of short follow-up periods, the small number of studies for each comparison, heterogeneity among trials, and incomplete reporting.[61] Warfarin may reduce AVG thrombosis but increases the risk for hemorrhage and vascular calcification.[62] A large trial showed that dipyridamole plus aspirin had a statistically significant but modest clinical effect in prolonging the duration of primary unassisted patency of newly created AVGs.[49] Fish oil reduced AVG thrombosis and also improved unassisted patency of newly created AVG in RCTs.[63,64] In a large randomized study, clopidogrel improved fistula thrombosis but not functional maturation and usability.[65]

Clinical trials in patients undergoing AVF and AVG creation, who had perivascular biodegradable collagen wraps with sirolimus placed at the anastomosis, demonstrated safety and feasibility of the sirolimus wrap. A phase III RCT is ongoing to assess the safety, efficacy, and patency outcomes of a perivascular sirolimus-eluting implant placed at the AVF anastomosis in HD patients receiving new AVFs.[66]

Vascular Access–Induced Ischemia

Vascular access–induced upper limb ischemia is a serious complication that without prompt intervention may lead to amputation. The incidence of symptomatic ischemia varies from 2% to 8% of the HD population.67 Elderly patients, diabetics, patients with prior ipsilateral AV access, and those with peripheral or coronary arterial occlusive disease are most at risk for ischemia. Access-induced ischemia occurs more often with proximally located AVFs and high flow rates; such AVFs can induce a steal phenomenon with lowering of distal perfusion pressures, and when collateral circulation is inadequate, symptoms may occur. Pain during HD is a characteristic early symptom. A grade 1 to 4 classification for access-induced ischemia can be used to outline the severity of the disease; this ranges from minor symptoms to finger necrosis.68

- Grade 1: Pale and blue or cold hand without pain
- Grade 2: Pain during exercise or HD
- Grade 3: Ischemic pain at rest
- Grade 4: Ulceration, necrosis, and gangrene

For grades 1 and 2, conservative treatment of ischemia is advocated. With grades 3 and 4, interventional treatment is mandatory.

Diagnosis of Ischemia

Physical examination, including observation and palpation of peripheral vessels, may be inadequate and misleading for the diagnosis of symptomatic ischemia. Additional noninvasive testing with measurement of digital pressures and calculation of the digit-brachial index, transcutaneous oximetry (TcPo2), ultrasound of forearm arteries, and access blood flow measurement are important steps in the diagnosis and decision-making process.69 Finally, contrast angiography with visualization of the upper extremity arterial tree from the proximal subclavian artery to the distal palmar arches with and without AVF compression to enhance distal flow is obligatory to outline the strategy for treatment and determine whether endovascular or surgical options are preferred.

Endovascular and Surgical Management of Ischemia

The treatment strategy depends on the cause of the ischemia. Inflow arterial obstruction and distal arterial lesions are recanalized with small-caliber balloons or stent placement70; high-flow AVFs are suitable for flow-reducing procedures such as access banding and arterial inflow reduction by an interposition graft to a smaller forearm artery (revision using distal inflow [RUDI]) (Fig. 96.6).71 72 Steal in itself may be corrected by ligation of the artery distal to the AV anastomosis or revascularization procedures such as the distal revascularization–interval ligation (DRIL) procedure (Fig. 96.7) or other procedures.73 Intraoperative digital pressure measurement (or TcPo2) is mandatory to guarantee an adequate surgical intervention with acceptable outcome. A digital-brachial pressure index above 0.60 or TcPo2 above 40 mm Hg is indicative of sufficient distal hand perfusion. In some patients, AVF ligation and transition to chronic CVC access or a change of dialysis modality to peritoneal dialysis may be the only solution.

Catheter-Related Infection

Catheter-related bloodstream infections are a significant cause of morbidity and mortality in HD patients. CVC use is associated with a higher risk of mortality compared with AV access.1 Switching from CVCs to an AV access is associated with a lower risk of mortality compared with continuing CVC use.74 CVC-related infections include bacteremia, tunnel infections and exit site infections. Any of these types of infection can progress to metastatic complications of osteomyelitis, septic arthritis, epidural abscess, and endocarditis. Nontunneled CVC have a higher rate of infection compared with tunneled CVC.38 Each facility should track and monitor CVC-related infection rates, with a goal bacteremia rate of less than 1.5 per 1000 CVC days.1

Prevention of Catheter-Related Infection

The most important measure to prevent CVC infection is meticulous handling of the CVC at all times. The CVC should be inserted with use of maximal infection control precautions, per local facility guidelines. The dialysis nurses, technicians, or patient/caregiver (if home dialysis) needs to access the CVC under strict aseptic or sterile conditions; it is of the utmost importance that CVCs are never accessed by untrained

Surgical Techniques for Banding of a High-Flow Vascular Access

A

B

D

C

E

Fig. 96.6 Surgical Techniques for Banding of a High-Flow Vascular Access. (A) Open venoplasty. (B) Interrupted mattress suturing. (C) Continuous mattress suturing. (D) Polytetrafluoroethylene (PTFE) banding. (E) PTFE interposition graft. The choice of technique is made by the surgeon on a case-by-case basis.

personnel. An exemplar protocol for safe connection and disconnection of CVCs can be found in the KDOQI Vascular Access Guidelines 2019.[1] Catheter locking with trisodium citrate solutions appears to reduce bleeding and may reduce bacteremia compared with locking with heparin solutions.[75] However, it is unclear whether citrate alone has the same protective effect against systemic infection as it does when combined with other antimicrobial agents[76,77] and may depend on the concentration of citrate used.[77] Mupirocin ointment applied to the exit site may reduce the incidence of CVC-associated bacteremia, but there are concerns of CVC material breakdown and mupirocin resistance. Topical application of povidone, medi-honey, and Polysporin triple ointment to exit sites has been shown in multicenter RCTs to reduce the rate of CVC-related bacteremia. Polysporin triple has sustained efficacy with no demonstrated resistance after long-term follow-up.[1,78]

Treatment of Catheter-Related Infection

Managing catheter-related infections involves treating the patient and managing the catheter. Patients should have appropriate culture and sensitivities obtained and treated with antibiotics according to the results of the sensitivities. Until they return, the infected patient should be treated with empiric broad-spectrum antibiotics to cover both gram-positive and gram-negative organisms.

Various societies have issued recommendations for the management of catheter infections.[1,79] A recommended treatment algorithm is shown in Fig. 96.8. A more detailed algorithm can be found in the KDOQI Vascular Access Guidelines 2019, including durations of antibiotic use and special management considerations depending on the infecting organism. For example, if the infecting organism is Staphylococcus aureus causing bacteremia, an infectious disease consult may be considered. All such patients should undergo a 2D echocardiogram to evaluate for the presence of vegetations or endocarditis, and antibiotic treatment should be at least 4 weeks in duration.

Infections Involving Temporary Nontunneled Catheters

When a temporary nontunneled CVC becomes infected, it should always be removed. There is no role for trying to salvage temporary nontunneled catheters.[1]

Exit Site Versus Tunnel Tract Infections

An exit site infection is a localized cellulitis confined to the 1 to 2 cm where the catheter exits the skin. The majority of these infections respond well to oral antibiotics and meticulous exit site care, and the removal of the CVC is generally not required.1 78 However, exit site infections can progress to tunnel tract infections, which involve the potential space surrounding the CVC more than 2 cm from the exit site (Fig. 96.9). Tunnel infections should be treated with intravenous antibiotics. Patients with a tunnel infection sometimes but not always have an associated exit site infection; untreated, they can rapidly develop bacteremia. Patients with a tunnel infection present with fever and local signs of pain, swelling, fluctuance, and erythema along the tract of the catheter. There may be purulent discharge from the exit site. Because tunnel infections involve a potential space in an area with limited vascular supply and an implanted synthetic device, they respond poorly to antibiotics alone and require catheter removal.1 78

Catheter-Associated Bacteremia

When a patient with a dialysis catheter has a fever, CVC-related bacteremia must be considered but other causes ruled out. If the patient does not have a clear and convincing alternative explanation for the fever, blood cultures should be obtained peripherally (e.g., dialysis circuit), as well as through the catheter hub80; as indicated earlier, the patient should be started on empiric antibiotics and adjusted based on culture results.[1] The most common organism is S. aureus, although a wide range of gram-positive and gram-negative organisms have been reported. An aminoglycoside or a cephalosporin is a good choice for gram-negative coverage; however, the presence of residual kidney function and local microbiologic epidemiology must be considered, especially with regard to antibiotic resistance.

Distal Revascularization-Interval Ligation
(DRIL) for Ischemia in an Upper Arm
Vascular Access

Management of Catheter-Related Infection

The decision to remove a tunneled cuffed CVC because of an episode of CVC-associated bacteremia is not straightforward. The clinical condition of the patient and response to initial therapy, the presence of an infected fibrin sheath, metastatic complications, the infecting organism, and the availability of other vascular access sites must be taken into consideration (see Fig. 96.8).

The conventional approach is to remove the CVC with interval replacement at a different site after the infection has resolved. The efficacy of this approach is uncertain, and it requires temporary CVC insertion before a new CVC is placed. Further, if the CVC is removed without identifying and disrupting an infected fibrin sheath, a nidus of continual infections remains. A new CVC may inadvertently be placed back into the infected sheath. The ineffectively treated nidus of infection may explain why attempts to salvage an infected CVC with systemic antibiotic therapy is only successful in about 30% of patients.

Another treatment option is to combine systemic antibiotics with antibiotic “lock” solutions. Many different combinations of antibiotics mixed with either heparin or citrate have been tested; the appropriate antibiotic lock depends on the culture sensitivities. A suitable broadspectrum regimen is vancomycin 2.5 mg/mL, gentamicin 1 mg/mL, and heparin 2500 U/mL. Infection clearance rates of 50% to 70% are reported with antibiotic locking.

CVC exchange over a guidewire after 48 hours of antibiotic treatment can be more effective than treatment with antibiotics alone and is at least as effective as removal of the CVC and delayed replacement, with the advantages of only one invasive procedure and preservation of the venous access site.[76 81] This also has the advantage of disrupting a fibrin sheath, if present.[82 83]

AV graft

Arterial bypass

Arterial
ligature

Fig. 96.7 Distal revascularization–interval ligation for ischemia in an upper arm vascular access. AV, Arteriovenous.

Management of Central Venous Dialysis Catheter Infections
Clinical suspicion of infection

Obtain cultures and start antibiotics

Temporary catheter

Remove catheter

Type of catheter

Tunneled catheter

Yes

Tunnel tract infection
or
Metastatic infection
or
Poor clinical response
to treatment

May proceed with antibiotic
lock or exchange over
guidewire

No

Fig. 96.8 Algorithm for the management of central venous dialysis catheter infections. (Modified from Manian FA. IDSA guidelines for the diagnosis and management of intravascular catheter-related bloodstream infection. Clin Infect Dis. 2009;49[11]:1770–1772.)

Fig. 96.9 Dialysis catheter tunnel infection. (Courtesy Dr. I.M. Leidig, University Hospital Erlangen, Germany.)

Catheter Thrombotic Obstruction

Catheter obstruction may be caused by endoluminal fibrin deposits, restricting the CVC lumen or obstructing CVC side holes or at the tip, or external fibrin sleeves surrounding the CVC, resulting in inadequate flow and excessive extracorporeal blood pressure alarms during the dialysis session. Depending on the location of the fibrin clot (arterial or venous line), there may be high negative arterial pressure (obstruction at the arterial CVC) or high positive venous pressure (obstruction at the venous CVC).

Prevention of clot formation in the CVC lumen and tip during the interdialytic period is crucial. This is achieved by installing an anticoagulant lock solution (heparin or trisodium citrate).1 Catheter malfunction might be treated with regular thrombolytic locking (e.g., urokinase or tPA); further, routine prophylactic locking was found to reduce CVC malfunction and CVC-related bacteremia in a multicenter RCT.84

RCTs have shown that regular use of low-dose warfarin or antiplatelet agents does not improve CVC function but increases the risk of major bleeding in HD patients.1 62

There are few established maneuvers to prevent CVC-related malfunction beyond the use of regular tPA, as demonstrated in the PRECLOT study84; however, the latter may become cost prohibitive. If a patient depends on CVC for HD access, the CVC may require multiple exchanges over guidewires. It is therefore critical to properly lay out the patient's ESKD Life-Plan and have a PLAN for each patient in order to appropriately limit CVC use and maximize safe, complication-free vascular access options for each patient.

SELF-ASSESSMENT QUESTIONS

1. The PLAN includes which of the following components?
A. The patient's ESKD Life-Plan only
B. A plan for the patient's individualized vascular access care only
C. The patient's ESKD Life-Plan and corresponding access needs (insertion/creation plan, contingency plan, succession plan, vessel preservation plan)
D. The plan for the hemodialysis access (insertion/creation plan, contingency plan, succession plan, vessel preservation plan)
2. AV access (fistulas and grafts) is preferred to CVCs because of:
A. the lower rate of thrombotic complications.
B. the lower rate of infections.
C. the lower rate of nonthrombotic complications.
D. all the above.
3. Ischemia in elbow fistulas with adequate access flow (800 mL/min) is best treated by:
A. access banding.
B. the DRIL procedure.
C. the revision using distal inflow procedure.
D. distal radial artery ligation.
4. Tunneled cuffed CVCs are preferred over nontunneled catheters because of:
A. ease of insertion.
B. lower occlusion rate.
C. higher dialysis flows.
D. lower infection rate.
5. The primary treatment option for symptomatic central vein occlusion is:
A. percutaneous transluminal angioplasty.

B. stent placement.
C. surgical bypass.
D. vascular access ligation.

REFERENCES

1. Lok CEHT, Lee T, et al. KDOQI Vascular Access Guideline Work Group. KDOQI clinical practice guideline for vascular access: 2019 update. Am J Kidney Dis. 2020;75(suppl 2):S1–S164.
2. Ravani P, Marcelli D, Malberti F. Vascular access surgery managed by renal physicians: the choice of native arteriovenous fistulas for hemodialysis. Am J Kidney Dis. 2002;40(6):1264–1276.
3. Rooijens PP, Burgmans JP, Yo TI, et al. Autogenous radial-cephalic or prosthetic brachial-antecubital forearm loop AVF in patients with compromised vessels? A randomized, multicenter study of the patency of primary hemodialysis access. J Vasc Surg. 2005;42(3):481–486; discussions 487.
4. Goh MA, Ali JM, Iype S, Pettigrew GJ. Outcomes of primary arteriovenous fistulas in patients older than 70 years. J Vasc Surg. 2016;63(5):1333–1340.
5. Korten E, Toonder IM, Schrama YC, Hop WCJ, van der Ham AC, Wittens CHA. Dialysis fistulae patency and preoperative diameter ultrasound measurements. Eur J Vasc Endovasc Surg. 2007;33:467–471.
6. Biuckians A, Scott EC, Meier GH, Panneton JM, Glickman MH. The natural history of autologous fistulas as first-time dialysis access in the KDOQI era. J Vasc Surg. 2008;47(2):415–421; discussion 420–411.
7. Wilmink T, Hollingworth L, Powers S, Allen C, Dasgupta I. Natural history of common autologous arteriovenous fistulae: consequences for planning of dialysis. Eur J Vasc Endovasc Surg. 2016;51(1):134–140.
8. Al-Jaishi AA, Oliver MJ, Thomas SM, et al. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and metaanalysis. Am J Kidney Dis. 2014;63(3):464–478.
9. Cheung AK, Imrey PB, Alpers CE, et al. Intimal hyperplasia, stenosis, and arteriovenous fistula maturation failure in the hemodialysis fistula maturation study. J Am Soc Nephrol. 2017;28(10):3005–3013.
10. Allon M, Imrey PB, Cheung AK, et al. Relationships between clinical processes and arteriovenous fistula cannulation and maturation: a multicenter prospective cohort study. Am J Kidney Dis. 2018;71(5):677–689.
11. Pisoni RL, Zepel L, Fluck R, et al. International differences in the location and use of arteriovenous accesses created for hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2017.
12. Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: results from the DOPPS. Kidney Int. 2002;61(1):305–316.
13. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). J Am Soc Nephrol. 2006;17(11):3204–3212.
14. Silva Jr MB, Hobson 2nd RW, Pappas PJ, et al. Vein transposition in the forearm for autogenous hemodialysis access. J Vasc Surg. 1997;26(6):981–986; discussion 987–988.
15. Tordoir JH, van Loon MM, Peppelenbosch N, Bode AS, Poeze M, van der Sande FM. Surgical techniques to improve cannulation of hemodialysis vascular access. Eur J Vasc Endovasc Surg. 2010;39(3):333–339.
16. Lok CE, Oliver MJ, Su J, Bhola C, Hannigan N, Jassal SV. Arteriovenous fistula outcomes in the era of the elderly dialysis population. Kidney Int. 2005;67(6):2462–2469.
17. Zeebregts CJ, Tielliu IF, Hulsebos RG, et al. Determinants of failure of brachiocephalic elbow fistulas for haemodialysis. Eur J Vasc Endovasc Surg. 2005;30(2):209–214.
18. Beathard GA, Lok CE, Glickman MH, et al. Definitions and end points for interventional studies for arteriovenous dialysis access. Clin J Am Soc Nephrol. 2018;13(3):501–512.
19. Koksoy C, Demirci RK, Balci D, Solak T, Kose SK. Brachiobasilic versus brachiocephalic arteriovenous fistula: a prospective randomized study. J Vasc Surg. 2009;49(1):171–177.e175.

20. Woo K, Farber A, Doros G, Killeen K, Kohanzadeh S. Evaluation of the efficacy of the transposed upper arm arteriovenous fistula: a single institutional review of 190 basilic and cephalic vein transposition procedures. J Vasc Surg. 2007;46(1):94–99; discussion 100.

21. Ayez N vHV, de Smet AA, van Well AM, Akkersdijk GP, van de Ven PJ, Fioole B. The basilic vein and the cephalic vein perform equally in upper arm arteriovenous fistulae. Eur J Vasc Endovasc Surg. 2012;44:227–231.
22. Dawoud D, Lok CE, Waheed U. Recent advances in arteriovenous access creation for hemodialysis: new Horizons in dialysis vascular access. Adv Chron Kidney Dis. 2020;27(3):191–198.
23. Lok CE, Rajan DK, Clement J, et al. Endovascular proximal forearm arteriovenous fistula for hemodialysis access: results of the prospective, multicenter Novel Endovascular Access Trial (NEAT). Am J Kidney Dis. 2017;70(4):486–497.
24. Hull JE, Jennings WC, Cooper RI, Waheed U, Schaefer ME, Narayan R. The pivotal multicenter trial of ultrasound-guided percutaneous arteriovenous fistula creation for hemodialysis access. J Vasc Intervent Radiol. 2018;29(2):149–158.e145.
25. Jun Yan Wee I, Mohamed IH, Patel A, Choong A. A systematic review and meta-analysis of one-stage versus two-stage brachiobasilic arteriovenous fistula creation. J Vasc Surg. 2018;68(1):285–297.
26. Lazarides MK, Georgiadis GS, Papasideris CP, Trellopoulos G, Tzilalis VD. Transposed brachial-basilic arteriovenous fistulas versus prosthetic upper limb grafts: a meta-analysis. Eur J Vasc Endovasc Surg. 2008;36(5):597–601.
27. Antoniou GA, Lazarides MK, Georgiadis GS, Sfyroeras GS, Nikolopoulos ES, Giannoukas AD. Lower-extremity arteriovenous access for haemodialysis: a systematic review. Eur J Vasc Endovasc Surg. 2009;38(3):365–372.
28. Aitken E, Thomson P, Bainbridge L, Kasthuri R, Mohr B, Kingsmore D. A randomized controlled trial and cost-effectiveness analysis of early cannulation arteriovenous grafts versus tunneled central venous catheters in patients requiring urgent vascular access for hemodialysis. J Vasc Surg. 2017;65(3):766–774.
29. Al Shakarchi J, Inston N. Early cannulation grafts for haemodialysis: an updated systematic review. J Vasc Access. 2019;20(2):123–127.
30. Glickman MH, Stokes GK, Ross JR, et al. Multicenter evaluation of a polytetrafluoroethylene vascular access graft as compared with the expanded polytetrafluoroethylene vascular access graft in hemodialysis applications. J Vasc Surg. 2001;34(3):465–472; discussion 472–463.
31. Kaufman JL, Garb JL, Berman JA, Rhee SW, Norris MA, Friedmann P. A prospective comparison of two expanded polytetrafluoroethylene grafts for linear forearm hemodialysis access: does the manufacturer matter? J Am Coll Surg. 1997;185(1):74–79.
32. Lenz BJ, Veldenz HC, Dennis JW, Khansarinia S, Atteberry LR. A threeyear follow-up on standard versus thin wall ePTFE grafts for hemodialysis. J Vasc Surg. 1998;28(3):464–470.
33. Garcia-Pajares R, Polo JR, Flores A, Gonzalez-Tabares E, Solis JV. Upper arm polytetrafluoroethylene grafts for dialysis access. Analysis of two different graft sizes: 6 mm and 6-8 mm. Vasc Endovasc Surg. 2003;37(5):335–343.
34. Schmidli J, Widmer MK, Basile C, et al. Editor’s choice - vascular access: 2018 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(6):757–818.
35. U.S. Renal Data System. USRDS 2017 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2017 (Chapter 3): Vascular Access.
36. Pisoni RL, Zepel L, Port FK, Robinson BM. Trends in US vascular access use, patient preferences, and related practices: an update from the US DOPPS practice monitor with international comparisons. Am J Kidney Dis. 2015;65(6):905–915.

37. Chan MR, Yevzlin AS. Tunneled dialysis catheters: recent trends and future directions. Adv Chron Kidney Dis. 2009;16(5):386–395.
38. Weijmer MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. Nephrol Dial Transplant. 2004;19(3):670–677.
39. Hod T, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS. Arteriovenous fistula placement in the elderly: when is the optimal time? J Am Soc Nephrol. 2015;26(2):448–456.

References

40. Tordoir JHM, Zonnebeld N, van Loon MM, Gallieni M, Hollenbeck M. Surgical and endovascular intervention for dialysis access maturation failure during and after arteriovenous fistula surgery: review of the evidence. Eur J Vasc Endovasc Surg. 2018;55(2):240–248.
41. Farber A, Imrey PB, Huber TS, et al. Multiple preoperative and intraoperative factors predict early fistula thrombosis in the Hemodialysis Fistula Maturation Study. J Vasc Surg. 2016;63(1):163–170.e166.
42. Robbin ML, Greene T, Allon M, et al. Prediction of arteriovenous fistula clinical maturation from postoperative ultrasound measurements: findings from the hemodialysis fistula maturation study. J Am Soc Nephrol. 2018;29(11):2735–2744.
43. Aitken E, Jackson A, Kearns R, et al. Effect of regional versus local anaesthesia on outcome after arteriovenous fistula creation: a randomised controlled trial. Lancet. 2016;388(10049):1067–1074.
44. Lin CC, Chang CF, Lai MY, Chen TW, Lee PC, Yang WC. Far-infrared therapy: a novel treatment to improve access blood flow and unassisted patency of arteriovenous fistula in hemodialysis patients. J Am Soc Nephrol. 2007;18(3):985–992.
45. Lin CC, Yang WC, Chen MC, Liu WS, Yang CY, Lee PC. Effect of far infrared therapy on arteriovenous fistula maturation: an open-label randomized controlled trial. Am J Kidney Dis. 2013;62(2):304–311.
46. Hofstra L, Bergmans DC, Hoeks AP, Kitslaar PJ, Leunissen KM, Tordoir JH. Mismatch in elastic properties around anastomoses of interposition grafts for hemodialysis access. J Am Soc Nephrol. 1994;5(5):1243–1250.
47. Sawo P, Moufarrej A, Sloff M, et al. The effect of geometric graft modification on arteriovenous graft patency in haemodialysis patients: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2020;60(4):568–577.
48. Lawson JH, Glickman MH, Ilzecki M, et al. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. Lancet. 2016;387(10032):2026–2034.
49. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. N Engl J Med. 2009;360(21):2191–2201.
50. Lok CE, Moist L, Hemmelgarn BR, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. JAMA. 2012;307(17):1809–1816.
51. Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. Adv Chron Kidney Dis. 2009;16(5):329–338.
52. Lee T, Ul Haq N. New developments in our understanding of neointimal hyperplasia. Adv Chron Kidney Dis. 2015;22(6):431–437.
53. Turmel-Rodrigues L, Pengloan J, Baudin S, et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. Nephrol Dial Transplant. 2000;15(12):2029–2036.
54. Lookstein RA, Haruguchi H, Ouriel K, et al. Drug-coated balloons for dysfunctional dialysis arteriovenous fistulas. N Engl J Med. 2020;383(8):733–742.
55. Trerotola SO, Lawson J, Roy-Chaudhury P, Saad TF. Lutonix AVCTI. Drug coated balloon angioplasty in failing AV fistulas: a randomized controlled trial. Clin J Am Soc Nephrol. 2018;13(8):1215–1224.
56. Oakes DD, Sherck JP, Cobb LF. Surgical salvage of failed radiocephalic arteriovenous fistulae: techniques and results in 29 patients. Kidney Int. 1998;53(2):480–487.
57. Tordoir JH, Bode AS, Peppelenbosch N, Van Der Sande FM, de Haan MW. Surgical or endovascular repair of thrombosed dialysis vascular access: is there any evidence? J Vasc Surg. 2009;50(4):953–956.
58. Mansour M, Kamper L, Altenburg A, Haage P. Radiological central vein

treatment in vascular access. J Vasc Access. 2008;9(2):85–101.
59. Gallieni M, Matoussevitch V, Steinke T, et al. Multicenter experience with the surfacer inside-out access catheter System in patients with thoracic venous obstruction: results from the SAVE registry. J Vasc Intervent Radiol. 2020;31(10):1654–1660.e1651.
60. Mickley V. Central vein obstruction in vascular access. Eur J Vasc Endovasc Surg. 2006;32(4):439–444.

61. Tanner NC, Da Silva A. Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts. Cochrane Database Syst Rev. 2015;(7):CD002786.
62. Crowther MA, Clase CM, Margetts PJ, et al. Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. J Am Soc Nephrol. 2002;13(9):2331–2337.
63. Schmitz PG, McCloud LK, Reikes ST, Leonard CL, Gellens ME. Prophylaxis of hemodialysis graft thrombosis with fish oil: double-blind, randomized, prospective trial. J Am Soc Nephrol. 2002;13(1):184–190.
64. Lok CE, Moist L, Hemmelgarn BR, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. JAMA. 2012;307(17):1809–1816.
65. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008;299(18):2164–2171.
66. Lee T, Misra S. New Insights into dialysis vascular access: molecular targets in arteriovenous fistula and arteriovenous graft failure and their potential to improve vascular access outcomes. Clin J Am Soc Nephrol. 2016;11(8):1504–1512.
67. Morsy AH, Kulbaski M, Chen C, Isiklar H, Lumsden AB. Incidence and characteristics of patients with hand ischemia after a hemodialysis access procedure. J Surg Res. 1998;74(1):8–10.
68. Tordoir JH, Dammers R, Van Der Sande FM. Upper extremity ischemia and hemodialysis vascular access. Eur J Vasc Endovasc Surg. 2004;27(1):1–5.
69. van Hoek F, Scheltinga MR, Luirink M, Raaymakers LC, van Pul C, Beerenhout CH. Access flow, venous saturation, and digital pressures in hemodialysis. J Vasc Surg. 2007;45(5):968–973.
70. Guerra A, Raynaud A, Beyssen B, Pagny JY, Sapoval M, Angel C. Arterial percutaneous angioplasty in upper limbs with vascular access devices for haemodialysis. Nephrol Dial Transplant. 2002;17(5):843–851.
71. Vaes RH, Wouda R, van Loon M, van Hoek F, Tordoir JH, Scheltinga MR. Effectiveness of surgical banding for high flow in brachial artery-based hemodialysis vascular access. J Vasc Surg. 2015;61(3):762–766.
72. Minion DJ, Moore E, Endean E. Revision using distal inflow: a novel approach to dialysis-associated steal syndrome. Ann Vasc Surg. 2005;19(5):625–628.
73. Zanow J, Kruger U, Scholz H. Proximalization of the arterial inflow: a new technique to treat access-related ischemia. J Vasc Surg. 2006;43(6):1216–1221; discussion 1221.
74. Allon M, Daugirdas J, Depner TA, Greene T, Ornt D, Schwab SJ. Effect of change in vascular access on patient mortality in hemodialysis patients. Am J Kidney Dis. 2006;47(3):469–477.
75. Lok CE, Appleton D, Bhola C, Khoo B, Richardson RM. Trisodium citrate 4%-an alternative to heparin capping of haemodialysis catheters. Nephrol Dial Transplant. 2007;22(2):477–483.
76. Grudzinski A, Agarwal A, Bhatnagar N, Nesrallah G. Benefits and harms of citrate locking solutions for hemodialysis catheters: a systematic review and meta-analysis. Can J Kidney Health Dis. 2015;2:13.
77. Weijmer MC, van den Dorpel MA, Van de Ven PJ, et al. Randomized, clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients. J Am Soc Nephrol. 2005;16(9):2769–2777.
78. Lok CE, Mokrzycki MH. Prevention and management of catheter-related

infection in hemodialysis patients. Kidney Int. 2011;79(6):587–598.
79. Manian FA. IDSA guidelines for the diagnosis and management of intravascular catheter-related bloodstream infection. Clin Infect Dis. 2009;49(11):1770–1772.
80. Quittnat Pelletier F, Joarder M, Poutanen SM, Lok CE. Evaluating approaches for the diagnosis of hemodialysis catheter-related bloodstream infections. Clin J Am Soc Nephrol. 2016;11(5):847–854.
81. Langer JM, Cohen RM, Berns JS, Chittams J, Cooper ET, Trerotola SO. Staphylococcus-infected tunneled dialysis catheters: is over-the-wire exchange an appropriate management option? Cardiovasc Intervent Radiol. 2011;34(6):1230–1235.

References

82. Merport M, Murphy TP, Egglin TK, Dubel GJ. Fibrin sheath stripping versus catheter exchange for the treatment of failed tunneled hemodialysis catheters: randomized clinical trial. J Vasc Intervent Radiol. 2000;11(9):1115–1120.
83. Saleh HM, Tawfik MM, Abouellail H. Prospective, randomized study of long-term hemodialysis catheter removal versus guidewire exchange to treat catheter-related bloodstream infection. J Vasc Surg. 2017;66(5):1427–1431.e1421.
84. Hemmelgarn BR, Moist LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med. 2011;364(4):303–312.

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Diagnostic and Interventional Nephrology

Haimanot Wasse, Stephen R. Ash

A variety of procedures are essential to the care of nephrology patients and include ultrasound, kidney biopsy, insertion of hemodialysis (HD) and peritoneal dialysis (PD) catheters, creation of arteriovenous fistulas (AVF), and diagnostic and interventional procedures to maintain HD access function. These procedures have traditionally been performed by other specialists but are increasingly performed by nephrologists. The field of diagnostic and interventional nephrology is most developed in the United States, where the American Society of Diagnostic and Interventional Nephrology (ASDIN) (https://www.asdin.org) has established training standards and certification procedures. This chapter covers insertion of dialysis catheters and interventions in vascular access, focusing on the applications of these procedures and their performance by nephrologists. Kidney biopsy is covered in Chapter 7, and placement of AVF and arteriovenous grafts (AVG) in Chapter 96. The role and interpretation of ultrasound are further covered in Chapters 5 and 6.

PERITONEAL DIALYSIS CATHETERS

Successful PD depends on proper catheter insertion and management, which can be done safely and successfully by nephrologists,1-3 thus facilitating uptake of PD. Tenckhoff catheters are the most popular chronic peritoneal access devices; they are constructed of silicone rubber with a 5-mm external diameter and internal diameters of 2.6 to 3.5 mm and numerous intraperitoneal side holes. The intraperitoneal portion can be straight, straight with perpendicular silicone disks, or curled. Several design modifications have been developed in attempts to diminish outflow obstruction, including a version sold in Europe with a weighted tip. The subcutaneous portion is either straight or bent and has one or two extraperitoneal Dacron cuffs that prevent fluid leaks and bacterial migration around the catheter. One type of catheter has a silicone ball and Dacron disc at the parietal peritoneal surface. The subcutaneous portion is curved to give a lateral or downward direction of the exit site. An upward-directed exit site collects debris and fluid, increasing the risk for exit site infection. The method of catheter placement has more effect on the outcome than does the catheter type.

Catheter Insertion

There are four techniques for PD catheter insertion: dissection (surgical), the Seldinger technique (blind or with fluoroscopy), peritoneoscopic, and laparoscopic.4 The Seldinger technique with fluoroscopy is the procedure used by most nephrologists, because it uses the same fluoroscope and some disposables used in placement of central venous catheters and angioplasty of AVGs and AVFs. Peritoneoscopic insertion is a single-puncture technique using a small (2.2-mm diameter) optical peritoneoscope for direct inspection of the peritoneal cavity and identification of a suitable site for the optimal intraperitoneal portion of the catheter. Peritoneoscopic placement is performed using local anesthesia (sometimes with conscious sedation) and manual infusion of about 1 L of air to allow visualization of the anterior peritoneal surfaces. This technique is not used by many nephrologists because it involves specialized training and equipment including the peritoneoscope, a video camera to display images, and a table allowing Trendelenburg positioning of the patient.

Laparoscopic techniques are performed with the patient under general anesthesia using larger scopes, multiple insertion sites, and automated gas infusion (usually CO_2). Both peritoneoscopic and laparoscopic techniques allow direct visualization of anterior peritoneal surfaces, to identify adhesions and hernias, and to choose the optimal location of the PD catheter. Laparoscopic placement allows advanced techniques for improving catheter function including omentopexy, correction of hernias, and removal of adhesions, which improve the long-term success of PD catheters.[5,6]

Any of the methods for PD catheter placement can be successful if the physician performing placement has sufficient experience with the technique. Randomized and nonrandomized studies have documented that the peritoneoscopic and fluoroscopic Seldinger techniques can result in fewer catheter complications (infection, outflow failure, pericatheter leak) and improved catheter survival compared with surgical placement.[2,7] The superior results with peritoneoscopic placement may relate to direct visualization of the abdominal cavity, less tissue dissection, and avoidance of general anesthesia. Because tissue dissection is minimal during placement, the catheter can be used for intermittent dialysis immediately, although there is an increased risk of peri-catheter leaks if the catheter is used immediately and continually for fluid exchange.[8,9]

For peritoneoscopic insertion (Fig. 97.1), a small skin incision (2–3 cm) is made and dissection of subcutaneous tissue down to the rectus muscle.[10] The anterior rectus sheath is identified but not incised. A preassembled cannula with trocar and a spiral sheath is then inserted at a 45-degree angle into the abdominal cavity through the rectus muscle toward the pelvis (see Figs. 97.1A and 97.2). The trocar is then removed and replaced by the 2.2-mm diameter peritoneoscope to confirm the intraabdominal position of the cannula (see Fig. 97.1B). Air is then infused (600–1000 mL) to separate the visceral peritoneum and parietal peritoneum, using a sterile syringe or rubber bulb. Alternatively, a Veress needle can be used for first insertion to the peritoneum, but this needle does not allow inspection of the peritoneal surfaces before gas infusion.[11] During peritoneoscopy, bowel loops, mesentery, the dome of the bladder, and intraabdominal adhesions are identified. The cannula and surrounding spiral sheath are advanced toward the pelvis, avoiding any areas of peritoneal adhesions (see Fig. 97.1C). The cannula and the peritoneoscope are then removed, the spiral sheath is dilated to 6-mm diameter (see Fig. 97.1D), and the catheter is inserted through the sheath while stiffened by a stylet (see Fig. 97.1E).

Steps for the Insertion of a Peritoneal Dialysis Catheter by Peritoneoscopy

A

C

B
Internal stylette
Dilator
Double cuff PD
catheter

D

E

F

Fig. 97.1 Steps for the Insertion of a Peritoneal Dialysis (PD) Catheter by Peritoneoscopy. (A) A trocar and cannula with a sheath are inserted into the abdominal cavity. (B) A peritoneoscope is passed through and locked into the cannula. (C) The sheath has been passed into the abdominal cavity and the peritoneoscope and cannula removed sequentially. (D) The sheath is secured with forceps while it is being dilated. (E) A PD catheter (with double cuff) is passed through the dilated sheath by use of an internal stylet. (F) The deep cuff is implanted into the rectus muscle. (Modified from Y-Tec Instructions. Laparoscopic and Peritoneoscopic Placement of Peritoneal Dialysis Catheters. Medigroup Inc. [division of Janin Group, Inc.]; 2004:1–5.)

The deep cuff is implanted into the rectus muscle using an implanter tool without dissection of the anterior rectus sheath or the muscle (see Fig. 97.1F). A tunnel and an exit site are created, and the superficial cuff is implanted into the subcutaneous tissue. The dermis is sutured with absorbable material, and the epidermis is closed with nylon. No sutures are placed on the external rectus sheath or at the skin exit site.

Instead of using a trocar, the cannula can be advanced into the peritoneal space over a 0.035-inch guidewire by placing a 7-mm dilator inside the cannula. This step is useful to inspect the peritoneum during a fluoroscopic placement, in case the guidewire does not progress as expected within the peritoneum.

The Seldinger technique using fluoroscopy begins with blunt dissection down to the level of the lateral border of the rectus sheath. An 18-gauge needle with internal blunt stylet or a 22-gauge needle from a 5-French micropuncture set is inserted at an angle of 45 degrees, directed toward the lower pelvis into the peritoneum (ultrasound is helpful to identify thickness of the rectus muscle and presence of adhesions to the parietal peritoneum).12 The location of the needle within the peritoneal cavity is confirmed by injecting 1 to 5 mL of contrast material, which forms a classic “spider web” appearance on fluoroscopy as dye moves into small spaces between bowel loops and

Fig. 97.2 Peritoneoscopic Insertion of a Peritoneal Dialysis Catheter. During peritoneoscopic insertion of a peritoneal dialysis catheter, a Quill guide trocar and cannula (arrow), with its wrapped spiral sheath, is being inserted through the rectus muscle under local anesthesia.

A

B

Fig. 97.3 (A) Fluoroscopic image after injecting a few milliliters of radiopaque dye through an 18-gauge needle after insertion through the rectus muscle and into the peritoneal space. Dye moves quickly away from the needle, and the image is not static. (B) Image after injecting a few milliliters of dye into an 18-gauge needle after insertion through the rectus muscle, with the tip of the needle in the preperitoneal space. Dye collects around the tip of the needle, at least one flat surface outlines the parietal peritoneum, and the image changes very little with time. (From Ash S, Sequeira A, Narayan R. Imaging and peritoneal dialysis catheters. Semin Dial. 2017;30[4]:338–346.)

parietal peritoneum (Fig. 97.3A).12 If the tip of the needle is in the preperitoneal space, the dye collects around the tip of the needle, forms an outline of the parietal peritoneum, and appears static over a minute or so (Fig. 97.3B). If the tip of the needle appears to be preperitoneal, advancing the needle under fluoroscopic visualization allows the tip to penetrate the parietal peritoneal surface as confirmed by injection of a few milliliters of dye. If a micropuncture needle is used, an 0.018-inch guidewire is then inserted through the needle under fluoroscopy. Once the wire is in the lower pelvis, a 5-French catheter and internal dilator are advanced over the wire. Contrast material is again injected through the catheter to confirm the position. If an 18-gauge needle is used, a 0.035-inch guidewire is passed directly through the needle. Dilators are advanced sequentially over the guidewire up to the final 18-French dilator and peel-away sheath. The guidewire is removed, and the PD catheter with an internal metal stylet is advanced through the sheath, splitting the sheath as the deep cuff advances. This cuff is pushed into the rectus muscle while the sheath is in place, and the sheath is then removed around the cuff and catheter. The catheter is tunneled laterally with a tunneling tool (Fig. 97.4).13 14 (For additional details, see reference15.)

Burying (Embedding) the Peritoneal Dialysis Catheter

If the catheter will not be used immediately, the external portion can be buried under the skin for weeks to months before it is exteriorized and used. The catheter is placed in the usual manner, tunneled through a 1-cm skin exit site, filled with heparin solution (1000 U/mL), and blocked with a plug. The outside tip is then directed back into the exit site and tunneled through the subcutaneous space in a direction toward midline, caudal to the umbilicus. In the original publications, the catheter was tied off with silk suture and coiled into a pouch under the exit site.16 Direct line tunneling of the external portion of the catheter (described earlier) avoids creation of a pocket just below the exit site and creates a normal exit site anatomy when exteriorized. The primary incision and exit site are closed over the catheter. Embedding the catheter allows ingrowth of tissue into the cuffs of the catheter with less chance of bacterial colonization. This diminishes the incidence of early pericatheter infections and peritonitis.16 17 Exteriorization of the catheter is done by making a small incision (1 cm) through the original exit site and using hemostats to locate and

Fig. 97.4 Subcutaneous Tunnel Being Created for a Peritoneal Dialysis Catheter. With use of a disposable tool, a subcutaneous tunnel is created for the catheter. The superficial cuff (shown) will be implanted

in the subcutaneous tunnel.

bring the catheter and surrounding tunnel to the exit site. The tunnel is incised and the catheter exteriorized.
Catheters buried in this fashion have been successfully exteriorized and used several years after insertion.18 We recommend embedding the catheter when the catheter will not be used for at least a month, which obviates the need for care of the exit site and flushing the catheter after placement. The procedure allows time for ingrowth of fibrous tissue to the catheter cuffs and allows PD catheter placement to be performed electively rather than urgently (similar to creation of an AVF or AVG).

Complications of Peritoneal Dialysis Catheter Insertion

Bowel perforation is the most feared complication of peritoneal catheter insertion. The incidence is 1% to 1.4% with surgical insertion2 3 and up to 0.8% with peritoneoscopic or fluoroscopic insertion.1 3 19 During peritoneoscopic insertions, the diagnosis of bowel perforation is established by direct visualization of bowel mucosa or bowel contents, discharge of fecal material, or emanation of foul-smelling gas through the cannula.
In fluoroscopic procedures it is recognized by a characteristic pattern of

injected dye outlining the bowel mucosa. Some physicians suggest this complication should be treated surgically,20 but successful conservative management with bowel rest and intravenous antibiotics is possible if the perforation is recognized early in the procedure (before dilation of the tract or insertion of the catheter).13 21 To minimize risk for perforation, a needle with a blunt and self-retracting stylet (such as a Veress needle or a Hawkins 18-gauge needle with obturator) can be used instead of a trocar or sharp needle to gain access to the abdominal cavity.11 Previous abdominal surgery is a relative contraindication to PD catheter placement because of risk of bowel perforation due to intraperitoneal adhesions.22 23 However, with careful ultrasound examination before needle placement, an area free of adhesions can be identified in almost every patient. If the visceral peritoneal surface moves freely versus the parietal peritoneal surface with each inspiration, then there are no major adhesions in that area of the peritoneum the risk of bowel perforation is low.

Peritoneoscopy or laparoscopy is useful for patients at high risk for adhesions. The scope can be used to identify intraperitoneal adhesions, assess their extent, and locate another site more suitable for catheter placement. With either fluoroscopic or peritoneoscopic techniques, the incidence of bowel perforation is no higher than with surgery, and the early success rate of catheters exceeds 95%.1 24

Catheter Repositioning

Outflow failure of a PD catheter occurs whenever the outflow fluid volume is less than the inflow volume. Peritonitis that fails to resolve is the number one reason for removal of PD catheters, but outflow failure is a close second in causes of PD catheter failure. Outflow failure is caused principally by omental attachment to the catheter. If omentum attaches to only a few side holes of the PD catheter, the omentum then acts as a “flap valve” limiting outflow through the PD catheter. As the omentum retracts and moves, the tip of the catheter often migrates to the upper abdomen. However, outflow failure due to adhesions can occur without catheter migration.

A variety of techniques have been used for repositioning PD catheters, including guidewire or stylet insertion, manipulation using a Fogarty catheter, and laparoscopy. Several techniques for catheter repositioning are feasible for nephrologists to perform. Fogarty catheter manipulation is the simplest method and works best with straight Tenckhoff catheters rather than coiled catheters. A Fogarty catheter is advanced past the tip of the catheter, the balloon is inflated, and tugging movements are used to reposition the catheter into the pelvis. Infusion and drainage of dialysate and fluoroscopy are performed to determine patency and position of the PD catheter. Peritoneal catheters can also be repositioned using stiff guidewires or stylets. Fluoroscopic images are helpful in determining the degree of catheter entrapment and the progress of the repositioning procedure.12 The long-term success rate of repositioned catheters is only 27% to 48%,25 26 probably because the primary problem is attachment of omentum to the catheter rather than migration of the catheter.

Insertion of a new catheter is the most effective therapy in many patients.

Removal of Peritoneal Dialysis Catheters

A Tenckhoff curled or straight PD catheter can be safely removed in an outpatient procedure room; an operating room and general anesthesia are not required.8 Local anesthetic is infiltrated at the site of the original primary incision, and the incision is incised. Dissection is carried down to the subcutaneous portion of the catheter, which is elevated while the surrounding fibrous sheath is opened. The catheter is clamped with a hemostat, and a nylon suture is placed through the catheter just outside the hemostat. The catheter is cut between the tag and hemostat. Dissection is continued toward the deep cuff by incising the fibrous tunnel adjacent to the catheter (Fig. 97.5). Additional anesthetic is infiltrated around the deep cuff. For catheters that have been in place for less than a month, blunt dissection is usually sufficient to free the deep cuff. Catheters in place for more than a month require sharp dissection, clamping and cautery to free the deep cuff from the rectus muscle. Before removing the deep cuff from the musculature, a purse-string suture is placed into the rectus sheath around the cuff. The deep cuff is then separated from the surrounding tissue, the intraperitoneal portion of the catheter is gently withdrawn from the peritoneal cavity, and the defect in the rectus sheath is closed by tying purse-string suture. The nylon tag is then pulled to expose the remaining subcutaneous portion of catheter segment within the primary incision, and dissection is performed in the direction of the superficial cuff. Once the superficial cuff is free, the external portion of the catheter is cut off at the skin level, and the outer portion of the catheter is removed through the primary incision site. Absorbable suture material in the dermis is used to close the skin incision, reinforced by nylon sutures in the epidermis or sterile adhesive strips if needed. The exit site is not sutured to allow drainage of fluid or pus if it develops.

Fig. 97.5 Peritoneal Dialysis Catheter Removal. The catheter (arrows show lateral margins of catheter) has been exposed by dissection of the subcutaneous tunnel.

Training and Certification

ASDIN has established training guidelines and criteria for certification of physicians in the insertion of PD catheters by fluoroscopy or peritoneoscopy.27 In addition to appropriate didactic training, there should be two practice insertions (into models, animals, or human cadavers), observation of two insertions into patients, and then six successful PD catheter insertions into patients with the physician as primary operator.

TUNNELED HEMODIALYSIS CATHETERS

Central venous catheters are used as a temporary HD access, as a bridge to AVF or AVG use, and when all other permanent access sites have been exhausted. Nontunneled catheters are used when a limited number of dialysis sessions is anticipated or there are contraindications to tunneled catheters (systemic infection, risk for bleeding), but they are more appropriate for use in inpatients. Tunneled catheters can be placed in both inpatient and outpatient settings, can be inserted at multiple vein locations, are relatively low in cost, and provide immediate access. However, there are significant disadvantages, including morbidity from infection and thrombosis and the risk of central vein stenosis or occlusion28 29 (see Chapter 96).

Tunneled Catheter Insertion

The right internal jugular vein is the preferred catheter location compared with the left internal jugular and subclavian vein sites; it provides a straight route to the right atrium, thereby reducing the risk for central vein stenosis. Catheters also may be placed in the femoral veins.

Catheter insertion should be performed in a sterile setting, ideally in an operating room environment with fluoroscopy available or at a minimum in a dedicated procedure room with cardiac monitoring. Before cannulation the vein should be located by ultrasound to detect anatomic variation or venous thrombosis. The patient's neck is then prepared and draped in sterile fashion; under ultrasound guidance, the vein is cannulated with a micropuncture needle (18–22 gauge), and a micropuncture guidewire is inserted and positioned in the superior vena cava. The needle is then removed, and the micropuncture dilator is inserted over the guidewire so it can be replaced with a standard guidewire. The use of the smaller needle rather than the standard 15-gauge needle minimizes trauma to the vein. A small subcutaneous incision is made adjacent to the dilator or guidewire, additional dilation is performed, and the catheter is placed over the guidewire, with care taken to hold the guidewire in place. If a tunneled catheter is to be placed, a catheter exit site is selected inferior to the clavicle and sufficiently lateral to the venotomy to avoid a kink in the catheter. A 1-cm superficial incision is made at this point, and a subcutaneous tract adjacent to the venotomy is infiltrated with lidocaine. A double-lumen catheter, generally 24 or 28 cm in length, is attached to the tunneling device and pulled through the subcutaneous tunnel in a curved path. A guidewire is passed through the dilator and into the inferior vena cava. The venotomy site is then serially dilated over the guidewire. The catheter can then be inserted over the guidewire through the venous port. When a split-tip catheter is used, the guidewire is passed in and out of the two venous ports and through an arterial port or through a hollow intracatheter stiffener. Alternatively, a peel-away sheath is placed over the guidewire and the catheter inserted through the sheath after the removal of the guidewire; however, this method has greater potential for blood loss and air embolism. Fluoroscopy is used to confirm tip placement at the level of the right atrium, with the arterial port facing away from the atrial wall, and to ensure there are no kinks in the catheter (Fig. 97.6). Each port of the catheter is then flushed with saline and locked with the appropriate amount of heparin based on

catheter length and priming volume designation, followed by placement of the catheter hub caps.

Catheter Dysfunction

Catheter dysfunction is the failure to maintain a blood flow sufficient to perform HD without significantly extending treatment time; this is usually 300 mL/min or greater for conventional dialysis.30 Causes of immediate dysfunction include a kink in the catheter, incorrect position or orientation (e.g., arterial port against the vessel wall), and errant venous cannulation. These problems should be ascertained and corrected at the time of catheter placement. Catheter thrombosis is the most common cause of late dysfunction. Extrinsic thrombosis is less common than intrinsic thrombosis and is caused by central vein, mural, or right atrial thrombosis. Intrinsic obstruction results from thrombus within the catheter lumen or tip or most commonly from a fibrin sheath. Fibrin sheaths typically develop weeks to months after catheter insertion and result when a sleeve of connective tissue forms at the venotomy site and extends and encases the catheter tip, creating a flap valve.

First-line treatment of catheter thrombosis includes forceful flush of the catheter with saline. If flow is not restored, a fibrinolytic agent should be instilled. Tissue plasminogen activator (tPA) is commonly used and appears more effective than urokinase in restoring patency and adequate flow.31,32 Typically, 2 mg of tPA is instilled per occluded catheter lumen with 0.9% sodium chloride without preservative to fill the internal volume of each lumen and is allowed to dwell 30 minutes or until the next dialysis session. If this fails, the catheter should be exchanged. Strategies to minimize dialysis catheter thrombosis are discussed in Chapter 96.

Catheter Exchange and Fibrin Sheath Removal

Catheter exchange over a guidewire is useful in the setting of catheter thrombosis or bacteremia and allows the preservation of the venotomy, tunnel, and exit sites. The tunnel and exit sites must appear free of infection if the same sites are to be used. Catheter exchange should take place within 72 hours of the initiation of antibiotic therapy.30 Under sterile conditions, the exit site is anesthetized and the cuff is freed. Once the catheter is pulled back 8 to 10 cm, contrast material is injected through the catheter under fluoroscopy to check for a fibrin sheath (Fig. 97.7). To obliterate a sheath, a guidewire is passed down the venous port of the catheter and into the inferior vena cava. The catheter is then removed, and a balloon catheter is inserted over the guidewire to the sheath location and inflated to disrupt the sheath. A new catheter is then inserted over the guidewire. When the catheter tip is beyond the venotomy site, near the superior vena cava, contrast material can be injected again to check for sheath removal before proceeding with catheter insertion.

Training and Certification

The ASDIN guidelines for HD vascular access procedure certification specify formal didactic training in central venous anatomy, sonographic examination of central veins, fluoroscopy, and catheter design and complications. Practical training for certification includes satisfactory insertion of 25 tunneled long-term catheters (see https://www.asdin.org).

PROCEDURES ON ARTERIOVENOUS FISTULAS AND ARTERIOVENOUS GRAFTS

Fig. 97.6 Insertion of a Venous Catheter for Hemodialysis. Chest radiograph confirming that the tip of the catheter (arrow) is at the junction of the superior vena cava and the right atrium.

The most common indications for intervention are inadequate flow during dialysis, thrombosis, and failure of AVFs to mature. Specific interventions include angiography, thrombectomy, angioplasty, and stenting. All of these procedures require a dedicated facility, either

Fig. 97.7 Fibrin Sheath on a Tunneled Venous Catheter. Contrast material has been injected into a tunneled catheter after the tip (arrow) has been pulled back into the innominate vein. The contrast material fills a sheath that extends from the catheter tip as far as the arrowhead.

inpatient or outpatient, with fluoroscopy, monitoring equipment, and staff to assist with the procedures and deliver conscious sedation. There are many different techniques for AV access procedures and few data to indicate superiority of one method over the other, so the choice is generally one of personal preference and cost. However, the first step always should include careful physical and ultrasound examination of the access. An examination will generally identify the problem and allow detection of access infection, an absolute contraindication to intervention. Appropriate intervention then can be planned.

Monitoring and management of vascular access to minimize stenosis, thrombosis, and failure are discussed further in Chapter 96

Percutaneous Balloon Angioplasty

Stenosis in AVG and AVF is routinely managed by percutaneous balloon angioplasty, which causes minimal discomfort and allows immediate use of the access. Not all stenotic lesions are responsive, however, and some require repeated treatment. In fistulas, the stenosis is most commonly located at the “swing point,” including the portion of the native vein mobilized during creation of the AV anastomosis (Fig. 97.8), during vein transposition, or at the cephalic arch; in grafts, the venous anastomosis is the most common site of stenosis.33-37 Angioplasty is indicated if the stenosis is 50% or more and is associated with clinical or physiologic abnormalities.30 Treatment of stenosis increases access blood flow and longevity and reduces access thrombosis and accessrelated hospitalization.37-39 A relative contraindication to angioplasty is a newly created access (less than 4–6 weeks old).

The access is cannulated with an introducer needle, a sheath is inserted, and initial angiography is performed. This should include views of the access, draining veins (peripheral and central), and arterial anastomosis and is used to confirm the location and degree of stenosis. Unless contraindicated, short-acting sedation and analgesia are given once a lesion has been identified on initial angiography, because angioplasty is painful.

A guidewire is passed through the sheath and across the stenosis. An angioplasty balloon catheter is passed over the guidewire,

Fig. 97.8 Juxtaanastomotic Stenosis in a Radiocephalic Arteriovenous Fistula. Contrast material was injected at the arterial anastomosis (bottom left) and demonstrates a narrowing in the initial portion of the fistula (arrow).

PRE– PTA

A

POST– PTA

B

Fig. 97.9 Arteriovenous Graft Stenosis. (A) Stenosis in the outflow vein of an upper arm arteriovenous graft (arrow). (B) Angiogram performed immediately after percutaneous angioplasty. PTA, Percutaneous transluminal angioplasty.

positioned at the stenotic site, and inflated with a syringe or inflation device (Fig. 97.9). A variety of sheaths, guidewires, balloon sizes, and maximum pressures are available. The guidewire is left in place, and angiography is repeated to identify residual stenosis or any complications. Angioplasty is repeated for residual stenosis or when multiple lesions are present and may require a second cannulation of the access in the opposite direction for inflow stenoses. After removal of all devices, hemostasis at the cannulation site is achieved by manual pressure or suture placement. There is no evidence to support the use of antiplatelet agents or anticoagulation after intervention. According to Kidney Disease Outcomes Quality Initiative guidelines, a successful angioplasty is achieved when there is no more than 30% residual stenosis and physical indicators of stenosis have resolved.30

Percutaneous Thrombectomy

A variety of techniques are used for thrombus removal. In thromboaspiration—the least costly method, and as effective and efficient as mechanical and pharmacomechanical thrombolysis—low-dose tPA is instilled into the thrombosed access, the clot is manually macerated, flow returns, and angioplasty is used to dilate access stenoses.40 Thrombectomy by thromboaspiration combines angiography with balloon angioplasty and thrombectomy by clot aspiration. Absolute contraindications to thromboaspiration include access infection and

known right-to-left cardiac shunt; relative contraindications include a large clot burden and long-standing access occlusion.

The access is cannulated in an antegrade direction, and a guidewire is passed to the level of the central veins. A straight catheter is inserted over the wire to the central veins, and angiography is performed to confirm central venous patency. Anticoagulation and short-acting sedative and analgesic medications are administered in the central circulation. An angiogram is then obtained as the catheter is pulled back to identify the location of stenosis. The guidewire is then inserted beyond the stenotic lesion, followed by an angioplasty balloon catheter. The balloon catheter is insufflated by hand with a syringe or inflation device, and the stenotic lesion is dilated. The access is then cannulated in the retrograde direction, a sheath is inserted, and a Fogarty catheter is passed across the arterial anastomosis, inflated, and pulled back through the entire length of the access while clot fragments are aspirated. On return of flow through the access, angiography is performed to evaluate the inflow and the arterial anastomosis, and angioplasty is repeated if necessary. Hemostasis is achieved by manual pressure or a suture at the cannulation sites.

Stents

Fig. 97.10 Vein Rupture. Postangioplasty angiogram of an arteriovenous fistula showing extravasation of dye (arrow), indicative of a vein rupture. (Courtesy Dr. G. Beathard, Austin, TX.)

A

Stents are considered in the setting of failed balloon angioplasty (an elastic lesion), when there are few remaining access sites, if the patient is not a surgical candidate for a new access, or when an outflow vein ruptures after balloon angioplasty (Figs. 97.10 and 97.11).41 42 Results of randomized studies designed to demonstrate stent graft noninferiority to conventional angioplasty for AVG venous anastomotic stenosis show an increased primary patency for stent grafts.43-45 Further, data suggests improved patency with stent grafts used to treat outflow vein restenosis in AVG, AVF, and central veins.46-49 50 Finally, a stent may be useful in the setting of an expanding pseudoaneurysm.51 52 Despite these encouraging findings, stents should be used judiciously, particularly when surgical options may provide greater enduring patency. Stents should be avoided in situations in which their use will not extend the life of the access.

B

Fig. 97.11 Treatment of Vein Rupture With an Intraluminal Stent. (A) Placement of the stent (arrow). (B) An angiogram obtained after stent placement showing that venous outflow has been reestablished. (Courtesy Dr. G. Beathard, Austin, TX.)

Training and Certification

The ASDIN guidelines for HD vascular access procedure certification specify didactic training in venous anatomy, fluoroscopy, procedural equipment, and sedation and analgesia. Requirements for practical

training include 125 procedures in both fistulas and grafts of each of the following: angiography, angioplasty, and thrombectomy as primary operator (refer to https://www.asdin.org for more information). In general, several hundred procedures as secondary operator are required before one can become a primary operator.

SELF-ASSESSMENT QUESTIONS

1. tPA is generally effective in treating poor blood flow in tunneled central venous catheters resulting from fibrin sheath formation.
A. True
B. False
2. A 57-year-old man with ESKD with a mature left brachiocephalic AVF is referred for evaluation of prolonged bleeding from the AVF on removal of the dialysis needles. The AVF is pulsatile on examination and does not collapse when the left arm is raised above the heart. An angiogram identifies a 75% stenosis at the cephalic arch, and an angioplasty is performed. According to the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines, what defines a successful percutaneous angioplasty of an arteriovenous access?
A. Less than 10% residual stenosis at the angioplasty site
B. Ability to receive eight uncomplicated, consecutive dialysis sessions after the procedure
C. Less than 30% residual stenosis and resolution of physical indicators of stenosis
D. A and B
E. B and C
3. Embedding (or burying) a newly placed PD catheter under the skin:

A. allows ingrowth of tissue into the cuffs of the catheter without an opportunity for bacterial colonization.
B. diminishes the incidence of early pericatheter infections.
C. results in better catheter function in the future.
D. A and B.
E. is of no benefit other than cosmetic.
4. Which of the following statements about ultrasound of the renal and urinary tract is false?
A. For examination of the kidneys, a renal ultrasound is always indicated in the workup of chronic kidney disease.
B. A renal ultrasound is not indicated in every patient with acute kidney injury.
C. Ultrasound is not useful in the diagnosis of bladder outlet obstruction.
D. The ureters are usually visible only when dilated.
5. Insertion of PD catheters is commonly performed using:
A. laparoscopy.
B. surgical dissection.
C. peritoneoscopy.
D. the guidewire (Seldinger) technique.
E. all the above.

REFERENCES

1. Asif A, Byers P, Vieira CF, et al. Peritoneoscopic placement of peritoneal dialysis catheter and bowel perforation: experience of an interventional nephrology program. Am J Kidney Dis. 2003;42:1270–1274.
2. Pastan S, Gassensmith C, Manatunga AK, et al. Prospective comparison of peritoneoscopic and surgical implantation of CAPD catheters. ASAIO (Am Soc Artif Intern Organs) Trans. 1991;37:M154–M156.
3. Gadallah MF, Pervez A, el Shahawy MA, et al. Peritoneoscopic versus surgical placement of peritoneal dialysis catheters: a prospective randomized study on outcome. Am J Kidney Dis. 1999;33:118–122.
4. Ash SR. Chronic peritoneal dialysis catheters: procedures for placement, maintenance, and removal. Semin Nephrol. 2002;22:221–236.
5. Crabtree JH, Fishman A. A laparoscopic method for optimal peritoneal dialysis access. Am Surg. 2005;71(2):135–143.
6. Crabtree JH, Fishman A. A laparoscopic approach under local anesthesia for peritoneal dialysis access. Perit Dial Int. 2000;20(6):757–765.
7. Scalamogna A, De Vecchi A, Castelnovo C, Ponticelli C. Peritoneal catheter outcome effect of mode of placement. Perit Dial Int. 1994;14:S81.
8. Asif A, Byers P, Gadalean F, Roth D. Peritoneal dialysis underutilization: the impact of an interventional nephrology peritoneal dialysis access program. Semin Dial. 2003;16:266–271.
9. NEW REF 3, Htay H, Johnson DW, Craig JC, Teixeira-Pinto A, Hawley CM, Cho Y. Urgent-start peritoneal dialysis versus conventional-start peritoneal dialysis for people with chronic kidney disease. Cochrane Database Syst Rev. 2020.
10. Ash SR. Bedside peritoneoscopic peritoneal catheter placement of Tenckhoff and newer peritoneal catheters. Adv Perit Dial. 1998;14:75–79.
11. Asif A, Tawakol J, Khan T, et al. Modification of the peritoneoscopic technique of peritoneal dialysis catheter insertion: experience of an interventional nephrology program. Semin Dial. 2004;17:171–173.
12. Ash S, Sequeira A, Narayan R. Imaging and peritoneal dialysis catheters. Semin Dial. 2017;30(4):338–346.
13. Zaman F, Pervez A, Atray NK, et al. Fluoroscopy-assisted placement of peritoneal dialysis catheters by nephrologists. Semin Dial. 2005;18:247–251.
14. Maya ID. Ultrasound/fluoroscopy-assisted placement of peritoneal dialysis catheters. Semin Dial. 2007;20:611–615.
15. NEW REF 4, Ash S, Sequeira A, Narayan R. Imaging and peritoneal dialysis catheters. Semin Dial. 2017;30(4):338–346.
16. Moncrief JW, Popovich RP, Broadrick LJ, et al. The Moncrief-Popovich catheter. A new peritoneal access technique for patients on peritoneal dialysis. ASAIO J. 1993;39:62–65.
17. Prischl FC, Wallner M, Kalchmair H, et al. Initial subcutaneous embedding of the peritoneal dialysis catheter—a critical appraisal of this new implantation technique. Nephrol Dial Transplant. 1997;12:1661–1667.
18. Ash SR. Chronic peritoneal dialysis catheters: overview of design, placement, and removal procedures. Semin Dial. 2003;16:323–334.
19. NEW REF 5, Asif A, Byers P, Vieira CF, et al. Peritoneoscopic placement of peritoneal dialysis catheter and bowel perforation: experience of an interventional nephrology program. Am J Kidney Dis. 2003;42(6):1270–1274.
20. Simkin EP, Wright FK. Perforating injuries of the bowel complicating peritoneal catheter insertion. Lancet. 1968;1:64–66.
21. Rubin J, Oreopoulos DG, Lio TT, et al. Management of peritonitis and bowel perforation during chronic peritoneal dialysis. Nephron. 1976;16:220–225.
22. Nkere UU. Postoperative adhesion formation and the use of adhesion preventing techniques in cardiac and general surgery. ASAIO J. 2000;46:654–656.
23. Brandt CP, Franceschi D. Laparoscopic placement of peritoneal dialysis catheters in patients who have undergone prior abdominal operations. J Am Coll Surg. 1994;178:515–516.
24. Training Guidelines for Physicians Who Evaluate and Interpret Diagnostic Ultrasound Examinations. Laurel, MD: American Institute of Ultrasound

in Medicine; 1997.

25. Gadallah MF, Arora N, Arumugam R, Moles K. Role of Fogarty catheter manipulation in management of migrated, nonfunctional peritoneal dialysis catheters. Am J Kidney Dis. 2000;35:301–305.
26. Siegel RL, Nosher JL, Gesner LR. Peritoneal dialysis catheters: repositioning with new fluoroscopic technique. Radiology. 1994;190:899–901.
27. American Society of Diagnostic and Interventional Nephrology. Guidelines for training, certification, and accreditation in placement of permanent tunneled and cuffed peritoneal dialysis catheters. Semin Dial. 2002;15:440–442.
28. Schwab SJ, Beathard G. The hemodialysis catheter conundrum: hate living with them, but can’t live without them. Kidney Int. 1999;56:1–17.
29. Vanherweghem JL, Yassine T, Goldman M, et al. Subclavian vein thrombosis: a frequent complication of subclavian vein cannulation for hemodialysis. Clin Nephrol. 1986;26:235–238.
30. NKF-K/DOQI clinical practice guidelines for vascular access: update 2000. Am J Kidney Dis. 2001;37:S137–S181.
31. Haire WD, Atkinson JB, Stephens LC, Kotulak GD. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. Thromb Haemost. 1994;72:543–547.
32. Zacharias JM, Weatherston CP, Spewak CR, Vercaigne LM. Alteplase versus urokinase for occluded hemodialysis catheters. Ann Pharmacother. 2003;37:27–33.
33. Falk A, Teodorescu V, Lou WY, et al. Treatment of “swing point stenoses” in hemodialysis arteriovenous fistulae. Clin Nephrol. 2003;60:35–41.
34. Beathard GA, Arnold P, Jackson J, Litchfield T. Aggressive treatment of early fistula failure. Kidney Int. 2003;64:1491–1494.
35. Maya ID, Oser R, Saddekni S, et al. Vascular access stenosis: comparison of arteriovenous grafts and fistulas. Am J Kidney Dis. 2004;44:859–865.
36. Sivanesan S, How TV, Bakran A. Sites of stenosis in AV fistulae for haemodialysis access. Nephrol Dial Transplant. 1999;14:118–120.
37. Badero OJ, Salifu MO, Wasse H, Work J. Frequency of swing-segment stenosis in referred dialysis patients with angiographically documented lesions. Am J Kidney Dis. 2008;51:93–98.
38. Schwab SJ, Oliver MJ, Suhocki P, McCann R. Hemodialysis arteriovenous access: detection of stenosis and response to treatment by vascular access blood flow. Kidney Int. 2001;59:358–362.
39. Beathard GA. Angioplasty for arteriovenous grafts and fistulae. Semin Nephrol. 2002;22:202–210.
40. Schon D, Mishler R. Pharmacomechanical thrombolysis of natural vein fistulas: reduced dose of TPA and long-term follow-up. Semin Dial. 2003;16:272–275.
41. Vesely TM, Hovsepian DM, Pilgram TK, et al. Upper extremity central venous obstruction in hemodialysis patients: treatment with Wallstents. Radiology. 1997;204:343–348.
42. Funaki B, Szymski GX, Leef JA, et al. Wallstent deployment to salvage dialysis graft thrombolysis complicated by venous rupture: early and intermediate results. AJR Am J Roentgenol. 1997;169:1435–1437.
43. Haskal ZJ, Trerotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. N Engl J Med. 2010;362:494–503.
44. Haskal ZJ, Saad TF, Hoggard JG, et al. Prospective, randomized, Concurrently-Controlled study of a stent graft versus balloon angioplasty for treatment of arteriovenous access graft stenosis: 2-year results of the RENOVA study. J Vasc Intervent Radiol. 2016;27(8):1105–1114.
45. Vesely T, DaVanzo W, Behrend T, et al. Balloon angioplasty versus Viabahn stent graft for treatment of failing or thrombosed prosthetic hemodialysis grafts. J Vasc Surg. 2016;64(5):1400–1410.
46. Chan MR, Bedi S, Sanchez RJ, et al. Stent placement versus angioplasty improves patency of arteriovenous grafts and blood flow of arteriovenous

fistulae. Clin J Am Soc Nephrol. 2008;3:699–705.
47. Vesely TM, Amin MZ, Pilgram T. Use of stents and stent grafts to salvage angioplasty failures in patients with hemodialysis grafts. Semin Dial. 2008;21:100–104.

References

48. Bakken AM, Protack CD, Saad WE, et al. Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. J Vasc Surg. 2007;45:776–783.
49. Vogel PM, Parise C. Comparison of SMART stent placement for arteriovenous graft salvage versus successful graft PTA. J Vasc Interv Radiol. 2005;16:1619–1626.
50. Falk A, Maya ID, Yevzlin AS. Rescue Investigators. A prospective, randomized study of an expanded Polytetrafluoroethylene stent graft versus balloon angioplasty for in-stent restenosis in arteriovenous grafts and fistulae: two-year results of the RESCUE study. J Vasc Intervent Radiol. 2016;27(10):1465–1476.

51. Vesely TM. Use of stent grafts to repair hemodialysis graft-related pseudoaneurysms. J Vasc Interv Radiol. 2005;16:1301–1307.
52. Barshes NR, Annambhotla S, Bechara C, et al. Endovascular repair of hemodialysis graft-related pseudoaneurysm: an alternative treatment strategy in salvaging failing dialysis access. Vasc Endovasc Surg. 2008;42:228–234.

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Hemodialysis: Principles and Techniques

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Hemodialysis (HD) has been in practice for more than 50 years and has extended the lives of millions of patients with kidney failure worldwide. Although the basic principles of HD are still being applied today, dialysis technology has improved markedly. The main components of the dialysis system are the extracorporeal blood circuit, the dialyzer, the dialysis machine, and the water purification system.

DIALYZER DESIGNS AND MEMBRANES

The dialyzer provides countercurrent transfer of solutes and fluid across a semipermeable membrane. The semipermeable dialysis membrane separates the blood compartment from the dialysate compartment (Table 98.1). Most current membranes are made of entirely synthetic materials, such as polyacrylonitrile, polysulfone, polycarbonate, polyamide, and polymethylmethacrylate, and are more biocompatible than cellulose-based membranes.

Transport of molecules across the dialysis membrane is driven by (1) the concentration gradient (diffusive transport) and (2) the hydrostatic pressure gradient across the membrane (convective transport).

In the case of protein-bound solutes, only their free fraction is transported across the membrane, unless so-called albumin-leaky membranes are used. The flux of solutes is also affected by their charge and the protein concentration on the blood side (Gibbs-Donnan effect).

Dialyzer efficiency increases with surface area (usually between 0.8–2.1 m2; smaller dialyzers with surface areas between 0.075–0.245 m2 are used for treatment of neonates). The dialyzer mass transfer area coefficient (KoA) for urea is a measure of the theoretically maximal possible urea clearance (mL/min). Dialyzer efficiency can be categorized based on KoA for urea as low (<500 mL/min), moderate (500–700 mL/min), and high (>700 mL/min). High-flux and medium cut-off membranes have pores large enough to allow some passage of molecules such as β2-microglobulin (molecular weight 11,800 Da), tumor necrosis factor (TNF)-α (17 kDa), and beyond.

Water permeability is defined by the ultrafiltration coefficient (Kuf) that describes the transmembrane ultrafiltration volume per hour and unit of hydrostatic transmembrane pressure in millimeters of mercury. In high-flux dialyzers, Kuf can be as high as 80 mL/h/mm Hg. Highflux and medium cut-off membranes demonstrate substantial internal ultrafiltration at the proximal part of the dialyzer and backfiltration of dialysate into the blood at the distal end of the dialyzer blood compartment. Therefore, water quality is of paramount importance when high-flux and medium cut-off dialyzers are used (see later).

SAFETY MONITORS

Safety monitors are integral parts of the dialysis machine.

Pressure monitors measure hydrostatic pressures in critical positions (Fig. 98.1)1:

✓ • ✓ Between the arterial needle and the blood pump (prepump pressure): Overly negative values may signal reduced arterial inflow and access problems.

✓ • ✓ Between the blood pump and the dialyzer inlet (postpump): A high pressure may signal dialyzer clotting.

✓ • ✓ Between the dialyzer outlet and the air trap (venous pressure): A high pressure may point toward an obstruction in the venous limb; it is important to recognize that in the event of venous needle displacement, with external bleeding, the venous pressure will remain positive.

Venous air detectors and air trap are located downstream of the venous pressure monitor. A positive signal at the air detector automatically clamps the venous line and stops the blood pump.

A blood leak detector is placed in the dialysate outflow line. Dialysate temperature is constantly monitored. Dialysate is produced by a proportioning system that mixes acid and bicarbonate concentrates with highly purified water. The concentration of ions in the dialysate translates into conductivity, which is measured by a dialysis conductivity monitor.

DIALYSATE FLUID

Water and Water Treatment

A standard 4-hour HD session exposes the patient to 120 to 160 L of water at a rate of 600 to 800 mL/min. A typical water purification plant is shown in Fig. 98.2. Water from municipal sources is filtered to remove particulate matter. Activated carbon devices, which need regular replacement, adsorb substances such as endotoxins, chlorine, and chloramines. Downstream water softeners use a resin coated with sodium ions, which are exchanged for calcium and magnesium ions before the water enters the reverse osmosis (RO) system. During RO, water is pumped at high pressure (15–20 bar) through a membrane with pores of less than 1.0 nm diameter, providing an absolute barrier for molecules larger than 100 to 300 Da. Depending on the technology used, 20% to 60% of water is rejected by the RO, meaning that water requirements are much higher than the final dialysate volume.

Standards for chemical quality of water are widely accepted, but there is less consensus regarding acceptable levels of bacterial and endotoxin contamination. The microbiologic standards for HD water, dialysis fluid, and substitution fluid vary across countries (Table 98.2).[2] Municipal water supplies may contain undesirable added substances such as aluminum and chloramines. Aluminum accumulation may result in neurologic disorder, bone disease, and erythropoietinresistant anemia. Plasma aluminum levels should be less than 1 µmol/L. Chloramines have been associated with hemolysis and methemoglobinemia. Copper and zinc may leach from plumbing components and may cause hemolysis. Lead has been associated with abdominal pain and muscle weakness. Nitrate and nitrite may cause nausea and

Dialysis Membrane Properties

TABLE 98.1
Membrane

Membrane Name (Example)

High or Low Flux

Biocompatibility

Cellulose
Semisynthetic cellulose
Cellulose diacetate
Cellulose triacetate
Diethylaminoethyl-substituted cellulose
Synthetic polymers
Polymethylmethacrylate
Polyacrylonitrile methacrylate copolymer
Polyacrylonitrile methallyl sulfonate copolymer
Polyamide
Polycarbonate-polyether
Ethylene vinyl alcohol copolymer
Polysulfone

Cuprophan

Low

Low

Cellulose acetate
Cellulose triacetate
Hemophane

High and low
High
High

Intermediate
Good
Intermediate

PMMA
PAN
PAN/AN-69
Polyflux
Gambrane
EVAL
Polysulfone

High
High
High
High and low
High
High
High and low

Good

Good
Good
Good
Good
Good
Good

Blood Circuit for Hemodialysis

Blood
pump
Arterial
pressure
monitor

“Arterial”

“Venous”

Heparin

Venous
pressure
monitor

Automatic
clamp

Dialyzer

Air
detector

A
Pressure

1

Arterial
needle

0
2

B

Arterial
blood
lines

Blood
pump

Dialyzer

Venous blood line

Fig. 98.1 Blood Circuit for Hemodialysis. (A) The blood circuit. (B) The pressure profile in the blood circuit with an arteriovenous fistula as the vascular access.

seizures. High concentrations of calcium may cause the so-called hard water syndrome, a condition characterized by nausea, vomiting, blood pressure instability, and fatigue during and after dialysis.

Gram-negative bacteria produce endotoxins, and fragments of these endotoxins may be responsible for some dialysis-related symptoms. Exposure to endotoxin is associated with rigors, hypotension, and fever. Use of a polysulfone or polyamide filter in the dialysate line may be adequate to remove endotoxins. Liquid bicarbonate dialysis

fluid concentrate distributed in a central distribution system may be a source of bacterial growth and should be replaced daily; acid concentrates in canisters and bicarbonate powder represent no bacterial growth risk.

Ultrapure water is recommended for use with high-flux dialyzers. Water used for online hemodiafiltration (HDF) must be virtually sterile and nonpyrogenic, thus fulfilling major criteria for ultrapure water.

Dialysate Solution

Dialysate is made by mixing two components, which may be provided as liquid or dry (powder) concentrates (Table 98.3). The base concentrate contains sodium bicarbonate and sodium chloride. The acid concentrate typically contains chloride salts of sodium, calcium, magnesium, and potassium, glucose monohydrate, and an organic acid, the latter in the form of acetic acid, citric acid, or lactic acid. The acid concentrate may contain the salt of an organic acid, such as sodium acetate. The purpose of the acid is to lower the dialysate pH to less than 7.3 so that calcium and magnesium do not precipitate when bicarbonate is added. Base and acid components are mixed simultaneously with purified water to make the dialysate. Dialysate proportioning pumps ensure proper mixing. One typical mixing relationship is 1:1.72:42.28 (acid concentrate to base concentrate to water; the so-called 45X preparation). Some dry acid concentrates contain sodium diacetate (8 mmol/L), which is composed of equal parts of acetic acid and sodium acetate. After mixing with bicarbonate, the final dialysate contains 8 mmol/L sodium acetate.3 Dialysate composition can be modified by small changes in the mixing ratio and adding salt solutions; potential advantages and disadvantages of dialysate modifications are shown in Table 98.4

BIOCOMPATIBILITY

The contact of blood with some lines and membranes triggers an inflammatory response. Although many components of the dialysis procedure contribute to the degree of biocompatibility, it is the membrane itself that is most important. Biocompatibility is especially important when cellulose membranes are used, whereas synthetic and reused membranes activate complement to a much lesser extent (Fig. 98.3). Activation of complement peaks at 15 minutes after the start of dialysis and lasts up to 90 minutes. Symptoms associated with activation of complement system and proinflammatory pathways include shortness of breath, chest pain, headache, nausea, vomiting, and hypotension.

Water Purification Plant

.05 micron
UF filters

Distribution loop

Hot water

UV Lamp

Temperature
gauge
Blend valve

1 micron
filter

Cold water
Multi
media
filter

Backflow
preventers

Worker
carbon
tank

Polisher
carbon
tank

Water
softener

Water storage
tank

RO
Product
divert valve

Brine
tank

VFD
Boost pump

Fig. 98.2 Water Purification Plant. The four main functional domains are water supply, water pretreatment, primary purification, and delivery to the loop. A series of filters and water softeners are the key technical pretreatment components, whereas reverse osmosis is the main component of the primary purification. Note that several features are optional, such as the water storage tank. UF, Ultrafiltration; UV, ultraviolet light; VFD, variable frequency drive. (Courtesy Rob Levin and Randy Hux, New York, NY.)

TABLE 98.2

Microbiologic Standards for Water, Concentrates, and Dialysis Fluids

National and International Standards

Year Issued

Microorganisms (CFU/mL)

Endotoxins (EU/mL)

Water
EDTA-ERA
USA (AAMI RD 52) (minimum regulatory requirement)
ISO/DIS 13959 (preferred recommendation)

2001
2004
2014

<100
<200 (action level ≥ 50)
<100 (action level t ≥ 50)

<0.25
<2 (action level ≥ 1)
<0.25 (action level ≥ 0.125)

Concentrates (Acid and Basic)
USA (AAMI RD 52)
European Pharmacopoeia, 5th ed.

2004
2005

<200 (action level ≥ 50)
—

2 (action level ≥ 1)
<0.5a

Standard Dialysis Fluid
EDTA-ERA
USA (AAMI RD 52)
ISO/FDIS 23500-5:2018(E)

2001
2004
2018

<100
<100 (action level ≥ 50)
<100 (action level ≥ 50)

<0.25
<0.5 (action level ≥ 0.25)
<0.5 (action level ≥ 0.25)

Ultrapure Dialysis Fluid Before Last Filter for Hemodiafiltration Online
EDTA-ERA
2001
<0.1
USA (AAMI RD 52)
2004

<0.1
ISO/FDIS 23500-5:2018(E)
2018
<0.1

<0.03
<0.03
<0.03

Substitution Fluid Online
EDTA-ERA
USA (AAMI RD 52)
ISO/FDIS 23500-5:2018(E)

<0.25
<0.03
Nonpyrogenic

aDiluted

2001
2004
2018

<10−6
<10−6
Sterile

to user concentration.
AAMI, Association for the Advancement of Medical Instrumentation; EDTA-ERA, European Dialysis and Transplant Association European Renal Association; ISO/FDIS, International Organization for Standardization/Final Draft International Standard; RD, renal disease.

HEMOFILTRATION, HEMODIAFILTRATION, AND INTERNAL FILTRATION AND BACKFILTRATION

Hemofiltration (HF) and HDF involve the removal of large fluid volumes from the patient, with the removed fluid replaced by substitution fluid. It is the use of substitution fluid that sets these techniques apart from simple ultrafiltration.

TABLE 98.3 Composition of Dialysates for Bicarbonate Dialysis

	CONCENTRATION	
Component	Range	Typical
Electrolytes (mmol/L)		
Sodium	135–145	138
Potassium	1.0–4.0	2.0
Calcium	1.0–1.75	1.25
Magnesium	0.5–1.0	0.75
Chloride	87–124	105
Buffers (mmol/L)		
Acetate	2–4	3
Bicarbonate	20–40	35
pH	7.1–7.3	7.2
P_{CO_2} (mm Hg)	40–100	
Glucose	0–11 (0–200 mg/dL)	5.5 (100 mg/dL)

TABLE 98.4

HF (Fig. 98.4) is a convective elimination technique by which water and solutes from the blood compartment are driven solely by positive hydrostatic pressure across the dialyzer membrane into the filtrate compartment without the use of dialysate. As a result of solvent drag effects, small and larger solutes are eliminated at a rate depending on membrane characteristics.

HDF (Fig. 98.5) combines diffusive (HD) and convective (HF) solute transport using a high-flux membrane. Fluid is removed by ultrafiltration (convective volume) and the volume of filtered fluid exceeding the volume to achieve target weight loss is replaced by ultrapure infusion solution (substitution volume). Online HDF refers to the online production by the dialysis machine of ultrapure, nonpyrogenic dialysate, which is also used as infusion solution. High-volume HDF refers to an effective convection volume of more than 23 L per dialysis. HDF modalities are further characterized by the site of infusion of substitution fluid.

Postdilution Hemodiafiltration

The substitution fluid is infused to the patient downstream of the dialyzer. Filtration is limited by hemoconcentration in the dialyzer. Postdilution HDF is most efficient in terms of increasing solute removal.

Predilution Hemodiafiltration

Substitution fluid is added upstream of the dialyzer and immediately removed by convection. For an identical substitution volume, the efficiency of this mode is lower than that of postdilution HDF because of the dilution of solute blood concentrations before the dialyzer and consecutive and thus a reduction of in the transmembrane gradient.

Advantages and Disadvantages of Modifications in the Dialysate Composition

Component

Advantage

Disadvantage

Sodium
Increased

Hemodynamic stability

Postdialytic thirst; increased postdialytic serum sodium levels; increased intradialytic weight gain; high blood pressure
Intradialytic hemodynamic instability

Decreased
Potassium
Increased

Reduced osmotic stress in the presence of predialytic hyponatremia

Hyperkalemia

Decreased

Fewer arrhythmias in digoxin intoxication with hypokalemia; may improve hemodynamic stability
Increased dietary potassium intake

Calcium
Increased

Suppresses PTH, increased hemodynamic stability

Decreased

Permits more liberal use of calcium-containing phosphate binders

Hypercalcemia, vascular calcification, adynamic bone disease resulting from PTH suppression
Stimulation of PTH, reduced hemodynamic stability

Bicarbonate
Increased
Decreased

Acidosis control improved
No postdialytic alkalosis

Postdialytic alkalosis; increased mortality
Promotes acidosis; increased mortality

Hemodynamic stability, fewer arrhythmias, suppresses PTH
Permits use of magnesium-containing phosphate binders; improved bone mineralization; less bone pain

Altered nerve conduction, pruritus, renal bone disease
Arrhythmias, muscle weakness and cramps, elevated PTH

Avoidance of intradialytic hyperglycemia and hyperinsulinemia
Lower risk for disequilibrium
Heparin-sparing effect

Increased risk for disequilibrium (rare), hypoglycemia
Intradialytic hyperglycemia and hyperinsulinism
High blood citrate levels in liver failure

Magnesium
Increased
Decreased
Glucose
Decreased
Increased
Citrate

PTH, Parathyroid hormone.

Arrhythmias; risk for sudden death

Mechanisms of Dialysis Membrane Incompatibility
Blood
Factor XII
activation
Dialysis
membrane

Coagulation
Activation of kallikrein

Bradykinin release

Activation of alternative
complement pathway

Generation of C5a

Mast cell

Neutrophil

Mast cell activation

Neutrophil activation

Monocyte

Platelet

Monocyte activation

Platelet activation

Thrombocytopenia
Release of histamine Neutrophil degranulation Release of interleukin-1
and TNF-α
Thromboxane release
and leukotrienes
Release of adhesion
receptors and LTB4
Prostaglandin release
Bronchoconstriction
and vasodilation

Endothelial damage
Release of
β2-microglobulin

Hypotension and fever

Fig. 98.3 Mechanisms of Dialysis Membrane Incompatibility. Pathways involved in the body’s response
to dialysis membranes. LTB4 Leukotriene B4; TNF-α tumor necrosis factor-α

Circuit for Hemodiafiltration

Circuit for Hemofiltration

Blood in

Blood in
Predilution

Predilution

High-molecularweight uremic
toxin

Middle molecules
Substitution fluid
free water-soluble
low-molecularweight solutes

Low-molecularweight uremic
toxin

Substitution fluid

Diffusive flow

Convective flow
Filtrate out

Dialysate out (to waste)

Convective flow
Postdilution

Dialysate in

Postdilution

Blood out
Fig. 98.4 Circuit for Hemofiltration. Substitution fluid is typically administered either predilution or postdilution but not both.

Blood out
Fig. 98.5 Circuit for Hemodiafiltration. Substitution fluid is typically administered either predilution or postdilution but not both.

To achieve comparable efficiency to postdilution HDF, substitution volume needs to be doubled.

clearance and avoiding the consequences of a high transmembrane pressure and hemoconcentration.

Mixed Dilution Hemodiafiltration

Mid-Dilution Hemodiafiltration

Replacement fluid is infused both upstream and downstream of the dialyzer. The ratio of upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximizing

Replacement fluid is infused within specifically designed dialyzers partway down the blood pathway so that the first part of the blood circuit is operated in postdilution and the second part in predilution mode.

Internal Filtration and Backfiltration

Ultrafiltration does not occur in a uniform manner across the entire length of a dialyzer. Several characteristics such as blood and dialysate flows, membrane characteristics, and dialyzer geometries define the internal flow characteristics. In high-flux dialyzers, ultrafiltration dominates in the proximal (upstream) part, whereas backfiltration of dialysate takes place more distally (downstream). The backfiltration has raised concerns in the absence of ultrapure dialysate because endotoxin fragments and other bacterial substances may enter from the dialysate into the patient’s blood, possibly aggravating inflammatory response. Medium cut-off membranes were designed for high rates of filtration and backfiltration with the expectation that their use would enhance clearance of middle molecules. A recent randomized controlled trial (RCT) showed larger reduction ratios for complement factor D, free k light chains, TNF-α, and β2-microglobulin with a medium cut-off membrane versus a high-flux dialyzer.4 In a cross-over RCT, after 3 months of medium cut-off membrane use, a significant decrease in serum levels of albumin, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D was seen,5 possibly related to the loss of vitamin D–binding protein (52 kDa).

UREMIC TOXINS AND THEIR REMOVAL BY HEMODIALYSIS

Uremic toxins have been traditionally categorized based on their molecular weight and binding properties (Table 98.5). Recent research has identified the gut, in particular the colon, as an important source of uremic toxins and their precursors. These colon-derived toxins are products of bacterial metabolisms, such as phenols, indoles, and amines.

Low-molecular-weight compounds not bound to protein: These include urea and guanidines such as asymmetric dimethylarginine (ADMA), purines, pyrimidines, oxalate, phosphorus, and uric acid. Modern dialysis membranes achieve maximal removal of these compounds.

Low-molecular-weight compounds bound to protein: These include indoxyl and cresyl compounds, advanced glycation

TABLE 98.5

Organic Uremic Solutes

Free Water-Soluble Low-Molecular-Weight Solutes MW (Da) Protein-Bound Solutes MW (Da) Middle Molecules

Guanidines
ADMA
Argininic acid
Creatinine
Guanidine
Methylguanidine
Peptide
β-Lipotropin
Polyols
Erythritol
Myoinositol
Sorbitol
Threitol

Cytokines
Interleukin-1β
Interleukin-6

Tumor necrosis factor-α
Peptides
Adrenomedullin
ANP
β2-Microglobulin

5,729
3,080
11,818

251

β-Endorphin

3,465

Melatonin

126

Cholecystokinin

3,866

Cystatin C
Delta sleep-inducing peptide
Hyaluronic acid

13,300
848
25,000

Leptin
Neuropeptide Y

16,000
4,572

PTH
Retinol-binding protein

9,225
21,200

AGEs
3-Deoxyglucosone
Fructoselysine
Glyoxal
Pentosidine
Hippurate
Hippuric acid

179

461

Indoles
Indoxyl sulfate

122
180
182
122

202
175
113
59
73

Purines
Cytidine
Hypoxanthine
Uracil

234
136
112

Uric acid
Xanthine

168
152

Pyrimidines
Orotic acid
Thymine
Uridine

174
126
244

Ribonucleosides
1-Methyladenosine
Pseudouridine
Xanthosine

281
244
284

Other
Malondialdehyde
Oxalate
Urea

71
90
60

MW (Da)

162
308
58
342

Quinolinic acid

167

Phenols
Hydroquinone
p-Cresol
Phenol

110
108
94

Polyamines
Putrescine
Spermidine
Spermine

88
145
202

Other
Homocysteine

135

Other
Complement factor D

32,000
24,500
26,000

23,750

ADMA, Asymmetric dimethylarginine; AGEs, advanced glycation end-products; ANP, atrial natriuretic peptide; MW, molecular weight; PTH, parathyroid hormone.

end-products, TNF-α, and phenolic compounds. Clearances of the unbound fraction may be increased by use of HDF, especially postdilutional modes. “Leaky” dialysis membranes and possibly medium cut-off membranes increase the clearance of protein-bound solutes in relationship to the pore size distribution of the membrane.

Middle molecule compounds: Traditionally, middle molecules encompass substances with a molecular weight between 5 and 32 kDa.

Their removal is increased when using high-flux dialyzers, highvolume HDF, and medium cut-off membranes.

The clinical benefits of increased removal of protein-bound solutes and specific middle molecules have not been evaluated in appropriate clinical trials.

end with a lower one (e.g., 135 mmol/L). Some patients with hemodynamic instability may benefit from this option in which the initial sodium concentration is kept high and then slowly reduced to avoid sodium loading. Stepwise profiling was shown to be effective in reducing intradialytic hypotensive episodes.[10] Sodium profiling may result in dialytic sodium loading that may manifest itself in increased thirst, interdialytic weight gain, and blood pressure. In patients presenting with these signs and symptoms, the need for sodium profiling should be critically re-evaluated. Using conductivity measurements of dialysate, some modern dialysis machines allow the user to target a specific dialytic sodium balance.

Online Clearance Monitoring

Sodium and urea clearances are identical for practical purposes. The conductivity of the dialysate is largely a function of the dialysate sodium concentration, and online clearance monitors use this feature to compute the urea clearance (K) of a dialyzer during a dialysis treatment.

ADDITIONAL DEVICES AND TECHNOLOGIES

Relative Blood Volume Monitoring

Blood volume monitors provide continuous noninvasive monitoring of relative changes in blood volume by continuously measuring plasma protein concentration using ultrasound or hematocrit by optical scattering. A sharp decline in relative blood volume (RBV) may precede intradialytic hypotension. In the RCT Crit-Line Intradialytic Monitoring Benefit (CLIMB) study, mortality was higher in patients using RBV monitoring compared with conventional monitoring. However, because of an atypically low mortality rate in the conventional monitoring group, the authors pointed out that these findings should be generalized to the HD population in the United States with caution.[6] In an observational study of 842 maintenance hemodialysis patients, specific ranges of RBV ranges have been shown to be associated with improved all-cause mortality.[7] In this study, two-thirds of patients showed a decline of RBV by less than 8% 3 hours into the treatment, possibly indicating fluid overload. In clinical practice, flat RBV curves may prompt a re-evaluation of the target weight. In some dialysis machines, the rate of blood volume change is used to automatically adjust ultrafiltration rates and dialysate sodium concentration (feedback control). This approach has been shown to reduce the frequency of symptomatic intradialytic hypotension in some, but not all, studies.[8, 9]

Ultrafiltration Profiling

The ultrafiltration rate is usually kept constant but can be changed during the dialysis session in a preprogrammed manner (ultrafiltration profiling). It may be advantageous to remove a large proportion, such as two-thirds of the prescribed total ultrafiltration volume, in the first half of the HD session. The clinical benefits of ultrafiltration profiling are under debate.

Sodium Profiling

Normally, the dialysate sodium concentration is kept constant throughout the dialysis treatment. The variable sodium option allows dynamic changes of the dialysate sodium concentration during the treatment (sodium profiling). Typically, such treatments would start with a high dialysate sodium concentration (e.g., 145 mmol/L) and

TABLE 98.6

Blood Temperature Monitoring and Dialysate Cooling

In most patients, HD exerts a net positive thermal balance that may affect hemodynamic stability. “Cool” dialysate has been shown to improve vascular stability during dialysis. An RCT showed cardiac and brain white matter protection with individualized cooling at 0.5°C below body temperature.11 12 The most precise control of a patient’s temperature during dialysis is enabled by a body temperature monitor (BTM) that adjusts in a feedback loop the dialysate temperature to attain a prescribed thermal balance and core temperature. Alternatively, tympanic temperature can be used to prescribe the dialysate temperature (e.g., 0.5°C below tympanic temperature). In some studies, the dialysate temperature was set to 35°C irrespective of the patient’s body temperature.

Intradialytic Oxygen Measurement

Blood coming from a functioning arteriovenous access resembles arterial blood. Some devices and dialysis machines measure predialyzer blood oxygen saturation. In an observational study, patients with prolonged intradialytic hypoxemia showed greater morbidity and mortality.13 In HD patients with central venous catheter as vascular access, a low central venous oxygen saturation is associated with intradialytic hypotension.14

HOME HEMODIALYSIS

Home HD (HHD) offers several clinical benefits compared with conventional renal replacement therapies, such as better survival, enhanced blood pressure control and left ventricular geometry, normalization of phosphate balance, augmentation of kidney-specific quality of life scores, and improved fertility.15 HHD also provides greater patient autonomy in a cost-effective manner.16 There are variations in HHD prescription and practices (Table 98.6). Additionally, conventional HD platforms and low dialysate flow systems may be used in the home. Several considerations should be addressed before starting patients on HHD. Routinely, a home visit should be conducted before

Home Hemodialysis Prescription and Practices

Treatments per week
Treatment time (hours)
Blood flow rate (mL/min)
Dialysate flow rate (mL/min)

Conventional

Short Daily

Nocturnal

Low Dialysate Flow Systems

3
4

400
500

6
2–3
400
800

5–6
6–8
200
300

6
2.5–3.5
400
130

starting home dialysis to assess for feasibility and the potential need for renovations and modifications. The Advancing American Kidney Health Initiative was announced in 2019, which aimed to ensure that 80% of incident patients with end-stage kidney disease will receive home-based dialysis or a kidney transplant by 2025. Given the change in policy, it is anticipated that there will be a global growth in home therapies.

DIALYSIS MACHINE CHOICE AND OTHER EQUIPMENT

The choice of machine should be tailored to the patient's individual requirements and preference, and it will also determine the ease of dialysis fluid preparation. Additionally, the availability of appropriate water, electrical supply, and space may influence the choice of HD machine. Conventional HD platforms will require water filtration systems, whereas others (i.e., low-dialysate flow systems) may use prepackaged dialysate or generate online dialysis solutions. Premixed bags are available with bicarbonate-buffered or lactate-buffered dialysate. All types of vascular accesses may be used for HHD. Registry data suggest that permanent vascular access has superior outcomes compared with tunneled HD catheters. Moreover, the use of buttonhole cannulation (compared with the stepladder technique) is associated with higher infectious complications and hence should be reserved for selected patients only.

WATER PREPARATION, STANDARDS, AND PLUMBING

As for in-center HD, prevailing standards for water quality should be adhered to (see previous discussion). Depending on the local water conditions and regulations, water softener, backflow preventers, and blending devices may be necessary in the home. In certain circumstances, feeder tanks may be necessary to provide the water pressure necessary for the RO unit and dialysis machine to function properly.

SAFETY

All dialysis machines are equipped with monitors, as described earlier. Leak and moisture detectors should be placed around vascular access cannulation sites, under the dialysis machine, and at the water treatment system. For central venous catheters, special connectors or catheter safety lock boxes can be used. Telemonitoring systems have been employed for HHD, but they are not a prerequisite. Practically, most HHD users continue to rely on an "on-call" system for troubleshooting. Typically, arterial and venous pressure alarms are the most common type of alarms. The average number of alarms per night decreased significantly over time as patients gained experience with HHD (from a maximum of 1.98 ± 3.31 alarms/night to a low of 0.74 ± 1.63 alarms/night) according to the London Ontario experience.

Activities to Reduce the Environmental Footprint of Hemodialysis

BOX 98.1

Electricity
- Reporting of energy consumption
- Energy-efficient dialysis machine implementation
- Use of light sensors and lighting timers
- Switch to LED bulbs

- Reduced facility size
- Integration of dialysis unit into a high environmental-quality building
- Change or tuning of air treatment systems

Water

- Reporting of water usage
- Water-efficient dialysis machine implementation
- Change in water treatment system

Care-Related Waste

- Reporting of waste produced
- Regular audits of waste management
- Caregiver training for waste sorting

LED, Light-emitting diode.

Modified from Bendine G, Autin F, Fabre B, et al. Haemodialysis therapy and sustainable growth: a corporate experience in France. Nephrol Dial Transplant. 2020;35:2154–2160.

WEARABLE ARTIFICIAL KIDNEY

Wearable artificial kidneys (WAKs) have been successfully tested in clinical trials, proving that this technology is safe and a potential future form of renal replacement therapy. At their current stage, however, WAKs are not yet suitable for routine use, facing formidable challenges such as anticoagulation, toxin clearance, and fluid removal.

“GREEN” HEMODIALYSIS

Hemodialysis is a resource-intensive treatment that uses substantial amounts of energy and water and produces plastic and other waste. The annual per-patient carbon footprint of 6-chair satellite dialysis unit has been calculated to be 10.2 tonnes of CO_2 equivalents. Importantly, environmental responsibility awareness, staff education, and improved technology can substantially improve the environmental footprint of hemodialysis. By implementing systemwide changes (Box 98.1), between 2005 and 2018, a French dialysis network was able to reduce water use from 801 to 382 L/session, power use from 23.1 to 16.3 kWh/session, and waste from 1.8 to 1.1 kg/session.[17] Additional measures call for recycling reverse osmosis water, renewable energy use, commingled recycling, polyvinyl chloride plastic recycling, secured bicycle parking, shower and changing facilities for bike riders, videoconferencing, and telemedicine. Little is known about the ecological impact of peritoneal dialysis. “Green” dialysis is likely to evolve as a major topic in the years to come.

SELF-ASSESSMENT QUESTIONS

1. Which statement is correct?

A. Bacterial endotoxin in the HD fluid cannot pass through the dialysis membrane.

B. An increase in HD fluid sodium concentration will always raise the serum sodium level.

C. HD fluid buffers include anions such as bicarbonate diacetate, chloride, and citrate.

D. HD fluid potassium concentrations of 1 mEq/L are safer than 3 mEq/L.

2. Which statement is correct?

A. A high-protein diet will eventually reduce the level of uremic toxins in the blood.

B. Urea is considered a powerful uremic toxin.

C. Some uremic toxins are synthesized in the colon and absorbed into the bloodstream.
D. HDF is highly efficient in removing protein-bound uremic toxins.
3. Which statement is correct?
A. A typical symptom of hard water syndrome is spiking fever during hemodialysis.
B. Medium cut-off membranes showed significantly improved survival in a randomized controlled trial.
C. Predilution HDF is most efficient in terms of increasing solute removal.
D. Dialysate cooling is an effective means to increase hemodynamic stability.
4. Which statement is correct?
A. Intradialytic hypoxemia is associated with poor outcomes.

B. Sodium profiling is a preferred way to treat patients with intradialytic hypertension.
C. In patients with predialysis serum potassium levels greater than 6.2 mEq/L, a dialysate potassium concentration of 0 mEq/L is warranted.
D. Home HD is not advised in patients with diabetes mellitus.
5. Which statement is correct?
A. A positive venous pressure is a reliable indicator of correct needle placement.
B. Water treatment is key to the preparation of adequate dialysis fluid.
C. Intradialytic hypoxemia is associated with poor outcomes.
D. Modern dialyzer membranes combine polysulfone with cellulose.

REFERENCES

1. Misra M. The basics of hemodialysis equipment. Hemodial Int. 2005;9(1):30–36.
2. Glorieux G, Neirynck N, Veys N, et al. Dialysis water and fluid purity: more than endotoxin. Nephrol Dial Transplant. 2012;27(11):4010–4021.
3. Kohn OF, Kjellstrand CM, Ing TS. Dual-concentrate bicarbonate-based hemodialysis: know your buffers. Artif Organs. 2012;36(9):765–768.
4. Weiner DE, Falzon L, Skoufos L, et al. Efficacy and safety of expanded hemodialysis with the Theranova 400 dialyzer. A randomized controlled trial. Clin J Am Soc Nephrol. 2020;15:1310–1319.
✓ 5.✓ Belmouaz M, Bauwens M, Hauet T, et al. Comparison of the removal of uraemic toxins with medium cut-off and high-flux dialysers: a randomized clinical trial. Nephrol Dial Transplant. 2020;35:328–335.
6. Reddan DN, Szczech LA, Hasselblad V, et al. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. J Am Soc Nephrol. 2005;16(7):2162–2169.
7. Preciado P, Zhang H, Thijssen S, et al. All-cause mortality in relation to changes in relative blood volume during hemodialysis. Nephrol Dial Transplant. 2019;34(8):1401–1408.
8. Nesrallah GE, Suri RS, Guyatt G, et al. Biofeedback dialysis for hypotension and hypervolemia: a systematic review and meta-analysis. Nephrol Dial Transplant. 2013;28(1):182–191.
9. Leung KCW, Quinn RR, Ravani P, et al. Randomized crossover trial of blood volume monitoring–guided ultrafiltration biofeedback to reduce intradialytic hypotensive episodes with hemodialysis. Clin J Am Soc Nephrol. 2017;12(11):1831–1840.
10. Dunne N. A meta-analysis of sodium profiling techniques and the impact on intradialytic hypotension. Hemodial Int. 2017;21(3):312–322.
11. Odudu A, Eldehni MT, McCann GP, et al. Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. Clin J Am Soc Nephrol. 2015;10(8):1408–1417.
12. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. J Am Soc Nephrol. 2015;26(4):957–965.
13. Meyring-Wösten A, Zhang H, Ye X, et al. Intradialytic hypoxemia and clinical outcomes in patients on hemodialysis. Clin J Am Soc Nephrol. 2016;11(4):616–625.
14. Keane DF, Raimann JG, Zhang H, et al. The time of onset of intradialytic hypotension during a hemodialysis session associates with clinical parameters and mortality. Kidney Int. 2021;S0085–2538(21):00190–00193.
15. Walker R, Marshall MR, Morton RL, et al. The cost-effectiveness of contemporary home haemodialysis modalities compared with facility haemodialysis: a systematic review of full economic evaluations. Nephrology (Carlton). 2014;19(8):459–470.
16. Heidenheim AT, Leitch R, Kortas C, et al. Patient monitoring in the London daily/nocturnal hemodialysis study. Am J Kidney Dis. 2003;42(1 suppl):61–65.
1✓ 7.✓ Bendine G, Autin F, Fabre B, et al. Haemodialysis therapy and sustainable growth: a corporate experience in France. Nephrol Dial Transplant. 2020;35:2154–2160.

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Hemodialysis: Dialysis Prescription and Adequacy

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From an idealistic perspective, an adequately treated hemodialysis (HD) patient is physically active, well nourished, and euvolemic with a maintained good quality of life and a life expectancy comparable to that of similarly aged persons with normal kidney function. The HD treatment remains a critical aspect of the multifactorial management necessary to achieve these goals. Adequacy of HD treatment today encompasses more than just the fractional replacement of excretory kidney function (dialysis dose) and extends to the prevention of intradialytic and interdialytic complications, particularly the maintenance of hemodynamic stability and symptom control. Elderly patients, the largest group of prevalent and incident dialysis patients worldwide, are especially vulnerable to hemodynamic and osmotic effects of dialysis treatment and therefore require a special approach in dialysis prescription.

ASSESSMENT OF DIALYSIS DOSE

Similar to native kidney function, the delivered dose of dialysis is conventionally assessed by the mass removal of selected uremic solutes from the patient’s body. For decades, small solute clearance, assessed solely by urea as a surrogate marker, has been emphasized in clinical practice guidelines and used as measure for quality assessment and/or payment. However, evidence for relationships between small solute clearance, plasma levels of these solutes, and clinical outcomes and symptomatology is weak. Small solute clearance reflects only one of many aspects of dialysis care that are likely to affect outcomes.

Markers of Uremic Toxin Removal by Kidney Replacement Therapy

Urea Removal

Among all potential uremic toxins, only urea, a 60-Da water-soluble compound, is established as a marker of uremic solute retention and removal. Urea, which itself causes little toxicity, is a metabolite of amino acid metabolism, and urea generation therefore depends on protein intake and the balance between protein anabolism and catabolism. Urea removal was originally considered to be a good proxy for removal of pathogenic water-soluble solutes. However, it is now known that urea removal does not closely parallel the removal of other small water-soluble compounds and correlates poorly with removal of middle molecules and protein-bound solutes.1 Nevertheless, detailed knowledge of urea kinetics is essential for the general understanding of the physics and basic principles of solute accumulation and removal in dialysis.

In a state of homeostasis, urea is evenly distributed throughout whole body water. Urea easily transfers across cell membranes by diffusion and specific urea transporters, allowing for rapid equilibration within its distribution volume after dialytic removal from the blood compartment. For almost all other water-soluble small and middle

molecular weight toxins, the intercompartmental transfer rate is much slower, leading to protracted equilibration between the various compartments and thus different removal kinetics during dialysis.2 Urea removal from the body during dialysis is expressed either by urea reduction ratio (URR) or by the treatment index Kt/V. Although urea removal alone is not a sensitive marker of dialysis adequacy, it is still the standard measure to quantify removal of low molecular weight solutes during dialysis treatment. The dialysis dose ideally should be evaluated in conjunction with residual kidney function (RKF) assessed with the same uremic toxin.

Intradialytic Urea Kinetics

Dialyzers are highly efficient at removing urea from the blood, reducing plasma urea concentration during one dialyzer passage by over 90%. However, the urea clearance of the dialyzer itself is only a marker of dialyzer efficiency but not of dialysis dose, which is based on the fractional removal of urea from the whole body. The kinetics of plasma urea concentration during dialysis is satisfactorily described by a twocompartment model in which the intravascular blood compartment is replenished with urea through redistribution from extravascular compartments. The dynamics of urea redistribution depend on the urea gradient between the two compartments and on blood flow in the various tissue regions. Because intercompartmental redistribution is not immediate, urea concentration in the blood compartment during dialysis is lower than in the extravascular compartment. After a dialysis treatment, urea rebound occurs, which takes 30 to 60 minutes until full equilibration between all compartments is achieved.

Mathematical models based on the difference in predialysis and postdialysis serum urea concentration have been applied to describe intradialytic urea kinetics including URR, single-pool Kt/V (spKt/V), equilibrated Kt/V (eKt/V), and weekly standard Kt/V (stdKt/V).

The classic single-pool urea kinetic model (spKt/V) assumes singlecompartment characteristics where full equilibration between blood and tissue compartments occurs immediately and the change in serum urea follows first-order kinetics, with a linear decline and no urea rebound (see Fig. 99.1, dashed line).3 The more physiologic “equilibrated” doublepool urea kinetic model (eKt/V) considers the urea redistribution kinetics between the two compartments (Fig. 99.1, solid line).

Urea Reduction Ratio

URR, which refers to the treatment-related reduction of serum urea concentration, is a simple but rather imprecise way to quantify dialysis dose because it does not consider intradialytic urea generation and convective urea removal by ultrafiltration, and it is a single-pool measurement (Table 99.1). Despite these limitations, URR correlates quite well with dialysis outcome and is an accepted method for assessment of dialysis dose. A minimum URR of 65% to 70% is considered an adequate dialysis dose.2

Single-Pool Kt/V and Equilibrated Kt/V

The treatment index Kt/V is the most widely used parameter to assess dialysis dose. Kt/V is a dimensionless number representing the total plasma volume cleared (K × t, in liters) in relation to the individual volume of distribution (V, in liters). The concept of Kt/V may be applied to any substance but in clinical practice is almost exclusively used for urea, where K is the dialyzer blood water urea clearance (in liters/hour), t is dialysis session length (hours), and V is the distribution volume of urea (in liters), which equates closely to total body water. A delivered Kt/V of 1.0 implies that the volume of plasma cleared of urea (K × t) during a dialysis session is equal to urea distribution volume (V). However, because of the multicompartment kinetics of urea equilibration, and constantly ongoing urea generation, clearing a plasma volume equivalent to 1 unit of total body water (V) does not mean that all urea has been removed from body water.

In daily clinical practice, single-pool Kt/V (spKt/V) is computed from the Daugirdas equation, which is based on URR but also accounts for intradialytic urea generation and ultrafiltration volume.3 The Daugirdas equation is validated for an spKt/V range between 0.8 and

Urea Kinetics During Hemodialysis
80

Cpre

BUN (mg/dL)

Single pool
Double pool

Ceq
Cpost

20
0

1

2

3

4

5

6

Time (hours)

Fig. 99.1 Urea Kinetics During Hemodialysis. Urea kinetics is determined by the difference between predialysis (C pre) and postdialysis (Cpost) blood urea nitrogen (BUN). The single-pool Kt/V model assumes no relevant change in BUN concentration after termination of dialysis except for a slow constant increase as a result of BUN generation (orange dashed line). The double-pool Kt/V model (red line) more accurately describes the in vivo situation, in which intercompartmental urea redistribution leads to a urea rebound until full equilibration between blood and tissue compartments is reached. Equilibrated postdialysis BUN concentration (Ceq) can be mathematically predicted from postdialysis BUN (Cpost).

TABLE 99.1

2.0 and is widely used because of its simplicity and accuracy. However, spKt/V somewhat overestimates the delivered dialysis dose because nonequilibrated postdialysis urea concentration is used for computation. The magnitude of the difference between equilibrated and nonequilibrated postdialysis urea concentration depends on the intensity of dialysis; the shorter and more intense a treatment, the higher is the postdialysis urea rebound and the larger the difference. Using eKt/V formulas, which include an estimate of equilibrated postdialysis urea concentration, grants a more accurate estimate of delivered dialysis dose. Because equilibrated post-HD serum urea concentrations are higher than nonequilibrated concentrations, eKt/V is always lower than spKt/V for any treatment (Table 99.1).

Correct assessment of Kt/V requires accurate timing of blood collections. Predialysis blood samples are collected right at the start of the treatment and postdialysis samples immediately before termination of treatment after slowing the blood flow rate to reduce any potential effect of recirculation. Blood sampling procedures should be standardized.2 URR, spKt/V, or eKt/V should be assessed regularly and the dialysis prescription adjusted accordingly. In large observational studies, mortality was higher at spKt/V of less than 1.2, and a target spKt/V of 1.4 is recommended as the minimum dose for conventional thriceweekly dialysis schedules.2 Many HD machines today provide some option to monitor spKt/V online during each single dialysis session without the need for pre- or postdialysis blood sampling. However, a weakness of online methods remains the inability to measure the volume of urea distribution directly.

Weekly Dialysis Dose and Weekly Standard Kt/V

60

40

A useful way to compare native kidney function with dialysis dose across a wide variety of dialysis modalities and frequencies is by looking at an average clearance (in milliliters per minute) of a given solute achieved over a unifying period, such as 1 week. The established parameter developed for this comparison is the weekly standard Kt/V for urea (stdKt/V). With this concept, a thrice-weekly intermittently provided dialysis urea clearance (e.g., 250 mL/min for 4 hours thrice weekly and 0 mL/min for the remaining 6.5 days per week) is converted to an equivalent continuous extracorporeal urea clearance (in mL/min) related to urea distribution volume V (in milliliters).4 The resulting dimensionless stdKt/V value is directly compatible with the continuous native residual kidney clearance expressed as kidney Kt/V and peritoneal clearance (weekly peritoneal Kt/V). The principle of stdKt/V is visualized in Fig. 99.2, in which on the x-axis the eKt/V of a representative dialysis session is plotted onto a curve representing the prescribed treatment frequency, and the resulting stdKt/V is then derived from the intercept with the y-axis. The frequency curves are not linear because the decreasing transmembrane urea gradient over time results in decline of the efficiency in dialysis urea mass removal. Independent of the treatment schedule, a minimum stdKt/V of 2.1

Computation of Dialysis Dose a Results Derived From Different Model Equations

Formula

Result

Comment

$URR = (1 - Ct/C0) \times 100\%$
$Kt/V = \ln(C0/Ct)$
$spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5R) \times UF/W$
$eKt/V = spKt/V - 0.6 \times spKt/V/t + 0.03$
$eKt/V = spKt/V - 0.47 \times spKt/V/t + 0.02$

67%
1.10
1.33
1.16
1.20

Urea rebound, urea generation, and ultrafiltration not taken into account
Urea rebound, urea generation, and ultrafiltration not taken into account
Single-pool model; urea rebound not taken into account
Double-pool model for arteriovenous access, including urea rebound
Double-pool model for central venous access, including urea rebound

aCalculations

1101

based on t = 4 hours.
C0 = 90 mg/dL, Ct = 30 mg/dL, UF = 3 L, W = 72 kg, R = C t/C0.
BUN, Blood urea nitrogen; C0, predialysis BUN; Ct, nonequilibrated postdialysis BUN; eKt/V, equilibrated Kt/V; Kt/V, treatment index; spKt/V, singlepool Kt/V; t, dialysis duration; UF, ultrafiltration volume; URR, urea reduction ratio; W, postdialysis weight.

Intradialytic Kinetics of Phosphate Removal and Mobilization

8

No. of HD treatments per week
6
5
4
3

7
stdKt/V per week

Serum phosphate (% baseline)

The stdKt/V Concept

6
5
4
3

PD

2

1.0
0.8
0.6
iP-Serum-Conc.

0.4

iP-Mobilization
0.2
iP-Elimination

0.0

1

0.0

0
0.5

1.0

1.5

2.0

2.5

eKt/V per treatment

Fig. 99.2 Weekly stdKt/V Concept. The weekly stdKt/V for any hemodialysis (HD) frequency is derived by plotting eKt/V of a representative dialysis session onto the respective frequency curve. PD, Peritoneal

dialysis.

accounting for kidney Kt/V is recommended for all patients.2 5 In anuric patients this is achieved with a thrice-weekly delivered spKt/V of 1.2 per treatment.

MIDDLE MOLECULE REMOVAL

It is widely held that retention solutes of middle molecular size may play an important role in the pathogenesis of uremia and contribute significantly to the high mortality of dialysis patients. Because of higher membrane porosity, high-flux dialyzers can remove larger amounts of middle molecules than low-flux dialyzers, and this is further increased using convective dialysis strategies, such as hemodiafiltration (HDF) and expanded HD (HDx).6 Because of slow intercompartmental redistribution rates, middle molecule removal is limited during conventional 4-hour dialysis sessions, and β2-microglobulin, a surrogate for uremic middle molecules, is more effectively removed by high-flux dialysis. Predialysis β2-microglobulin levels were found to be related to mortality in patients randomly assigned to high-flux or low-flux dialyzers,7 and certain vulnerable patient groups (e.g., those with diabetes) may gain some extra benefit from high-flux dialysis, although this is controversial.8 9 The European Best Practice Guidelines recommend the use of synthetic high-flux membranes to reduce cardiovascular risk and improve control of hyperphosphatemia and anemia.10

High-volume online HDF provides the largest removal of the widest range of low and middle molecular size solutes. Diffusive and convective solute elimination are maximized to the benefit of the removal of larger molecular size solutes. Because diffusive urea clearance during standard HD treatment is already high and increases by less than 10% when convective clearance is added, urea removal is not an adequate marker of treatment dose in convective dialysis modes. In HDF, mass removal of middle molecules is directly related to ultrafiltration volume, which is also referred to as convection volume (CV) (see Chapter 98). The effective CV is used as key quantifier for HDF dosing, where the term effective principally relates to the undiluted blood water volume removed by filtration. Thus, in postdilution mode, the effective CV is identical to total CV, whereas in predilution or mixed-dilution mode, the effective CV is considerably lower than total CV.11

Various randomized controlled studies failed to demonstrate an overall survival advantage with postdilution high-volume online

0.5

1.0

1.5 2.0 2.5 3.0 3.5 4.0
Dialysis time (h)

Fig. 99.3 Intradialytic kinetics of phosphate removal and mobilization. iP, Inorganic phosphate.

HDF to conventional low-flux or high-flux HD. However, an individual patient data analysis of these trials demonstrated a significantly reduced mortality risk for patients receiving more than 23 L of effective CV normalized to a body surface area of 1.73 m^2 in postdilution HDF mode.12 Adjustment of target HDF dose to some measure of body size makes sense because the generation rate and distribution volume of uremic toxins are both related to body mass.

Phosphate Removal

Because hyperphosphatemia is a strong risk factor for cardiovascular mortality, predialysis serum phosphate levels should be lowered toward the normal range in all patients (see Chapter 88).13 Management of hyperphosphatemia is based on phosphate removal by dialysis, dietary phosphate restriction, and intestinal phosphate binding with use of phosphate binder medication. Despite its low molecular weight, the effective molecular size of phosphate (because of a rather stable coating with several water moieties) is much bigger than that of other low molecular weight solutes, which impairs intercompartmental and transmembrane phosphate redistribution during dialysis. Intradialytic phosphate kinetics resembles much more those of middle molecules, with serum phosphate levels steeply falling during the first 90 to 120 minutes into dialysis, driven by removal primarily from plasma and extracellular volumes and stabilizing thereafter (Fig. 99.3). This latter intradialytic plateau is explained by phosphate mobilization from extravascular compartments at a rate similar to that of dialyzer phosphate removal.[14] Phosphate removal is improved by high-flux HD and HDF, by the use of larger dialyzer surface area, and, most dramatically, by longer or higher frequency dialysis schedules, such as short daily or daily nocturnal HD. Long, frequent dialysis schedules, such as daily nocturnal HD, offer the highest phosphate mass removal and may even result in hypophosphatemia so that phosphate needs to be added to the dialysate.

PRESCRIPTION OF HEMODIALYSIS

Hemodialysis Dose

The National Kidney Foundation’s KDOQI guidelines recommend a target spKt/V of 1.4 per HD session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. In patients with significant residual native kidney function, a lower dose of HD may be appropriate (termed incremental dialysis), provided RKF is measured periodically to avoid inadequate dialysis. For HD schedules other than thrice weekly, a target stdKt/V of 2.1 per week including residual kidney function is recommended.[2]

Delivered dialysis dose depends on dialyzer efficiency (Kd), effective treatment time (t), and distribution volume (V). Dialyzer clearance Kd depends on the flow rates within the blood and dialysate compartments (Qb and Qd), dialyzer KoA, effective membrane surface area, hematocrit, and anticoagulation. Effective treatment time is essential for reaching the Kt/V target and can be substantially shorter than prescribed treatment time because of intermittent pump stops or patient demand. Urea distribution volume V does not substantially change during a single HD session but may change over time. Therefore, dialysis dose needs to be adjusted when lean body mass and thus V increases. On the contrary, if there is a loss in muscle mass, which is associated with a decrease in V, dialysis dose should not be reduced but rather based on a higher (ideal) patient V to support gains in body mass.[2]

A standard dialysis prescription should consist of a high-flux dialyzer, a minimum treatment time of 4 hours, a blood flow rate of at least 250 mL/min, and a dialysate flow rate of 500 to 800 mL/min. The prescription is then adjusted to meet the target spKt/V of 1.4 volumes. In severe and long-standing uremia, the target dose is approached slowly over the course of several sessions to avoid the dialysis disequilibrium syndrome. Confronted with an inadequate URR or Kt/V, it is sensible to check whether the studied session was representative of the average session, because unusual problems may have occurred (e.g., shortened time, vascular access recirculation, single-needle HD). Frequent causes of inadequately low delivered dialysis dose with recirculation are vascular access problems, particularly of arterial supply. Blood sampling errors also should be considered because delayed post-HD blood sampling results in falsely low Kt/V results. If a low Kt/V remains unexplained, treatment time should be increased and a more efficient dialyzer and higher blood and dialysate flow rates should be considered (Fig. 99.4). Delivered Kt/V should be checked whenever the dialysis prescription has been modified substantially.

Hemodiafiltration Dose

The two major aims governing the prescription of high-volume onlineHDF dose are adequate delivery of the target effective CV and the prevention of excess hemoconcentration. High-flux membranes offering high hydraulic permeability, as well as high middle-molecule clearance, are required for effective HDF. Hydraulic permeability is reflected by the membrane ultrafiltration coefficient, whereas membrane permeability is defined by the sieving coefficients for selected middle molecules. For high-volume online HDF a high-flux membrane with an ultrafiltration coefficient greater than 20 mL/h/mm Hg/m^2 and a sieving coefficient for β_2-microglobulin of 0.6 is required.[15] The major determinants of achieving a prescribed target CV in postdilution HDF are blood flow rate (Qb), ultrafiltration rate (UFR), and treatment time (t). Because ultrafiltration is applied to undiluted blood, hemoconcentration necessarily occurs together with a lowering of blood flow rate within the dialyzer. Under certain circumstances, this leads to the deposition of plasma proteins on the membrane surface, clogging of membrane pores, and occlusion of dialyzer capillaries. To prevent excessive hemoconcentration, UFR and Qb need to be individually adjusted so that the filtration fraction (FF), which is defined as the ratio of UFR to Qb, does not exceed 25%. Higher FF up to 30% can be safely achieved only with modern HD machines designed to optimize filtration rate based on constant assessment and optimization of transmembrane pressure. Effective treatment time in high-volume HDF with a fixed target CV will thus always depend on achievable Qb and UFR.

Treatment Time and Frequency

The European best practice guidelines recommend that dialysis should be delivered at least 3 times per week and the total duration should be at least 12 h/wk, unless supported by significant residual kidney

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Management of Low Kt / V
Was HD prescription followed?
Check for
- Effective vs. prescribed treatment time
- Delivered Qb
- Delivered Qd
- Dialyzer specifications
- Vascular access problems
- Complications during HD

No

Adjust
HD treatment
and repeat
measurement

Yes
Vascular access recirculation?
- Check needle placement
- Distance between needles?
- Access aneurysms?

Yes

Revise access

No
Optimize Qb to

300 mL/min
low Kt/V

Prescribe dialyzer with higher KoA

Check for
recirculation
Check Kt/V
Check Kt/V

low Kt/V
Increase treatment time

Check Kt/V

low Kt/V
Increase Qd to 800 mL/min

Check Kt/V

low Kt/V
Prescribe intradialytic exercise (if
not already being used) to
increase tissue perfusion

Check Kt/V

low Kt/V
Increase dialysis frequency

Check weekly
std-Kt/V

Fig. 99.4 Management of low and inadequate treatment index (Kt/V). HD, Hemodialysis; KoA, the dialyzer urea mass transfer area coefficient; Qb, blood flow rate; Qd, dialysate flow rate; stdKt/V, equilibrated Kt/V.

function with GFR greater than 3 mL/min.10 Conventional thriceweekly dialysis remains the standard of care in most countries, where treatment time is typically governed by dialysis dose (Kt/V), with the consequence of longer dialysis in patients with higher urea distribution volumes. Acknowledging the difficulties in removing adequate amounts of fluid and low/middle molecular uremic solutes during short dialysis sessions, a minimum treatment time of 4 hours per HD session is recommended in many countries. More frequent in-center dialysis and longer dialysis hours delivered by in-center or home HD are increasingly used alternatives to conventional thrice-weekly treatment. Both modalities offer the opportunity for improved solute clearance and complete removal of interdialytic weight gain (IDWG) with fewer intradialytic problems, particularly hypotension.

Several epidemiologic studies in larger patient populations suggested a survival advantage for patients treated with extended time and/or frequency dialysis schedules, such as daily in-center or nocturnal HD 4 to 6 times a week. The randomized controlled Frequent Hemodialysis Network (FHN) study was designed to compare short daily (6 times weekly) HD vs. thrice-weekly in-center HD and, separately, nocturnal home HD 5 to 6 times weekly vs. conventional thrice weekly home HD. After 12 months of follow-up, daily in-center HD resulted in lower phosphate levels, a reduction in left ventricular mass, and an improvement in self-reported physical health.16 Analysis of patient survival over a median of 3.6 years after randomization suggested that short daily in-center HD reduced long-term mortality.17

No such benefit was observed in the nocturnal FHN trial, but this may have been due to inadequate statistical power and unexpectedly low patient recruitment.18 19

Dialysate Composition

During a standard HD treatment session, a patient’s blood is exposed to 120 to 200 L of dialysate. The several ingredients of dialysate composition should therefore be prescribed with great care. Generation of near-sterile dialysate and prescription of dialysate temperature are addressed in Chapter 98

Sodium

A positive sodium balance is a typical feature of end-stage kidney disease (ESKD) and an important factor in the pathogenesis of hypertension and fluid overload in HD patients. Chronic sodium accumulation may be associated with increased nonosmotic tissue sodium storage and left ventricular hypertrophy.20-22 Judicious control of interdialytic sodium intake to approximately 5 to 6 g salt (2300 mg or 100 mmol sodium) per day is effective in normalizing blood pressure. Sodium movement during dialysis depends on the transmembrane sodium gradient between dialysate and plasma water. To avoid a positive intradialytic sodium balance, dialysate and plasma sodium concentrations should be aligned or care should be taken that dialysate sodium does not exceed the patient’s average predialysis serum sodium concentration by more than 2 to 3 mmol/L. A positive intradialytic sodium balance may lead to increased interdialytic fluid intake and higher ultrafiltration volumes. However, the associations between serum and dialysate sodium levels and morbidity and mortality require further studies.

Potassium

Potassium removal during dialysis ideally should be equal to the amount accumulated during the interdialytic period. The dialysate potassium concentration must be set at a level that avoids pre-HD hyperkalemia, as well as intradialytic hypokalemia, which may provoke dialysis-induced arrhythmia. Postdialysis hypokalemia less than 3.0 mmol/L is associated with increased risk of mortality, especially in patients presenting with predialysis potassium levels less than 4.0 mmol/L.23 The typical dialysate potassium concentration is set between 2.0 and 4.0 mmol/L. Prescription of potassium dialysate concentrations less than 2.0 mmol/L is associated with an increased risk for tachyarrhythmia and sudden cardiac death24 and should be avoided.

Calcium

In light of accelerated vascular calcification in ESKD, intradialytic calcium delivery to the patient should be minimized, and in patients using calcium salts as phosphate binders, a negative intradialytic calcium mass balance is desirable.25 A dialysate calcium concentration of 1.25 to 1.50 mmol/L is recommended by KDIGO, but many patients will be in positive balance even at 1.25 mmol/L. A positive calcium balance may be associated with tissue calcium accumulation, whereas lower dialysate calcium will stimulate parathyroid hormone (PTH) secretion. In most patients a dialysate calcium concentration of 1.25 mmol/L is now used.

Bicarbonate

Chronic metabolic acidosis is associated with decreased protein synthesis and increased protein catabolism and contributes to mineral and bone disorders. Pre-HD bicarbonate levels in the range of 20 to 23 mmol/L are associated with improved survival. Dialysate bicarbonate concentration is typically set between 35 and 40 mmol/L to generate a transmembrane concentration gradient favoring bicarbonate delivery

to the patient. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that both high (>27 mmol/L) and low (<17 mmol/L) predialysis serum bicarbonate levels are associated with increased risk for mortality and hospitalization.26

Magnesium

In the past, dialysate magnesium levels of 1.5 mmol/L were used frequently. Currently recommended levels are between 0.5 and 1.0 mmol/L. Whereas observational studies suggested an inverse association between serum magnesium levels and mortality,27 other studies showed that magnesium dialysate does not improve intradialytic hemodynamics or abrogate myocardial stunning.28 It is unclear to what extent dialysate magnesium levels have a sustained effect on serum levels.

Ultrafiltration Rate

Fluid overload is an established risk factor for the development of left ventricular hypertrophy and cardiovascular mortality. Similarly, predialysis extracellular fluid depletion is also associated with increased mortality.29 Adequate HD aims to normalize body water homeostasis and extracellular volume to a postdialysis level comparable with that of patients of similar age and normal kidney function. This ideal, nearnormal postdialysis body weight is frequently termed dry weight, which often differs substantially from the target weight prescribed. Because of the difficulties in detecting fluid overload of 2 to 3 L clinically, technical methods, such as bioimpedance, relative blood volume monitoring, and imaging (ultrasound, chest radiograph) for assessing volume status should be applied regularly.30 A successful clinical approach to define dry weight has been the gradual and stepwise reduction in postdialysis weight by 0.2 to 0.5 kg per session until some cramps occur and blood pressure is in the normal range. Postdialysis target weight is then set at 0.5 kg above cramping level. UFRs above 10 mL/kg/h are associated with higher odds of intradialytic hypotension and a greater risk for mortality.31 It is important to realize that IDWG and fluid overload are not synonymous, and that postdialysis fluid depletion may result in high IDWG.

DIALYSIS ADEQUACY AND GOAL-DIRECTED DIALYSIS

Dialysis adequacy used to be defined as prescribing and delivering a dialysis dose that is associated with the best long-term outcome, but it has meanwhile become evident that the outcome and quality of life of HD patients cannot be influenced by dialysis prescription alone. Therefore, multiple measures and goals should be considered when prescribing dialysis, including small solute clearance, residual kidney function, volume status, biochemical measures, nutritional status, cardiovascular function, intra- and interdialytic symptoms and complications and the patient’s individual experiences and goals. Patients may interpret adequacy different than clinicians, and therefore treatment goals should be individualized and reassessed over time while recognizing accepted minimums for small solute removal during dialysis.1

The term goal-directed dialysis specifically refers to using shared decision-making between patient, their family/delegate, and the care team to establish realistic care goals to allow patients to meet their own life goals and allow the clinician to provide individualized, high-quality dialytic care. The aim of goal-directed dialysis is to provide the best health outcome possible for an individual on dialysis (HD or peritoneal dialysis [PD]) in terms of maintaining their clinical well-being, quality of life, and ability to meet life goals and also minimize patient and caregiver treatment burden. The components of goal-directed dialysis include those directly affected by the dialysis prescription and

Components of Goal-Directed Dialysis
Directly affected by
dialysis procedure

Symptoms

Small
solute
levels

Fluid
intake
Electrolyte
concentrations

Blood
pressure
Sodium
intake

Volume
status

Cognitive
function
Anemia

Treatment
burden

Not directly affected by
dialysis procedure

Protein
&
calorie
intake

Comorbidity
manifestations
Medication
adherence
Phosphorus
intake
Depression,
anxiety

Physical
function

Fig. 99.5 Components of Goal-Directed Dialysis. Some individual goals can be directly affected by dialysis procedure (left), whereas others cannot be directly affected by dialysis procedure (right). Most goals, however, are overlapping the zones and can only partly be affected by dialysis procedure.

procedure, such as solute clearance electrolyte concentrations, volume status, and intradialytic symptoms, as well as those only indirectly affected by the dialysis procedure, such as symptom burden, nutritional status, activity level, work capacity, and social engagement (Fig. 99.5).32

Prevention of Intradialytic Hypotension

Depending on the definition, intradialytic hypotension (IDH) occurs in 10% to 30% of treatments and is associated with damage to the brain, gut, heart, kidney, and poor outcome.33 Early IDH occurring during the first half of a dialysis session is associated with particularly poor outcome and may be triggered independent of intravascular volume changes.34 In contrast, IDH occurring later during dialysis is often due to high rates of ultrafiltration occasioned by the necessity to remove large IDWGs during a relatively short treatment.31 In addition, an individual inability to preserve organ perfusion in the face of dialysis-related hypotension or intravascular hypovolemia (e.g., secondary to uremic and/or diabetic autonomic dysfunction) may lead to short-term changes (e.g., intradialytic cardiac stunning) and long-term consequences (e.g., heart failure and cardiac mortality outcomes).35 Prevention of high IDWG may help: potential strategies include dietary counseling to reduce sodium intake, lengthening of dialysis duration, dialysate cooling, use of α-sympathetic agonists such as midodrine, and avoidance of food during dialysis. In addition, prevention and management of postural hypotension immediately after dialysis is essential to prevent falls. Intradialytic hypotension is also discussed in Chapter 100

Preservation of Residual Kidney Function

Most patients starting dialysis still have considerable RKF, but by the end of the first year, the majority may have lost RKF completely. Only 10% to 20% of patients still have RKF after more than 3 years of dialysis. A kidney clearance of 2 to 3 mL/min, which for a patient with total body water of 40 L is equivalent to a stdKt/V of 0.5 to 0.75/wk, contributes significantly to the elimination of uremic toxins with lower β2 microglobulin, phosphate, potassium, urea, creatinine, and uric acid

levels, as well as maintained endocrine, metabolic, and antioxidative stress functions; higher hemoglobin concentration; enhanced nutritional status; better quality of life scores; and a reduced need for dietary and fluid restrictions.36

Loss of RKF is associated with left ventricular hypertrophy. Risk factors for the loss of RKF include activation of the immune system by cellulose-based membranes and dialysate water impurities; intradialytic hypotension and kidney hypoperfusion; use of angiotensinconverting enzyme inhibitors or nephrotoxic agents (e.g., radiocontrast media, aminoglycosides, and nonsteroidal antiinflammatory drugs); and hypercalcemia. Loss of RKF may be delayed by adequate target post-HD weight prescription and prevention of intradialytic hypotensive episodes.37

Maintenance or Improvement of Nutritional Status

HD patients are at risk for malnutrition secondary to protein-energy wasting, decreased appetite, infection, intercurrent illnesses, hospital admissions, and missed meals after dialysis.38 The recommended daily intake of 1.2 g protein per kilogram of ideal body weight and 30 to 35 kcal per kilogram of ideal body weight are often not met. The nutritional status of dialysis patients should be assessed regularly by clinical and biochemical means and by technical means such as bioimpedance. Eating during dialysis or intradialytic oral nutritional supplements including supplemental vitamins may be beneficial in patients with low spontaneous energy and protein intake. Nutrition in HD patients is also discussed in Chapter 90

Goal-Directed Dialysis in the Elderly

Patients older than 75 years represent the largest incident and fastestgrowing prevalent patient population in HD worldwide, and the unique medical and social needs of these patients require consideration. Studies in this population show that the parameters that correlate with clinical outcomes are not the traditional markers of HD dose, such as Kt/V and treatment time, but rather cardiovascular comorbidity, nutritional status, functional capacity, and frailty.39 Therefore, the focus of dialysis adequacy in elderly patients should shift

Adequate Cardiovascular Regulation
(no or mild cardiovascular comorbidities)
Euvolemia
Feeling uneasy

Cramps

Heart failure

→Physiologic
cardiovascular
adaption

Hypotension

A

Hypertension

Hemodynamic
tolerability of
intradialytic IVV
changes

Hypovolemia

Intravascular volume

Lung edema
Hypervolemia

Impaired Cardiovascular Regulation
(more severe cardiovascular comorbidities)

Heart failure

Myocardial stunning
Cerebral symptoms

Lung edema
Hemodynamic instability

Hypotension

B

Hypovolemia

Intravascular volume

Hypervolemia

Fig. 99.6 Intradialytic Vulnerability. The occurrence of complications (arrows) in response to intradialytic changes in intravascular volume (IVV) depends on the functionality of physiologic cardiovascular (CV) adaptation mechanisms, such as an increase in heart rate and constriction of arterioles and venous capacity vessels. The individual hemodynamic tolerability of intradialytic IVV changes (yellow field) is higher in patients on hemodialysis (HD) with no or mild CV comorbidities and intact CV responses (A)

than in typically older and multimorbid HD patients with impaired cardiovascular regulation (e.g., secondary to diabetic autonomous neuropathy; B). (Modified from Chauveau P, Combe C, Laville M, et al. Factors influencing survival in hemodialysis patients aged older than 75 years; 2.5-year outcome study. Am J Kidney Dis. 2001;37:997–1003.)

from urea-based assessment of dialysis dose to the use of a more multidimensional measure.32 Elderly dialysis patients with multiple comorbidities tolerate HD treatments less well than younger patients. Typical complications, such as intradialytic hypotension, cramps, atrial fibrillation, and postdialysis fatigue contribute to the rapid loss of independence occurring in this vulnerable patient population. The underlying etiology is reduced tolerance to intravascular volume reduction during dialysis, which is at least partially caused by impaired cardiovascular hemodynamic responses in combination with uremic and/or diabetic autonomic neuropathy (Fig. 99.6). Significant reductions in organ perfusion occurring in the gut, liver, kidneys, heart, and brain contribute to the development of inflammation, malnutrition, heart failure, loss of RKF, frailty, depression, and dementia.33 To protect vulnerable elderly patients from the dramatic short- and long-term consequences of intradialytic tissue hypoxia, the HD prescription should be individualized. The following list provides some interventions that may help make HD treatments more tolerable in elderly patients, with the goal to reduce cardiovascular complications, sustain nutritional status, and slow the development of frailty.

✓ • ✓ Carefully evaluate individual susceptibility to intradialytic hypotension in relation to UFR.

✓ • ✓ Assess vascular refilling capacity by monitoring intradialytic changes in blood volume.

✓ • ✓ Individualize maximum UFR (ideally <10 mL/kg body weight/h).

✓ • ✓ Consider ultrafiltration profiling and/or the use of dialysis machines with biofeedback control of UFR.

✓ • ✓ Lower dialysate temperature to prevent the intradialytic increase in body core temperature associated with an increased risk for intradialytic hypotension.

✓ • ✓ Reduce IDWG (dietary counseling regarding salt intake, prescribe adequately dosed diuretics).

✓ • ✓ Avoid intradialytic positive sodium balance (individualize dialysate composition).

✓ • ✓ Increase dialysis frequency in case the patient does not tolerate a long interdialytic interval.

✓ • ✓ Reduce β-blocker medication to allow cardiac compensation for changes in intravascular volume.

✓ • ✓ Reduce or pause antihypertensive medication before dialysis in hypotension-prone patients.

✓ • ✓ Assess the effect of food intake during dialysis on hemodynamic stability.

✓ • ✓ Regularly adjust postdialysis target weight (bioimpedance).

✓•✓ If hypertensive, gradually reduce postdialysis weight, avoiding intradialytic hypotensive episodes.
✓•✓ Consider supine position during dialysis.
✓•✓ Consider online HDF.
✓•✓ Consider peritoneal dialysis in patients with otherwise intractable IDH.

✓•✓ Treat intradialytic hypoxia by intradialytic oxygen application.
✓•✓ Ensure three meals per day, including the dialysis day.
✓•✓ Prescribe oral nutritional supplements during and between dialysis treatments.
✓•✓ Prevent immobilization by early rehabilitation and physical therapy.

SELF-ASSESSMENT QUESTIONS

1. Which of the following factors related to the hemodialysis prescription in a patient without much residual kidney function is likely to result in the worst outcome?
A. Kt/V of 1.15 over months
B. Use of low-flux dialyzers
C. 3-hour dialysis times
D. Dialysate potassium of 2 mEq/L
2. Hypertension is very common in dialysis patients. Which factor alone is least likely to reduce BP?
A. Use of antihypertensive drugs
B. Longer dialysis times with fluid removal
C. Postdialysis weight reduction
D. Dietary sodium restriction
3. Which action is not useful when the BP falls frequently during dialysis?
A. Decrease dialysate temperature
B. Apply abdominal pressure

C. Reduce the ultrafiltration rate
D. Increase postdialysis target weight
4. The recommended target convective volume in high-volume online hemodiafiltration is 23 L/1.73 m2/treatment. Which of the following actions is not useful to increase the convective volume?
A. Increase ultrafiltration rate
B. Increase filtration fraction
C. Increase blood flow rate
D. Increase dialysate flow rate
E. Increase treatment time
5. In patients with residual kidney function, an intrinsic urea clearance of 3 mL/min is approximately equivalent to a weekly standard KtV of:
A. 0.10.
B. 0.25.
C. 0.75.
D. 1.05.
E. 1.50.

REFERENCES

1. Vanholder R, Glorieux G, Eloot S. Once upon a time in dialysis: the last days of Kt/V? Kidney Int. 2015;88:460–465.
2. Daugirdas JT, Depner TA, Inrig J, et al. National Kidney Foundation: KDOQI clinical practice guideline for hemodialysis adequacy: 2015Update. Am J Kidney Dis. 2015;66:884–930.
3. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–1213.
4. Gotch FA. The current place of urea kinetic modeling with respect to different dialysis modalities. Nephrol Dial Transplant. 1998;13(suppl 6):10–14.
5. Daugirdas JT. Dialysis dosing for chronic hemodialysis: beyond Kt/V. Semin Dial. 2014;27:98–107.
6. Daniel E. Weiner, Luke Falzon, Line Skoufos, Angelito Bernardo, Werner Beck, Mengqi Xiao, and Ha Tran. Efficacy and safety of expanded hemodialysis with the Theranova 400 dialyzer; A randomized controlled trial. Clin J Am Soc Nephrol. 2020;15(9):1310–1319.
7. Cheung AK, Rocco MV, Yan G, et al. Serum β2-microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17:546–555.
8. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–2019.
9. Locatelli F, Martin-Malo A, Hannedouche T, et al. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol. 2009;20:645–654.
10. Tattersall J, Martin-Malo A, Pedrini L, et al. EBPG guideline on dialysis strategies. Nephrol Dial Transplan. 2007;22(suppl 2):ii5–ii21.
11. Locatelli F, Carfagna F, Del Vecchio L. La Milia V; Haemodialysis or haemodiafiltration: that is the question. Nephrol Dial Transplant. 2018;33(11):1896–1904.
12. Peters SAE, Bots ML, Canaud B, et al. Hemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled studies. Nephrol Dial Transplant. 2016;31:978–984.
13. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease–mineral and bone disorder (CKDMBD). Guideline update: what’s changed and why it matters. Kidney Int. 2017;92:26–36.
14. Kuhlmann MK. Phosphate elimination in modalities of hemodialysis and peritoneal dialysis. Blood Purif. 2010;29:137–144.
15. Tattersall JE. Ward RA on behalf of the EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;22:542–550.
16. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287–2300.
17. Chertow GM, Levin NW, Beck GJ, et al. Long-term effects of frequent in-center hemodialysis. J Am Soc Nephrol. 2016;27(6):1830–1836.
18. Rocco MV, Daugirdas JT, Greene T, et al. Long-term effects of frequent nocturnal hemodialysis on mortality: the Frequent Hemodialysis Network (FHN) nocturnal trial. Am J Kidney Dis. 2015;66(3):459–468.
19. Pauly RP, Miller BW. Contextualizing the FHN nocturnal trial a decade later: how nocturnal home hemodialysis is performed matters to outcomes. Clin J Am Soc Nephrol. 2021;16:966–968.
20. Lemoine S, Salerno FR, Akbari A, McIntyre CW. Influence of dialysate sodium prescription on skin and muscle sodium concentration. Am J Kidney Dis. 2021;78:156–159.

21. Flythe JE, Mc Causland FR. Dialysate sodium: rationale for evolution over time. Semin Dial. 2017;30(2):99–111.
22. Schneider MP, Raff U, Kopp C, et al. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. J Am Soc Nephrol. 2017;28:1867–1876.

23. Ohnishi T, Kimachi M, Fukuma S, Akizawa T, Fukuhara S. Postdialysis hypokalemia and all-cause mortality in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol. 2019;14(6):873–881.
24. Pun PH, Lehrich RW, Honeycutt EF, et al. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int. 2011;79:218–227.
25. Pirklbauer M, Schupart R, Mayer G. Acute calcium kinetics in haemodialysis patients. Eur J Clin Invest. 2016;46(12):976–984.
26. Bommer J, Locatelli F, Satayathum S, et al. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPS). Am J Kidney Dis. 2004;44:661–671.
27. Sakaguchi Y, Fujii N, Shoji T, et al. Hypomagnesemia. is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. Kidney Int. 2014;85(1):174–181.
28. Jefferies HJ, Lemoine S, McIntyre CW. High magnesium dialysate does not improve intradialytic hemodynamics or abrogate myocardial stunning. Hemodial Int. 2020;24(4):506–515.
29. Dekker MJ, Marcelli D, Canaud BJ, et al. Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. Kidney Int. 2017;91(5):1214–1223.
30. Zhu F, Rosales L, Kotanko P. Techniques for assessing fluids status in patients with kidney disease. Curr Opin Nephrol Hypertens. 2016;25:473–479.
31. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int. 2011;79:250–257.
32. Chan CT, Blankestijn PJ, Dember LM, et al. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcome (KDIGO) controversies conference. Kidney Int. 2019;96(1):37–47.
33. McIntyre C, Crowley L. Dying to feel better: the central role of dialysisinduced tissue hypoxia. Clin J Am Soc Nephrol. 2016;11:549–551.
34. Keane DF, Raimann JG, Zhang H, Willetts J, Thijssen S, Kotanko P. The time of onset of intradialytic hypotension during a hemodialysis session associates with clinical parameters and mortality. Kidney Int. 2021;99:1408–1417.
35. McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. Sem Dial. 2010;23:449–451.
36. Bargman JM, Golper TA. The importance of residual renal function for patients on dialysis. Nephrol Dial Transplant. 2005;20:671–673. 36.
37. Marants R, Qirjazi E, Grant CJ, Lee TY, McIntyre CW. Renal perfusion during hemodialysis: intradialytic blood flow decline and effects of dialysate cooling. J Am Soc Nephrol. 2019;30(6):1086–1095.
38. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23:77–90.
39. Chauveau P, Combe C, Laville M, et al. Factors influencing survival in hemodialysis patients aged older than 75 years; 2.5-year outcome study. Am J Kidney Dis. 2001;37:997–1003.
40. Wong J, Vilar E, Davenport A, Ferrington K. Incremental hemodialysis. Nephrol Dial Transplant. 2015;30:1639–1648.

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Acute Complications During Hemodialysis

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Although technical advances in hemodialysis (HD) have made the procedure increasingly safe and well tolerated, important acute complications can occur in patients receiving HD in both acute and chronic clinical settings. These complications, etiology, and their management are discussed in this chapter.

CARDIOVASCULAR COMPLICATIONS

Intradialytic Hypotension

Intradialytic hypotension occurs in 15% to 50% of treatments depending on the definition and ranges from asymptomatic episodes to marked compromise of organ perfusion, resulting in myocardial ischemia, cardiac arrhythmias, vascular thrombosis, loss of consciousness, seizures, or death.[1-3] Furthermore, in patients with acute kidney injury, intradialytic hypotension may reduce the likelihood of recovery. Recurrent HD-induced ischemic cardiac injury (myocardial stunning) is a prominent cause of intradialytic hypotension and is more common at higher ultrafiltration rates and less frequent with longer and more frequent dialysis treatments.[4] Like intradialytic hypotension and postdialysis orthostatic hypotension, myocardial stunning is an independent risk factor for mortality.[5] The pathogenesis of intradialytic hypotension is complex and is summarized in Fig. 100.1. Most commonly, intradialytic hypotension results from the need to deal with excessive fluid weight gain between dialysis treatments. The subsequent rate of fluid removal required exceeds the achievable rate of intravascular filling, resulting in relative intravascular volume depletion. Recent data demonstrate an increased risk for death as the ultrafiltration rate increases, regardless of the threshold used.[6]

The immediate treatment for intradialytic hypotension is to restore the circulating blood volume by placing the patient in the Trendelenburg position, reducing or stopping ultrafiltration, and infusing boluses of 0.9% isotonic saline (≥100 mL, as necessary). Salt-poor albumin and other hypertonic solutions offer no proven advantage over isotonic saline and are more expensive.[7] Blood flow rate should not be routinely reduced to manage hypotension, as this has not been shown to be beneficial and will compromise overall solute clearance. Of course, in the setting of excessive weight gain, the administration of boluses of saline or cessation of ultrafiltration makes achieving the target dry weight more difficult. Because cardiac factors can precipitate intradialytic hypotension, the clinician should maintain a high index of suspicion for cardiac ischemia, especially if hypotension is accompanied by chest pain or dyspnea, and an electrocardiogram and serum troponin values should be obtained. Similarly, recurrent and unexplained episodes of hypotension might warrant echocardiography to rule out pericarditis or pericardial effusion.

Preventive strategies include correction of anemia, treatment of congestive heart failure or arrhythmias, avoidance of antihypertensive drugs on the day of or at least in the hours before dialysis (especially those that reduce arteriolar tone), and avoiding food before and during dialysis, as these may result in shunting of blood to the gut. Patients should be counseled to avoid excessive interdialytic weight gain (IDWG), because this is the predominant cause of intradialytic hypotension and particular attention should be given to ensuring minimal salt intake. Finally, an accurate assessment of the patient’s dry weight is required. Midodrine, an oral selective α1-agonist, 5 to 10 mg before dialysis, can be a useful preventive therapy if the earlier-mentioned strategies fail.

Preventive strategies through modification of the dialysis procedure include use of bicarbonate dialysate (as opposed to acetate buffered dialysate) and volumetric control of ultrafiltration. Subsequently, reducing the ultrafiltration rate by increasing either treatment time or the frequency of dialysis can be tried.[2,8] The strategy of isolated ultrafiltration followed by HD (i.e., sequential dialysis) has been recommended for many years, although there is limited evidence to support it.[2] A higher dialysate sodium may improve single-treatment blood pressure but at the expense of higher IDWG and volume overload in the longer term[2] (see Chapter 42). The data to support sodium profiling or modeling are limited, with one study suggesting that the routine use of sodium modeling/profiling to limit or prevent intradialytic hypotension is associated with increased all-cause mortality.[9] Online blood volume monitoring and biofeedback techniques have been developed in an attempt to improve intradialytic cardiovascular (CV) stability.[10] Although online blood volume devices may decrease the incidence of intradialytic hypotension in an at-risk population, there is limited evidence that blood volume monitoring can predict intradialytic hypotension in individual patients or produce a long-term morbidity and mortality benefit, especially in the wider HD population.[10] A recent small crossover study failed to show a benefit of ultrafiltration profiling in preventing intradialytic hypotension or treatment-related cardiac stress.[11] Cooling of dialysate to 35.5°C to 36°C (95.9–96.8° F), a measure that induces release of catecholamines, resulting in vasoconstriction or at least preventing vasodilation, may lessen hypotension. Modulation of dialysate temperature is achieved by measuring the blood temperature in the arterial and venous circuits and feeding back the information to the arterial and venous thermostats in the dialysis machine. The machine can be programmed to allow a constant body temperature and a negative overall energy transfer, so-called isothermic or thermoneutral HD, which aims to prevent energy transfer between the dialysate and extracorporeal blood. A recent systematic review of the randomized controlled trials using biofeedback-modulating dialysate temperature demonstrated significant reductions in the incidence of intradialytic hypotension compared with conventional dialysis.[12] However, large multicenter randomized trials are needed to determine whether reduced temperature dialysis reduces CV events and patient death.

Causes of Intradialytic Hypotension

Excessive fluid removal
Ultrafiltration rate >0.35 mL/min/kg
(>1.5 L/h in a 70-kg patient)
Decrease in plasma volume >20%

Reduced
plasma
refilling rate

Reduced effective
circulating volume

Impaired
vasoconstriction

Hemorrhage
Intradialytic hypotension
Cardiac factors
Myocardial infarction
Structural heart disease
Arrhythmias
Pericardial tamponade
Myocardial stunning

Hemolysis
Dialyzer
reaction

Patient-related factors
Autonomic neuropathy (e.g., diabetic, uremic)
Antihypertensive medications
Lack of appropriate rise in plasma norepinephrine (“sympathetic failure”)
Decreased sensitivity of the renin-angiotensin and arginine-vasopressin systems
Food ingestion (splanchnic vasodilation)
Tissue ischemia (adenosine mediated)
Bacterial sepsis
Intradialytic venous pooling
Increase in core body temperature
Anemia
Dialysis-related factors
Low dialysate sodium and/or ionized calcium concentrations
Complement activation (C3a and C5a mediated)
Cytokine generation (interleukin-1 and nitric oxide mediated)
Acetate dialysate vasodilation (adenosine mediated)

Air
embolism

Fig. 100.1 Pathogenesis and causes of intradialytic hypotension.

Across Europe and many other countries, hemodiafiltration (HDF) has become a common mode of dialytic therapy. Although claims of improved mortality with this modality remain a matter of debate, most accept that HDF is associated with improved intradialytic CV stability and less frequent hypotension, but this is also disputed by some.13

Intradialytic Hypertension

Intradialytic hypertension (IDH) occurs in 5% to 30% of treatments depending on the definition used.2 14 Hypertension during or immediately after HD constitutes an important risk factor for CV mortality.

Moreover, an intradialytic increase in systolic blood pressure (BP) is associated with an increased risk for hospitalization or death.15

In most circumstances, an intradialytic elevation of BP indicates significant volume overload. However, in a number of patients BP remains elevated despite fluid removal, a syndrome called dialysisrefractory hypertension. These patients are usually young, with preexisting hypertension, and have excessive IDWG and a hyperactive renin-angiotensin system in response to fluid removal.16 In these patients the hypertension is still mediated by the previous volume expansion, but there is often a lag of days to 2 or more weeks before the BP becomes normal after reduction of the dry target weight (known as the dialysis “lag phenomenon”). Often patients can discontinue most of their antihypertensive agents once this period has elapsed. Chapter 42 presents more details on the diagnosis and management of hypertension associated with hemodialysis.

Erythropoietin (EPO) and other erythropoiesis-stimulating agents have been associated with a 20% to 30% incidence of newonset hypertension or exacerbation of hypertension. Furthermore, among patients receiving intravenous (not subcutaneous) EPO, elevated levels of endothelin-1 (a potent vasoconstrictor) have been shown to correlate with increased BP. Such EPO-induced rises in BP are usually associated with a rapid rise in hemoglobin and can be avoided by a more conservative approach to correcting the hemoglobin.

IDH can be precipitated by the use of high-sodium dialysate, which is intended to mitigate the intradialytic decrease in serum osmolality that occurs with the diffusive removal of urea and sodium.17 Although this approach stabilizes BP during dialysis by improving intravascular filling, high-sodium dialysate results in a positive intradialytic sodium balance and is associated with increased postdialysis thirst, resulting in significant weight gain in the interdialytic period. To circumvent these problems, sodium modeling has been adopted as an approach that uses variable sodium concentrations in the dialysate, generally with sodium reduced in a continuous or stepwise manner from an initial level of 150 to 154 mmol/L to 138 to 142 mmol/L. Although sodium modeling has been widely promoted, results from both randomized and nonrandomized crossover studies do not suggest any definitive benefit.9 18

Other hypothesized mechanisms of IDH include hyperactivity of the sympathetic nervous system19 and increased cardiac output resulting from fluid removal, particularly in patients with cardiomyopathy.20

Clinicians also should be aware of possible dialytic removal of certain antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers.

Increasing hypertension during a dialysis session requires intervention if systolic BP is greater than 180 mm Hg. This is best treated with a short-acting agent, such as the ACE inhibitor captopril. Successful treatment of hypertension for a longer period requires an accurate determination of the patient’s dry weight and its achievement by gradual ultrafiltration over several weeks of dialysis. Once dry weight is achieved, optimization of antihypertensive drug therapy is warranted, potentially including the use of minimally dialyzable or nondialyzable medications such as angiotensin receptor blockers, calcium channel blockers, clonidine, and carvedilol. However, use of antihypertensive agents may make achievement of dry weight difficult because of induced intradialytic hypotension. Evidence from the Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial21 suggests that optimal control of BP in HD patients is via control of extracellular fluid volume (salt and water) and not the use of antihypertensive agents.

One common error in management is to treat dialysis hypertension with increasing BP medications as opposed to opting to achieve dry weight. The use of vasodilator drugs (hydralazine, minoxidil) can lead to increased fluid retention that worsens volume overload. Minoxidil also can cause pleural and pericardial effusions and should be avoided in dialysis patients if at all possible.

TABLE 100.1

Cardiac Arrhythmias

Function	Abnormality
PR interval	Usually normal; prolongation in long-term HD. Calcification of mitral valve annulus may involve His bundle, resulting in complete heart block.

Intradialytic arrhythmias are common and are often multifactorial in origin.22 23 Left ventricular hypertrophy, congestive cardiomyopathy, uremic pericarditis, silent myocardial ischemia, and conduction system calcification are frequently encountered in adult dialysis patients. In addition, polypharmacy coupled with the constant alterations in fluid, electrolyte, and acid-base homeostasis may precipitate intradialytic arrhythmias. Intradialytic hypotension is also associated with intradialytic cardiac arrhythmias.24 The range of electrocardiographic abnormalities that may be encountered in kidney failure is shown in Table 100.1. QTc dispersion, the difference between maximum and minimum QTc interval on a standard 12-lead electrocardiogram, is prolonged after HD and has been proposed as a prognostic indicator of cardiac complications in dialysis patients.

Preventive measures include the use of bicarbonate dialysate and careful attention to dialysate potassium and calcium levels as well as careful attention to preventing intradialytic hypotension (see earlier). There are very few trials of the most appropriate dialysate potassium level, although recent observational evidence suggests that dialysate potassium levels below 2 mmol/L should be avoided in most patients.25 Zero potassium dialysate should be avoided in the hyperkalemic individual because of its arrhythmogenic potential, particularly in patients receiving digoxin. Serum digoxin levels should be regularly monitored and the need for the drug regularly reassessed.

Sudden Death

Cardiac arrest occurs in 7 per 100,000 HD sessions and is more common in the elderly, patients with diabetes, and patients using central venous catheters.26 Sudden deaths during dialysis are observed more frequently after the 3-day (classically weekend) interdialytic interval in patients receiving dialysis three times per week.27 28 The etiology is complex but likely related to cardiac structural abnormalities related to long-standing hypertension and uremia coupled with the more marked fluid and solute accumulation seen in the long interdialytic period. Both peritoneal dialysis patients and patients undergoing frequent long-hours HD do not show this high event rate on a particular day of the week.28 Recent analysis of data from implantable cardiac monitors in HD patients with sudden cardiac death found that the vast majority were due to bradycardia and asystole, rather than malignant ventricular arrhythmias, raising uncertainty regarding β-blocker use in this population.29

Although coronary heart disease increases the risk for sudden death, other catastrophic intradialytic events need to be ruled out. The prompt recognition and treatment of hyperkalemia, as a reversible cause of cardiac dysfunction, is imperative. Profound generalized muscle weakness may be a warning sign of imminent life-threatening hyperkalemia.

When cardiopulmonary arrest occurs during dialysis, an immediate decision must be made as to whether the collapse is the result of an intrinsic disease or technical errors, such as air embolism, unsafe dialysate composition, overheated dialysate, line disconnection, or sterilant in the dialyzer. Air in the dialysate, grossly hemolyzed blood, and hemorrhage caused by line disconnection can be easily detected. However, if no obvious cause is identifiable, blood should not be returned to the patient, particularly if the arrest occurred immediately on initiation of dialysis. A patient exposed to formaldehyde may have reported earlier burning at the access site; fortunately, this agent is rarely used today. If the possibility of a problem with dialysate composition is remote, blood may be returned to the patient. However, blood and dialysate samples should be immediately sent for electrolyte analysis, the dialyzer and blood lines saved for later analysis, and the dialysis machine replaced

Electrocardiographic Abnormalities in Kidney Failure

QRS interval
Amplitude

Increases during ultrafiltration (correlates with reduction in LV dimensions).
LVH on voltage criteria found in up to 50%.

Duration

Prolonged (within normal range) by hemodialysis.
Late potentials increased only in patients with preexisting coronary heart disease.
Prolonged in hyperkalemia.

ST segment

Depression during HD does not predict coronary artery disease.
Depression or elevation may occur in hyperkalemia.
Depression during ambulatory monitoring poorly predictive of coronary artery disease.

QTc interval

Increases during HD (correlates with reduction in K+ and Mg2+).
Increased QT dispersion reported in patients on dialysis.

T wave

Peaking or inversion may occur in hyperkalemia.
Inversion in anterolateral leads in LVH with strain pattern.

Rhythm

Bradycardia and asystole in long intradialytic break and during HD.
Atrial and ventricular arrhythmias during HD.

Risk factors include LV dysfunction, wall motion abnormalities, known coronary artery disease, abnormal perfusion scans (even without coronary artery disease), use of cardiac glycosides, and low dialysate potassium concentration.
HD, Hemodialysis; LV, left ventricle; LVH, left ventricular hypertrophy.

until all its safety features have been thoroughly evaluated for possible malfunction. It should be standard practice to have defibrillators in dialysis units. The management of cardiopulmonary arrest during dialysis should follow the standard principles of cardiopulmonary resuscitation; the diagnosis and management of technical errors are discussed later. All dialysis units should have established protocols for managing cardiac arrest and other common dialysis emergencies.
Prevention of sudden cardiac death in HD patients, including the role of implantable defibrillators, is discussed further in Chapter 85

Dialysis-Associated Steal Syndrome

The clinical presentation, differential diagnosis, and evaluation of dialysis-associated steal syndrome are discussed further in Chapter 96

NEUROMUSCULAR COMPLICATIONS

Muscle Cramps

Muscle cramps occur in 5% to 20% of patients late during dialysis and frequently involve the legs. They account for 15% of premature discontinuations of dialysis.[30] Electromyography shows increased tonic muscle electrical activity throughout dialysis, and serum creatine kinase may be elevated.

Although the pathogenesis is unknown, dialysis-induced volume contraction and hypoosmolality appear to be common predisposing factors. Indeed, the onset of muscle cramps may give an indication that the target weight has been reached. However, hypomagnesemia and carnitine deficiency also may play a role.

The acute management is directed at increasing plasma osmolality. Cessation of ultrafiltration is not useful. Parenteral infusion of 23.5% hypertonic saline (15–20 mL), 25% mannitol (50–100 mL), or 50% dextrose in water (25–50 mL) is equally effective. However, hypertonic saline may result in postdialytic thirst, and both hypertonic saline and mannitol cause transient warmth and flushing during the infusion. Furthermore, large and repetitive infusions of mannitol may lead to increased thirst, IDWG, and fluid overload. Overall, dextrose in water is preferred, particularly in nondiabetic patients.

Preventive measures include dietary counseling about excessive IDWG, in particular reducing dietary sodium intake. In patients without clinical signs of fluid overload, it is reasonable to increase the dry weight by 0.5 kg and to observe the clinical response. Quinine sulfate (250–300 mg) or oxazepam (5–10 mg) given 2 hours before dialysis also may be effective. Although the US Food and Drug Administration regards quinine sulfate as unsafe and ineffective for the prevention of cramps, this drug works well in some patients and is used freely in most parts of the world. Some reports also promote the use of vitamin E in this role.31 The use of sodium gradients during dialysis may have some benefit as well. Proposed strategies include starting with a dialysate sodium concentration of 145 to 155 mmol/L and a linear decrease to 135 to 140 mmol/L by the completion of the treatment. A comparison of sodium modeling with an exponential, linear, or step program has yielded similar results.18 32 In anecdotal reports, 5 mg of enalapril twice weekly may be effective, presumably by inhibiting angiotensin II–mediated thirst. Stretching exercises, magnesium, creatine monohydrate (12 mg before dialysis), and l-carnitine supplementation (20 mg/kg per dialysis session) also may be beneficial. An intradialytic blood volume biofeedback control system has been shown to reduce the incidence of muscle cramps.33

Restless Legs Syndrome

Restless legs syndrome is common in dialysis patients. The typical report is of crawling sensations in the legs that occur with inactivity, and symptoms may worsen during dialysis. The etiology, prevention, and management of restless legs syndrome are discussed in Chapter 89

Dialysis Disequilibrium Syndrome

Despite a decline in its incidence, dialysis disequilibrium syndrome (DDS) is still observed sporadically in patients who are initiated on HD on high-flux dialyzers with large surface areas and short dialysis time. Risk factors (Table 100.2) include young age, severe uremia, rapid and marked intradialytic falls in urea at dialysis initiation, low dialysate sodium concentration, and preexisting neurologic disorders (see Chapter 89).

DDS commonly manifests with restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, disorientation, tremor, and hypertension. More severe manifestations include obtundation, seizures, and coma. DDS usually develops toward the end of dialysis but may be delayed for up to 24 hours. Although cerebral edema is a consistent finding on computed tomographic scanning, DDS remains a clinical diagnosis because laboratory tests, including electroencephalography, are nonspecific. It is usually self-limited, but full recovery may take several days. The differential diagnoses for DDS are detailed in Table 100.2 34

The pathogenesis of DDS is still a subject of debate. The reverse urea effect theory, which proposes that a transient osmotic disequilibrium occurs during dialysis as a result of a more rapid removal of urea from blood than from cerebrospinal fluid, has been disputed.35 In animals undergoing rapid dialysis, despite the correction of

TABLE 100.2

Dialysis Dysequilibrium

Differential diagnosis

Subdural hematoma
Uremia
Nonketotic hyperosmolar coma
Acute cerebrovascular event
Dialysis dementia
Excessive ultrafiltration and seizure
Hypoglycemia
Malignant hypertension
Hyponatremia

Risk factors

Younger age
Severe uremia
Rapid and marked intradialytic fall in urea at dialysis initiation
Low dialysate sodium concentration
Preexisting neurologic disorders

Prevention

Early recognition of uremia states
Stepped initiation of dialysis with short initial treatment times
Use of volumetric-controlled hemodialysis machines
Low blood flow rates
Utilize small surface area dialyzers
Targeted reduction in blood urea ~30%
Sodium profiling, high not low sodium dialysate concentration

systemic acidosis, a paradoxical cerebrospinal fluid acidosis develops that is aborted by slower dialysis. An additional mechanism is the intracerebral accumulation of idiogenic osmoles, such as inositol, glutamine, and glutamate.

In high-risk patients (see Table 100.2), preventive measures include the use of volumetric-controlled machines, bicarbonate dialysate, sodium modeling, earlier recognition of uremic states, and stepped initiation of dialysis (short initial treatment times with lower blood pump speeds). To this end, short and more frequent dialysis treatments are recommended with use of small surface area dialyzers and reduced blood flow rates. The target reduction in blood urea should initially be limited to 30%. The prophylactic use of mannitol or anticonvulsants is not recommended.

An extension of this syndrome may be one that mimics osmotic demyelination syndrome, similar to that seen with rapid correction of hyponatremia. Several cases have been reported in association with dialysis initiation, with clinical manifestations similar to those of the locked-in pontine picture of central demyelination. The difference is that with the dialysis-related condition, patients appear to recover over the ensuing 5 to 7 days, and the condition seems to be related to edema rather than demyelination.36

Seizures

Intradialytic seizures occur in fewer than 10% of patients and tend to be generalized but easily controlled. However, focal or refractory seizures warrant evaluation for focal neurologic disease, particularly intracranial hemorrhage. Causes of seizures are summarized in Fig. 100.2 and are discussed further in Chapter 89

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. Intravenous diazepam, alprazolam, or clonazepam, and phenytoin may be required. Intravenous 50% dextrose in water should be administered promptly if hypoglycemia is suspected.

Causes of Hemodialysis-Associated Seizures
Drugs
Dialytic removal of
anticonvulsants
Epileptogenic drugs:
theophylline, meperidine
(its toxic metabolite
normeperidine), penicillin
Erythropoiesis-stimulating
agents

Metabolic
Hypocalcemia
Hypomagnesemia
Hypoglycemia
Hyperosmolarity caused
by hypernatremia
Severe acid-base disturbance
Uremic encephalopathy

Hemodialysisassociated seizures

Other toxins
Acute aluminum intoxication
Alcohol withdrawal

Focal neurologic disease
Intracranial hemorrhage
Atheroembolism
Thrombotic microangiopathy

Dialysis disequilibrium syndrome
Hypertensive encephalopathy

Cerebral anoxia due to
sustained hypotension
Cardiac arrhythmia
Hypersensitivity reaction
Sepsis
Hemorrhage

Fig. 100.2 Causes of hemodialysis-associated seizures.

Headache

Dialysis headache is common and typically consists of a bifrontal discomfort that develops during dialysis and may become intense and throbbing, accompanied by nausea and vomiting. It is usually aggravated by the supine position, but there are no visual disturbances.[37]

Although its cause is unknown, dialysis headache may be a subtle manifestation of DDS or may be related to accumulation of acetate, which is present in low concentrations (3–4 mmol/L) in almost all dialysate fluid. A role for nitric oxide also has been postulated. Alternatively, it may be a manifestation of caffeine withdrawal caused by dialytic removal of caffeine.

Management consists of oral analgesics (e.g., acetaminophen [paracetamol]). Preventive measures include slow dialysis with reduced blood flow rates; change to bicarbonate dialysate, sodium, and ultrafiltration modeling; coffee ingestion during dialysis; and use of reprocessed dialyzers. Attention should also be paid to adequate flushing of the lines and dialyzer before commencement of dialysis. Changing the dialyzer (especially to a synthetic membrane or an alternative synthetic membrane) is sometimes useful in refractory cases.

HEMATOLOGIC COMPLICATIONS

Complement Activation and Dialysis-Associated Neutropenia

Complement activation and neutropenia, first seen with unsubstituted cellulose dialyzers that are now not used, can occur with widely used dialyzer membranes, including cellulose acetate and “synthetic” membranes such as polysulfone. However, this is very uncommon, especially in the case of the synthetic membranes, and the long-term clinical relevance of this phenomenon remains speculative. Its contribution to acute intradialytic morbidity is discussed later.

Intradialytic Hemolysis

Acute hemolysis can be caused by faulty dialysis equipment, chemicals, drugs, toxins, or patient-related factors (Fig. 100.3).38 With the advent

of better dialysis equipment design and the widespread use of reverse osmosis and/or deionization systems and carbon filters, traumatic red blood cell (RBC) fragmentation caused by poorly designed blood pumps and methemoglobinemia caused by water contamination with chloramine or copper are rarely seen today. However, nitrate or nitrite intoxication causing methemoglobinemia still occurs sporadically in patients on home HD who use well water contaminated with urine from domesticated animals. Furthermore, during dialyzer reprocessing, formaldehyde retention can result in hemolysis by inducing formation of cold agglutinins or inhibiting RBC metabolism.

The diagnosis of acute hemolysis is evident when grossly translucent hemolyzed blood is observed in the tubing. Patients with methemoglobinemia have nausea, vomiting, hypotension, and cyanosis, and oxygen therapy does not improve the black blood present in the extracorporeal circuit. Copper contamination should be suspected in the presence of skin flushing and abdominal pain or diarrhea.

Evaluation should include reticulocyte count, haptoglobin, lactate dehydrogenase, blood smear, Coombs test, and measurement of methemoglobin. Chromium 51 (51Cr)-labeled RBC survival and bone marrow examination may occasionally be indicated if there is recurrent hemolysis. More important, analysis of tap water for chloramines and assessment of the status of charcoal filtration (which removes chloramines) and metal contaminants and thorough analysis of the dialysis equipment for clues of increased blood turbulence are recommended.

Hemorrhage

Bleeding complications are commonly related to the use of intradialytic anticoagulation, which exacerbates the uremic bleeding diathesis (see Chapter 87). In addition, dialysis patients are prone to spontaneous bleeding at specific sites, such as gastrointestinal arteriovenous malformations; subdural, pericardial, pleural, retroperitoneal, and hepatic subcapsular spaces; and the ocular anterior chamber. Despite its limitations, the bleeding time remains the best indicator of hemorrhagic tendency.

Causes of Intradialytic Hemolysis
Glucose-6-phosphate
deficiency
Exacerbated by oxidants
(e.g., quinine sulfate)

Interference with red
cell metabolism
Copper: affects cellular thiols
Aluminum: affects iron uptake
Formaldehyde: inhibits glycolysis
Hypophosphatemia: causes
2,3-diphosphoglycerate deficiency

Traumatic fragmentation
Dialyzer roller pump
Excessive suction at arterial
access site
Single-needle dialysis
High blood flow through a small needle
Kinked dialysis catheter/tubing
Right atrial subclavian catheter
Incorrect osmolarity of dialysate

Microangiopathy
Drug induced
(e.g., quinine sulfate)

Cell membrane
fragility
Insufficient dialysis
Zinc deficiency

Intradialytic
hemolysis

Thermal damage
Overheated dialysate (>47°C)
Underheated dialysate (<35°C):
activation of anti-N cold agglutinins
(formaldehyde)

Reductive
damage
Formaldehyde
(also may activate
cold agglutinins)

Oxidative damage:
methemoglobulinemia
Chloramines
Nitrite/nitrate
Copper
Drugs (e.g., quinine sulfate)

Fig. 100.3 Causes of intradialytic hemolysis.

In addition to specific measures directed to the site of hemorrhage, reversal of uremic platelet dysfunction is imperative. Strategies include the use of erythropoiesis-stimulating agents or RBC transfusions to achieve a hematocrit above 30% to improve rheologic platelet–vessel wall interactions, intravenous conjugated estrogens at 0.6 mg/kg/day for 5 consecutive days, intravenous or subcutaneous 1deamino-8-d-arginine-vasopressin (DDAVP) at 0.3 μg/kg administered over 15 to 30 minutes, and intravenous infusion of cryoprecipitate (see Chapter 87). For patients experiencing severe bleeding, it is advisable to consider heparin-free dialysis with use of normal saline flushes every 15 to 30 minutes with ultrafiltration adjustments. An alternative approach is to utilize predilution HDF, which provides dialysate infusion prior to entry of the blood into the dialyzer. However, this approach requires high ultrafiltration volumes and does not have a proven benefit over normal saline flushes.39 40 Other alternatives may include regional heparin or citrate anticoagulation, and in the long term the use of low molecular weight heparin, heparin modeling, or prostacyclin may be considered. More recently, the use of heparin-bound dialyzers (such as hemophan or AN69ST)41 or citrate-containing dialysate have been advocated in patients at risk for bleeding, although they may not decrease the need for routine circuit anticoagulation.42 In patients scheduled for elective surgery or invasive procedures, cessation of aspirin should be considered a week in advance, the dose of anticoagulant reduced to a minimum, and the hematocrit maintained above 30%. In some patients, intravenous DDAVP to reverse the uremic platelet defect also may be required, although its efficacy has been questioned. Tranexamic acid, a potent fibrinolytic inhibitor, can be used as an adjuvant treatment to control hemorrhage in dialysis patients.43

Thrombocytopenia

Heparin-induced thrombocytopenia is an increasingly important cause of thrombocytopenia in dialysis patients. The diagnosis and management, including alternative strategies for anticoagulation for HD, are discussed in Chapter 87

PULMONARY COMPLICATIONS

Dialysis-Associated Hypoxemia

In most patients, the arterial Pao2 decreases by 5 to 20 mm Hg (0.6–4.0 kPa) during dialysis, reaching a nadir at 30 to 60 minutes, and resolves within 60 to 120 minutes after discontinuation of dialysis. This decrease is usually of no clinical significance to patients unless there is preexisting chronic cardiopulmonary disease.

Hypoventilation is the main implicated factor and is primarily central in origin as a result of a decrease in carbon dioxide production after acetate metabolism (specific to acetate-containing dialysate), loss of carbon dioxide in the dialyzer (with both acetate and bicarbonate dialysate), and rapid alkalinization of body fluids (particularly with large surface area dialyzers).44 In addition, acetate-induced respiratory muscle fatigue can lead to hypoventilation, especially in acutely ill patients. Furthermore, ventilation-perfusion mismatch may be caused by pulmonary leukocyte agglutination (in part resulting from complement activation) or impaired cardiac output (e.g., from myocardial stunning).

In high-risk patients with fluid overload, preventive measures consist of using intradialytic oxygen supplementation, biocompatible membranes, and avoiding acetate dialysate. Optimizing hematocrit/hemoglobin values and performing sequential ultrafiltration followed by HD may further reduce the likelihood of hypoxemia.

TECHNICAL MALFUNCTIONS

Air Embolism

The most vulnerable source of air entry into the extracorporeal circuit is the prepump tubing segment, in which significant subatmospheric pressures prevail. However, other sources need to be considered, including intravenous infusion circuits especially with glass bottles, air bubbles from the dialysate, and dialysis catheters. High blood flow rates may allow rapid entry of large volumes of air despite small leaks.

Clinical manifestations depend on the volume of air introduced, the site of introduction, the patient's position, and the speed at which air is introduced.45 In the sitting position, air entry through a peripheral vein bypasses the heart and causes venous emboli in the cerebral circulation. The acute onset of seizures and coma in the absence of precedent symptoms such as chest pain and dyspnea is highly suggestive of air embolism. In the supine position, air introduced through a central venous line will be trapped in the right ventricle, where it forms foam, interferes with cardiac output, and, if it is large enough, leads to obstructive shock. Dissemination of microemboli to the pulmonary vasculature results in dyspnea, dry cough, chest tightness, or respiratory arrest. Furthermore, passage of air across the pulmonary capillary bed can lead to cerebral or coronary artery embolism. In the left Trendelenburg position, air emboli migrate to the lower extremity venous circulation, resulting in ischemia as a result of increased outflow resistance. Foam may be visible in the extracorporeal tubing, and cardiac auscultation may reveal a peculiar churning sound, the so-called "millwheel murmur."

The immediate management of clinically suspected air embolism is summarized in Fig. 100.4. Prevention depends primarily on dialysis machines equipped with venous air bubble traps and foam detectors located just distal to the dialyzer and a venous pressure monitor at the venous end. The detector is attached to a relay switch that simultaneously activates an alarm, shuts off the blood pump, and clamps the venous blood line if air is detected. Therefore, dialysis should never be performed in the presence of an inoperative air detection alarm system. Glass bottles should be avoided because they create vacuum effects that can permit air entry into the extracorporeal system. Dialysis catheters should be aspirated and flushed with saline before connection. Extra care should be taken to ensure occlusion of catheters at two points at the end of treatment (clamp and line cap). Dialyzer rinsing, before use, should expand all compartments to remove residual air bubbles.

Incorrect Dialysate Composition

Incorrect dialysate composition results from technical or human errors. Because the primary solutes constituting the dialysate are electrolytes, the dialysate concentration will be reflected by its electrical conductivity. Therefore, proper proportioning of concentrate to water can be achieved by the use of a meter that continuously measures the conductivity of the dialysate solution as it is being fed to the dialyzer. Life-threatening electrolyte and acid-base abnormalities are avoidable if the conductivity alarm is functioning properly and the alarm limits are set correctly. However, in dialysis machines that are equipped with conductivity-controlled mixing systems, the system automatically changes the mixing ratio of the concentrates until the dialysate solution conductivity falls within the set limits. This may inadvertently lead to dialysate without any bicarbonate, with apparently acceptable conductivity. Therefore, if conductivity-controlled systems are used, it is safer to also check the dialysate pH before dialysis. Conductivity monitors can fail or can be improperly adjusted due to human error. Therefore, it is important to add human monitoring of dialysate composition before every treatment, whenever a machine has been sterilized or moved about, or whenever a new concentrate is used. Furthermore, as many nonstandard solutions are available, some of which may be used with an inappropriate proportioning system, it is also essential that the supplies match the machine-proportioning ratio for which they were prepared for the appropriate final dialysate composition to be obtained (note that different machine manufacturers use different proportioning ratios).

Double checking of concentrate variations (e.g., potassium and calcium concentration) should be practiced, as it is for intravenous drug administration.

Hypernatremia
Management of Clinically
Suspected Air Embolism
Clamp the venous blood line

Stop the blood pump

Place the patient in the left Trendelenburg position

Intradialytic hypernatremia occurs when concentrate or the ratio of concentrate to water is incorrect and the conductivity monitors or the alarms are not functioning properly. Hyperosmolality results in intracellular water depletion. Clinical manifestations include thirst, headache, nausea, vomiting, seizures, coma, and death. Aggressive treatment is mandatory and includes cessation of dialysis, hospitalization, and infusion of 5% dextrose in water. Dialysis should be resumed with a different machine; the dialysate sodium level should be 2 mmol/L lower than the plasma level, and isotonic saline should be concurrently infused. Dialysis against a sodium level 3 to 5 mmol/L lower than the serum level may increase the risk for disequilibrium. Ultrafiltration with equal volume replacement with normal saline is another option.

Hyponatremia
Provide cardiorespiratory support
High-flow oxygen administration
Endotracheal intubation
Mechanical ventilation

Aspirate air from the right ventricle using a percutaneously inserted needle or right atrial dialysis catheter

Consider hyperbaric oxygenation treatment if available

Fig. 100.4 Management of clinically suspected air embolism.

Failure to add concentrate, inadequate concentrate-to-water ratio, or conductivity monitor or alarm malfunction can cause intradialytic hyponatremia. Hyponatremia also can occur during the course of dialysis with a proportioning system if the concentrate container runs dry and the conductivity set limits are inappropriate. Acute hypoosmolality causes hemolysis with hyperkalemia and hemodilution of all plasma constituents. Symptoms include restlessness, anxiety, pain in the vein injected with the hypotonic hemolyzed blood, chest pain, headache, nausea, and occasional severe abdominal or lumbar cramps. Pallor, vomiting, and seizures may be observed. Treatment consists of clamping the blood lines and discarding the hemolyzed blood in the extracorporeal circuit. High-flow oxygen and cardiac monitoring are imperative because of hyperkalemia and potential myocardial injury. Dialysis should be restarted with a new dialysate batch containing low potassium, and high transmembrane pressure should be applied to remove excess water. Correction of serum sodium concentration should be achieved by no more than 1 to 2 mmol/L/h. Anticonvulsants are indicated for seizures and blood transfusions for severe anemia. Successful correction of severe hyponatremia has been reported in a single 3-hour HD session with a dialysate sodium concentration of 135 mmol/L without any adverse neurologic consequences despite a serum sodium correction rate of 3 mmol/L/h.46 This suggests that elevated blood urea levels might protect uremic patients from the development of demyelinating syndromes when hyponatremia is rapidly corrected.

Metabolic Acidosis

Although acute intradialytic metabolic acidosis can be a manifestation of improper mixing of concentrates or failure of pH monitors, other causes need to be ruled out, including diabetic or alcoholic ketoacidosis, lactic acidosis, ischemic tissues, toxic ingestions, and dilutional acidosis.47 The diagnosis is usually suggested by the acute onset of hyperventilation during HD and confirmed by laboratory evaluation. In most circumstances, correction of the underlying cause and use of bicarbonate dialysate at the appropriate concentration (32–35 mmol/L) are adequate measures.

Metabolic Alkalosis

Severe intradialytic metabolic alkalosis is rare and may be caused by errors in dialysate concentrates, reversed connection of bicarbonate and acid concentrate containers to the entry ports of the dialysis machine, pH monitor malfunction, or use of regional citrate anticoagulation. The most common cause, however, is hydrochloric acid loss as a result of vomiting or nasogastric suction. Attention should also be directed to identification of sources of added alkali.48

Acute treatment is rarely necessary unless a technical error has occurred. Removal of the alkali source is usually sufficient, and H2 antagonists or proton pump inhibitors may be successful if there is gastric acid loss. The administration of sodium chloride to anephric patients with chloride-sensitive alkalosis will not repair the alkalosis. If a more rapid reduction in serum bicarbonate is desired, modification of the dialysate bath by replacement of alkali with chloride, substitution of bicarbonate with acetate dialysate, use of acid dialysate, and infusion of hydrochloric acid are effective but cumbersome measures. The use of conventional or low-bicarbonate (25–30 mmol/L) dialysate is probably as effective.

Temperature Monitor Malfunction

Malfunction of the thermostat in the dialysis machine can result in the production of excessively cool or hot dialysate. Whereas cool dialysate is not dangerous and may have beneficial hemodynamic effects (see discussion regarding intradialytic hypotension), overheated dialysate can cause immediate hemolysis and life-threatening hyperkalemia, particularly if the dialysate temperature increases to more than 51°C. In such an event, dialysis must be stopped immediately and blood in the system discarded. The patient should be monitored for hemolysis and hyperkalemia. Dialysis should be resumed to cool the patient by use of a dialysate temperature of 34°C to treat hyperkalemia and allow blood transfusions if necessary. Visual and audible alarms are mandatory to prevent this complication.

Blood Loss

Intradialytic blood loss can result from arterial or venous needle disengagement from the access, separation of the venous or arterial line connections, femoral or central line dialysis catheter perforation or dislodgment, or rupture of a dialysis membrane with or without malfunction of the blood leak detector. Care should be taken to ensure needle insertion sites and line connection points are and remain visible during a dialysis treatment. Clinical findings include hypotension, loss of consciousness, and cardiac arrest. In addition, after traumatic insertion of a dialysis catheter, blood loss can result in pain or mass from a rapidly expanding hematoma; chest, shoulder, or neck pain from intrapericardial blood loss; back, flank, groin, or lower abdominal pain or distention from retroperitoneal bleeding; or hemoptysis from pulmonary bleeding. Acute management includes the discontinuation of HD, pressure application for local hemostasis, reversal of anticoagulation (e.g., protamine sulfate for heparin), hemodynamic support, oxygen administration, and surgical intervention if needed.

In the home dialysis setting, especially nocturnal HD, venous needle dislodgement is potentially catastrophic. A number of devices have been developed for early detection of blood leak resulting from needle dislodgment, including bed-wetting incontinence pads, Red-Sense and HEMOdialert blood detectors, and other proprietary techniques. However, the most important component is prevention by comprehensive and repeated patient education about adequate taping of dialysis needles and lines.

Clotting of Dialysis Circuit

Clotting of the extracorporeal circuit during dialysis is a common practical problem, has many underlying causes, and warrants a thorough investigation. Technical factors include an inadequate or poor priming technique, resulting in retention of air in the dialyzer, and lack of or inadequate priming of the heparin infusion line. Such operatorinduced errors are corrected through ongoing staff education and competency assessment. Incorrect heparin loading dose, insufficient time lapse after loading dose of heparin for systemic anticoagulation to occur, incorrect pump setting for constant heparin infusion, delayed start of the heparin pump, and failure to release the heparin line clamp are important correctible causes of clotting that also should be considered. Low molecular weight heparin is often used as a single bolus at the commencement of dialysis but may not maintain anticoagulation for extended hours of treatment (e.g., nocturnal HD). Vascular access–related problems from inadequate blood flow caused by needle or catheter positioning or clotting, excessive access recirculation, and frequent interruption of blood flow also can result in clotting. Immediate management requires prompt recognition of the underlying cause and implementation of corrective actions, including ongoing heparin dose adjustment and, if indicated, vascular access revision.

Heparin-free dialysis is sometimes medically indicated, such as in an actively bleeding patient or postoperatively. Although traditional approaches to avoid circuit clotting in this circumstance involve frequent saline flushes, an alternative approach is to employ predilution HDF as outlined earlier.

DIALYSIS REACTIONS

During HD, blood is exposed to surface components of the extracorporeal circuit, including the dialyzer, tubing, sterilization processes, and other foreign substances related to the manufacturing and reprocessing procedures. This interaction between the patient’s blood and the extracorporeal system can lead to various adverse reactions (Fig. 100.5).

Anaphylactic and Anaphylactoid Reactions

Clinical Presentation

Anaphylaxis is the result of an immunoglobulin E (IgE)-mediated acute allergic reaction in a sensitized patient, whereas anaphylactoid reactions result from the direct release of mediators by host cells. Symptoms usually develop within the first 5 minutes of dialysis,

Development and Prevention of Dialysis Reactions
Time Scale

Etiology

Pathogenesis

Ethylene
oxide

First use

Anaphylaxis

Management

IgE
Formaldehyde
(rare)
Glutaraldehyde
Renalin

Reuse
5-20 min
into HD
Bradykinin

Unmodified AN69*
membrane
Reused membranes

Stop HD
Do not return
extracorporeal
blood to patient
Epinephrine
Corticosteroids
Antihistamines

20-40 min
into HD

Any time during
HD

Mild reaction

Complement

Pyrogenic
reaction

Bacterial
contamination

Discontinue reuse

Use test dose
for iron dextran

Iron dextran
Desferoxamine
(rare)
Heparin (rare)

Cellulose
membranes

Rinse dialyzer
before use
Use gamma ray–
or steam-sterilized
dialyzers

Avoid unmodified
AN69 dialyzers with
ACE inhibitors
Discontinue reuse
with renalin

ACE inhibitor
interaction

Anaphylactoid

Histamine

Prevention

Continue HD
Symptoms
usually settle
in 1 h

Use noncellulose
dialyzers

Stop HD if
hypotension
is present
Blood cultures
Antibiotics
Antipyretics

Preventive strategy
(see Table 100.3)

Fig. 100.5 Development and prevention of dialysis reactions. *Acrylonitrile and sodium methallyl sulfonate copolymer. ACE, Angiotensin-converting enzyme; AN69, acrylonitrile; HD, hemodialysis; IgE, immunoglobulin E.

although a delay of up to 20 minutes is possible. Symptoms vary from subtle to severe and include burning or heat throughout the body or at the access site; dyspnea, chest tightness, and angioedema or laryngeal edema; paresthesias involving the fingers, toes, lips, or tongue; rhinorrhea, lacrimation, sneezing, or coughing; skin flushing; pruritus; nausea or vomiting; abdominal cramps; and diarrhea. Predisposing factors include a history of atopy, elevated total serum IgE, eosinophilia, and the use of ACE inhibitors. The etiology of dialysis reactions is diverse, and a thorough investigation is required.

First-Use Reactions

The majority of first-use reactions were ascribed to the manufacturer’s dialyzer sterilant ethylene oxide (ETO), which is now rarely used. The potting compound that anchors the hollow fibers in the dialyzer housing acts as a reservoir for ETO and may impede its washout from the dialyzer, leading to sensitization. When it is conjugated to human serum albumin (HSA), ETO acts as an allergen. By use of a radioallergosorbent test (RAST), specific IgE antibodies against ETO-HSA are detected in two-thirds of patients with such reactions. However, 10% of patients with no history of dialysis reactions have a positive RAST result.

Reuse Reactions

Because most residual ETO is washed out of the dialyzer during first use, reuse reactions are likely to be a result of the disinfectants used for dialyzer reprocessing. These agents include formaldehyde, glutaraldehyde, and peracetic acid–hydrogen peroxide in allergic patients; specific IgE antibodies against formaldehyde are occasionally detectable.

Bradykinin-Mediated Reactions

In the early 1990s, anaphylactoid reactions appeared in Europe among patients dialyzed with modified acrylonitrile (AN69) dialyzers who were also taking ACE inhibitors. Investigation of these incidents revealed that binding of factor XII to this sulfonate-containing, negatively charged membrane resulted in the formation of kallikrein and release of bradykinin, which in turn led to the production of prostaglandin and histamine, with subsequent vasodilation and increased vascular permeability. ACE inactivates bradykinin, and therefore ACE inhibitors can prolong the biologic activities of bradykinin.[49] These membranes have since been chemically modified, thereby reducing this risk, but are still in use for plasmapheresis.

Anaphylactoid reactions also have been observed in patients taking ACE inhibitors who were dialyzed with membranes that had been reprocessed with peracetic acid–hydrogen peroxide; these reactions abated once reprocessing was discontinued, despite continued use of ACE inhibitors. It has been speculated that Renalin may oxidize cysteine-containing proteins that are adsorbed on the dialyzer membrane, leading to the formation of cysteine sulfonate and contact activation of factor XII. Bradykinin-mediated reactions are rarely observed during contemporary hemodialysis treatments.

Drug-Induced Reactions

Anaphylactoid reactions to parenteral iron dextran occur in 0.6% to 1% of HD patients. Significantly higher rates of anaphylactoid reactions have been observed among users of higher molecular weight compared with lower molecular weight iron dextran. In vitro, dextran produces a dose-dependent basophil histamine release. The Kidney Disease Improving Global Outcomes Guidelines recommend that resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.50 Alternative preparations of iron provoke fewer anaphylactoid reactions than iron dextran and are discussed further in Chapter 86

Hypersensitivity to heparin formulations is rare and usually responds to substitution of beef with pork heparin or vice versa. An alternative is to substitute low molecular weight heparin. A nationwide outbreak in the United States of severe adverse reactions in HD patients was attributed to vials of heparin contaminated with oversulfated chondroitin sulfate.51

Treatment and Prevention

Treatment of anaphylactic and anaphylactoid reaction requires the immediate cessation of HD without returning the extracorporeal blood to the patient. Epinephrine, antihistamines, corticosteroids, and respiratory support should be provided, if needed. Specific preventive measures include rinsing the dialyzer immediately before first use, substituting ETO with dialyzers sterilized with gamma ray or steam, avoiding unmodified AN69 membranes in patients taking ACE inhibitors, and discontinuing reprocessing procedures in selected patients.

Mild Reactions

Mild reactions particularly occur 20 to 40 minutes after initiation of dialysis, predominantly with first use of unsubstituted cellulosic dialyzers, and consist of chest or back pain. Dialysis can be continued because symptoms usually abate after the first hour, suggesting a relation to the degree of complement activation. Indeed, these reactions decrease with the use of substituted and reprocessed unsubstituted cellulose membranes. Administration of oxygen and analgesics is usually sufficient. Preventive measures include automated cleansing of new dialyzers and use of noncellulose dialyzers.

Fever and Pyrogenic Reactions

Fever during dialysis can be due to infection or excessive microbial contamination of the dialysis apparatus. The latter, known as pyrogenic reaction, is usually a diagnosis of exclusion. Several factors during dialysis place patients at risk for exposure to bacterial products, including contaminated water or bicarbonate dialysate, improperly sterilized dialyzers, use of central venous dialysis catheters, and cannulation of infected arteriovenous fistulas or arteriovenous grafts.52

Soluble bacterial products such as endotoxin fragments can diffuse across the dialyzer into the blood, resulting in cytokine production and, consequently, pyrogenic reactions. Whereas high-flux dialyzers

have larger pores that may potentially allow larger fragments to cross from the dialysate to the patient, the synthetic high-flux membranes have a thick wall that tends to be very adsorptive for endotoxin fragments, thus mostly preventing this phenomenon.[53] Similarly, although HDF potentially has a higher risk for pyrogenic reactions because of the infusion of 10 to 25 L of dialysate, the customary use of two serial ultrafilters in the dialysate circuit make this an uncommon occurrence. Strategies for the prevention of pyrogenic reactions are summarized in Table 100.3[54]

When fever develops during HD, the first step is to address hemodynamic stability. If the patient is hypotensive, administration of fluids, cessation of ultrafiltration, and discontinuation of dialysis are often required, and refractory hypotension suggesting severe sepsis should trigger hospitalization.

Strategies to Prevent
Bacterial Contamination

TABLE 100.3

Fluid Type

Microbial Count Endotoxin
(cfu/mL)
(EU)

Water products

<100

Dialysate

<100

<0.50

Ultrapure dialysate (e.g., for HDF)

<0.1

<0.03

Reprocessed dialyzers

No growth

—

<0.25

Use appropriate germicide:
- 4% formaldehyde[a]
- 1% formaldehyde heated to 40°C[a,b]
- Glutaraldehyde[b]
- Hydrogen peroxide–peracetic acid mixture[b]
- Heat sterilization (105°C for 20 hours) for reprocessing of polysulfone membranes[b]

Wash and rinse the vascular access arm with soap and water.
Before cannulation, inspect vascular access for local signs of inflammation.
Scrub the skin with povidone-iodine or chlorhexidine and allow to dry for 5 minutes before cannulation.
Record temperature before and after dialysis.

When central delivery system is used:
🐧 •🐧 Clean and disinfect connecting pipes regularly.
🐧 •🐧 Remove residual bacteria or endotoxin by additional filtration.
When single-patient proportioning dialysis machine is used:
🐧 •🐧 Freshly prepare bicarbonate dialysate on a daily basis.
🐧 •🐧 Discard unused solutions at the end of each day.
🐧 •🐧 Rinse and disinfect containers with fluids that meet AAMI standards.
🐧 •🐧 Air dry containers before dialysate preparation.
Follow manufacturer’s guidelines for use of preservative-free medications.
Strict adherence to AAMI/ISO 11663:2014 standards.

[a] A minimum of 11- or 24-hour exposure to peracetic acid or formaldehyde is required, respectively.

[b] These germicides are equivalent or superior to 4% formaldehyde. The action level for the total viable microbial count in the product water and conventional dialysate is 50 cfu/mL, and the action level for the endotoxin concentration is 50% of the relevant standard.

AAMI, Association for the Advancement of Medical Instrumentation; cfu, colony-forming units; EU, endotoxin units; HDF, hemodiafiltration; ISO, International Organization for Standardization.

From Lata C, Girard L, Parkins M, James MT. Catheter-related blood stream infection in end-stage kidney disease: a Canadian narrative review. Can J Kidney Health Dis. 2016;3:24.

The next step is to identify a potential source of infection. The dialysis vascular access should be carefully examined. If an infectious source related to non–vascular access is identified, specific therapy should be instituted on the basis of the working diagnosis. Nontunneled and tunneled central venous dialysis catheters always should be suspected as a likely cause of infection, even in the absence of local signs of infection such as erythema and exit site drainage. Catheters with evident signs of infection at the insertion site should be removed and the tip cultured (detailed management is outlined in Chapter 96).

Antipyretics should be administered, and blood culture specimens should be obtained before initiation of antibiotic therapy; this should include cultures from temporary access devices. The initial choice of antibiotics should include gram-positive and gram-negative bacterial coverage, and the regimen should be adjusted according to the culture results and local guidelines.

In the presence of a dialysis catheter, paired blood culture specimens should be obtained from a peripheral vein and the catheter lumen, and a broad-spectrum antibiotic regimen should be initiated. Catheter lock solutions that use either antibiotics or sterilants such as calcium citrate have been demonstrated to significantly reduce the rate of catheter-related bacteremia.55 56 In the case of catheter-related bacteremia, removal of the dialysis catheter is strongly indicated, as is transesophageal echocardiography to rule out endocarditis, particularly with staphylococcal sepsis. A regimen of at least 14 days of antibiotic therapy after removal of the catheter is also recommended.

An outbreak of bacteremia among several dialysis patients involving a similar organism should prompt a thorough search for bacterial contaminants in the dialysis equipment.52 Attention should also be paid to multiuse vials that are punctured several times, such as vials of epoetin, which has been linked to an outbreak of bloodstream infection. Single-use vials are preferred, when available.

Investigation of a Dialysis Pyrogenic Outbreak

Although causes of dialysis outbreaks are usually easily identifiable, often the reason for the outbreak is less clear, such as water contamination with bacterial toxins,57 medication chemical impurities,51 bacterial contaminants, systemic embolization of degraded dialyzer membrane polymer after prolonged or improper storage,58 and hemolysis from faulty blood tube sets.59 Investigation of a dialysis outbreak requires a methodical approach, including a critical review of the medical records and the various steps of the dialysis procedure (Box 100.1).

MISCELLANEOUS COMPLICATIONS

Postdialysis Fatigue

An ill-defined “washed-out” feeling or malaise during or after HD is a common nonspecific symptom that is observed in about one-third of patients and has multifactorial origins. Reduced cardiac output, peripheral vascular disease, depression, poor conditioning, postdialysis hypotension, hypokalemia or hypoglycemia, mild uremic encephalopathy, myopathy caused by carnitine deficiency, and dialysis-induced cytokine generation have all been incriminated. The use of bicarbonate dialysate with or without additional glucose (5–10 mmol/L) and l-carnitine supplementation (20 mg/kg/day) have been shown to improve postdialysis well-being. A trial of thrice-weekly l-carnitine at 20 mg/kg for 6 months resulted in a marked decrease in C-reactive protein level, which was paralleled by an increase in body mass index.60 To date, however, there is no conclusive evidence that l-carnitine improves quality of life in unselected dialysis patients.50

Compared with thrice-weekly HD, more frequent dialysis, including short daily and nocturnal HD, has been associated with a marked shortening in the time it takes for patients to recover from a dialysis session and to resume their daily activities, which is a surrogate for postdialysis fatigue.

BOX 100.1 Investigation of Dialysis Pyrogenic Outbreak

Review of Medical Records

Demographics
Underlying diseases
Dialysis schedule
Dialysis machine
Dialyzer used
- Membrane
- Type
- Manufacturer’s sterilization method
- Reuse germicide (if applicable)

Medication history
Signs and symptoms of illness
Laboratory tests
Interview health care workers who were caring for patient during incident

Procedural Review

Water treatment systems and practices
- Disinfection
- Distribution
- Storage procedures

Disinfection and maintenance of reprocessed dialyzers
Disinfection and maintenance of dialysis machines
Review of patient’s dialysis sessions

Pruritus

Pruritus is common and can be a very troubling symptom. The cause is often multifactorial, including xerosis, hyperparathyroidism, neuropathy, derangements in the immune system, and inadequate dialysis. In many patients, pruritus is more severe during or after dialysis and may be a manifestation of an allergic reaction to heparin, ETO, formaldehyde, acetate, or the dialysis membrane. In this subgroup of patients, use of gamma ray–sterilized dialyzers, discontinuation of formaldehyde use, switching to bicarbonate dialysate, use of lowdialysate calcium and magnesium might result in cessation of itching.

Difelikefalin, a peripherally restricted and selective agonist of kappa opioid receptors, has recently shown significant promise in the treatment of uremic pruritus and depending on availability should be considered.61 A detailed discussion of the management of uremic pruritus can be found in Chapter 91 (see Fig. 91.3).

Finally, eczematous reactions to antiseptic solutions, rubber gloves or puncture needle components, puncture needles, or adhesive tapes used to secure dialysis needles also should be considered.62

Genitourinary Problems

Priapism occurs in less than 0.5% of male HD patients. It is not related to sexual activity and occurs while the patient is on dialysis. The patient is usually awakened from sleep by a painful erection. Although the majority of cases are idiopathic, secondary causes include hyperviscosity; high hematocrit from androgen or epoetin therapy; dialysis-induced hypoxemia and hypovolemia from excessive ultrafiltration, particularly in men with sickle cell disease; and use of α-blockers, such as prazosin, or an antidepressant, such as trazodone.63

Urgent urologic referral is mandatory. Acute treatment consists of corporal aspiration and irrigation. Although surgical bypass provides venous egress from the corpora cavernosa, secondary impotence commonly develops but may be effectively treated by a penile prosthesis.

An unusual case of testicular angina occurring during excessive ultrafiltration has been described. The patient was diabetic and had extensive vascular calcification evident on imaging. He eventually required orchidectomy.64 A similar mechanism for this type of "angina" also has been described for the mesentery and right colon.

Hearing and Visual Loss

Intradialytic hearing loss may be caused by bleeding in the inner ear as a consequence of anticoagulation, cochlear hair cell injury from edema, or flux of fluid and electrolytes across cochlear cell membranes. Intradialytic visual loss is rare but can be caused by central retinal vein occlusion, retinal hemorrhage secondary to heparin exposure in diabetics, precipitation of acute glaucoma, ischemic optic neuropathy secondary to hypotension, or Purtscher-like retinopathy secondary to leukocyte embolization.

SELF-ASSESSMENT QUESTIONS

1. The most common cause of intradialytic hypotension is:
A. new-onset sepsis.
B. cardiac ischemia.
C. intravascular volume depletion.
D. altered thermal balance.
E. use of antihypertensive medications.
2. The most appropriate preventive strategy to avoid intradialytic hypotension is:
A. isothermic dialysis.
B. sodium modeling.
C. hematocrit-controlled volume removal.
D. avoidance of excessive interdialytic weight gain.
E. use of agents such as midodrine.
3. Intradialytic hemolysis may be caused by all of the following except:
A. copper in the dialysate.
B. residual formaldehyde.
C. chloramine spillover.
D. faulty dialysis pumps.
E. heparin exposure.
4. Severe dialyzer reactions may occur as a result of exposure to:
A. new synthetic dialysis membranes.
B. potting compound.
C. sterilant effects related to steam or gamma radiation.
D. angiotensin-converting enzyme inhibitors.
E. peracetic acid.
5. Management options for intradialytic cramps include:
A. intravenous hypertonic saline.
B. oral magnesium salts.
C. oral carnitine supplementation.
D. intravenous 50% dextrose.
E. all the above.

REFERENCES

1. Lewicki M, Kerr PG, Polkinghorne KR. Blood pressure and blood volume: acute and chronic considerations in hemodialysis. Semin Dial. 2013;26:62–72.
2. Flythe JE, Chang TI, Gallagher MP, et al. Blood pressure and volume management in dialysis: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int. 2020;97:861–876.
3. Kuipers J, Verboom LM, Ipema KJR, et al. The prevalence of intradialytic hypotension in patients on conventional hemodialysis: a systematic review with meta-analysis. Am J Nephrol. 2019;49:497–506.
4. Jefferies HJ, Virk B, Schiller B, et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clin J Am Soc Nephrol. 2011;6:1326–1332.
5. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int. 2004;66:1212–1220.
6. Assimon MM, Wenger JB, Wang L, Flythe JE. Ultrafiltration rate and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2016;68(6):911–922.
7. Hryciw N, Joannidis M, Hiremath S, Callum J, Clark EG. Intravenous albumin for mitigating hypotension and augmenting ultrafiltration during kidney replacement therapy. Clin J Am Soc Nephrol. 2020. CJN.09670620.
8. Okada K, Abe M, Hagi C, et al. Prolonged protective effect of short daily hemodialysis against dialysis-induced hypotension. Kidney Blood Press Res. 2005;28:68–76.
9. Dasgupta I, Thomas GN, Clarke J, et al. Associations between hemodialysis facility practices to manage fluid volume and intradialytic hypotension and patient outcomes. Clin J Am Soc Nephrol. 2019;14:385–393.
10. Damasiewicz MJ, Polkinghorne KR. Intra-dialytic hypotension and blood volume and blood temperature monitoring. Nephrology. 2011;16:13–18.
11. Flythe JE, Tugman MJ, Narendra JH, et al. Effect of ultrafiltration profiling on outcomes among maintenance hemodialysis patients: a pilot randomized crossover trial. J Nephrol. 2020;34:113–123.
12. Mustafa RA, Bdair F, Akl EA, et al. Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and metaanalysis. Clin J Am Soc Nephrol. 2016;11:442–457.
13. Caplin B, Alson H, Davenport A. Does on-line hemodiafiltration reduce intradialytic patient symptoms. Nephron Clin Prac. 2013;124:184–190.
14. Chen J, Gul A, Sarnak MJ. Management of intradialytic hypertension: the ongoing challenge. Semin Dial. 2006;19:141–145.
15. Van Buren PN, Inrig JK. Mechanisms and treatment of intradialytic hypertension. Blood Purif. 2016;41:188–193.
16. Rahman M, Dixit A, Donley V, et al. Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. Am J Kidney Dis. 1999;33:498–506.
17. Sang GL, Kovithavongs C, Ulan R, et al. Sodium ramping in hemodialysis: a study of beneficial and adverse effects. Am J Kidney Dis. 1997;29:669–677.
18. Dunne N. A meta-analysis of sodium profiling techniques and the impact on intradialytic hypotension. Hemodial Int. 2017;21(3):312–322.
19. Ligtenberg G, Blankestijn PJ, Oey PL, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. N Engl J Med. 1999;340:1321–1328.
20. Gunal AI, Karaca I, Celiker H, et al. Paradoxical rise in blood pressure during ultrafiltration is caused by increased cardiac output. J Nephrol. 2002;15:42–47.
21. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized controlled trial. Hypertension. 2009;53:500–507.
22. Bailey RA, Kaplan AA. Intradialytic cardiac arrhythmias: I. Semin Dial. 1994;7:57–58.
23. Kant KS. Intradialytic cardiac arrhythmias: II. Semin Dial. 1994;7:58–60.

24. McCausland FR, Tumlin JA, Roy-Chaudhury P, et al. MID Investigators and Committees. Intradialytic hypotension and cardiac arrhythmias in patients undergoing maintenance hemodialysis:

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47.

results from the Monitoring in Dialysis Study. Clin J Am Soc Nephrol. 2020;15:805–812.
Jadoul M, Thumma J, Fuller DS, et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clin J Am Soc Nephrol. 2012;7:765–774.
Karnik JA, Young BS, Lew NL, et al. Cardiac arrest and sudden death in dialysis units. Kidney Int. 2001;60:350–357.
Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med. 2011;365:1099–1107.
Krishnasamy R, Badve SV, Hawley CM, et al. Daily variation in death in patients treated by long-term dialysis: comparison of in-center hemodialysis to peritoneal and home hemodialysis. Am J Kidney Dis. 2012;61:96–103.
Wong MCG, Kalman JM, Pedagogos E, et al. Bradycardia and asystole is the predominant mechanism of sudden cardiac death in patients with chronic kidney disease. J Am Coll Cardiol. 2015;65:1263–1265.
Canzanello VJ, Burkart JM. Hemodialysis-associated muscle cramps. Semin Dial. 1992;5:299–304.
Khajehdehi P, Mojerlou M, Behzadi S, Rais-Jalali GA. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. Nephrol Dial

Transplant. 2001;16:1448–1451.

Sadowski RH, Allred EN, Jabs K. Sodium modeling ameliorates intradialytic and interdialytic symptoms in young hemodialysis patients. J Am Soc Nephrol. 1993;4:1192–1198.

Basile C, Giordano R, Vernaglione L, et al. Efficacy and safety of haemodialysis treatment with the Hemocontrol biofeedback system: a prospective medium-term study. Nephrol Dial Transplant. 2001;16:328–334.

Zepeda-Orozco D, Quigley R. Dialysis disequilibrium syndrome. Pediatr Nephrol. 2012;27:2205–2211.

Arieff AI. Dialysis disequilibrium syndrome: current concepts on pathogenesis and prevention. Kidney Int. 1994;45:629–635.

Tarhan NC, Agildere AM, Benli US, et al. Osmotic demyelination syndrome in end-stage renal disease after recent hemodialysis: MRI of the brain. AJR Am J Roentgenol. 2004;182:809–816.

Sousa Melo E, Carrilho Aguiar F, Sampaio Rocha-Filho PA. Dialysis headache: a narrative review. Headache. 2017;57(1):161–164.

Eaton JW, Leida MN. Hemolysis in chronic renal failure. Semin Nephrol. 1985;5:133–139.

Krummel T, Cellot E, Thiery A, De Geyer G, Keller N, Hannedouche T. Hemodialysis without anticoagulation: less clotting in conventional hemodialysis than in predilution hemodiafiltration. Hemodial Int. 2019;23:426–432.

Brunot V, Serre JE, Mourad G, Klouche K, Pernin V. Heparin-free renal replacement therapy for chronic hemodialyzed patients at high risk for bleeding: a comparison of on-line predilution hemodiafiltration with conventional hemodialysis. Hemodial Int. 2018;22:463–473.

Lee KB, Kim B, Lee YH, et al. Hemodialysis using heparin-bound Hemophan in patients at risk of bleeding. Nephron Clin Pract. 2004;97:c5–c10.

Leung KC, Tai DJ, Ravani P, et al. Citrate vs acetate dialysate on intradialytic heparin dose: a double blind randomized crossover study. Hemodial Int. 2016;20(4):537–547.

Sabovic M, Lavre J, Vujkovac B. Tranexamic acid is beneficial as adjunctive therapy in treating major upper gastrointestinal bleeding in dialysis patients. Nephrol Dial Transplant. 2003;18:1388–1391.

Cardoso M, Vinay P, Vinet B, et al. Hypoxemia during hemodialysis: a critical review of the facts. Am J Kidney Dis. 1988;11:281–297.

O’Quin RJ, Lakshminarayan S. Venous air embolism. Arch Intern Med. 1982;142:2173–2176.

Oo TN, Smith CL, Swan SK. Does uremia protect against the demyelination associated with correction of hyponatremia during hemodialysis? A case report and literature review. Semin Dial. 2003;16:68–71.

Gennari FJ. Acid-base balance in dialysis patients. Semin Dial. 2000;13:235–239.

48. Gennari FJ, Rimmer JM. Acid-base disorders in end-stage renal disease: Part II. Semin Dial. 1990;3:161–165.
49. Coppo R, Amore A, Cirina P, et al. Bradykinin and nitric oxide generation by dialysis membranes can be blunted by alkaline rinsing solutions. Kidney Int. 2000;58:881–888.
50. KDIGO Anemia Work Group. KDIGO clinical practice guidelines for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
51. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. N Engl J Med. 2008;359:2674–2684.
52. Jaber BL, Pereira BJG. Dialysis reactions. Semin Dial. 1997;10:158–165.
53. Hoenich NA. Membranes for dialysis: can we do without them? Int J Artif Organs. 2007;30:964–970.
54. Quality of Dialysis Fluid for Hemodialysis and Related Therapies. ANSI/AAMI/ISO 11663:2014. Arlington: American National Standards. Association for the Advancement of Medical Instrumentation; 2014:1–18.
55. Lata C, Girard L, Parkins M, James MT. Catheter-related blood stream infection in end-stage kidney disease: a Canadian narrative review. Can J Kidney Health Dis. 2016;3:24.
56. Aslam S, Vaida F, Ritter M, Mehta RL. Systematic review and metaanalysis on management of hemodialysis catheter related bacteremia. J Am Soc Nephrol. 2014;25:2927–2941.

57. Carmichael WW, Azevedo SM, An JS, et al. Human fatalities from cyanobacteria: chemical and biological evidence for cyanotoxins. Environ Health Perspect. 2001;109:663–668.
58. Hutter JC, Kuehnert MJ, Wallis RR, et al. Acute onset of decreased vision and hearing traced to hemodialysis treatment with aged dialyzers. JAMA. 2000;283:2128–2134.
59. Duffy R, Tomashek K, Spangenberg M, et al. Multistate outbreak of hemolysis in hemodialysis patients traced to faulty blood tubing sets. Kidney Int. 2000;57:1668–1674.
60. Savica V, Santoro D, Mazzaglia G, et al. l-Carnitine infusions may suppress serum C-reactive protein and improve nutritional status in maintenance hemodialysis patients. J Ren Nutr. 2005;15:225–230.
61. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. KALM-1 trial investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. N Engl J Med. 2020;382:222–232.
62. Weber M, Schmutz JL. Hemodialysis and the skin. Contrib Nephrol. 1988;62:75–85.
63. Singhal PC, Lynn RI, Scharschmidt LA. Priapism and dialysis. Am J Nephrol. 1986;6:358–361.
64. Sequeira A, Buffington M, Gu X, Abreo K. Testicular angina during hemodialysis: an unusual complication of ultrafiltration. Hemodial Int. 2013;17:323–326.

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Peritoneal Dialysis: Principles, Techniques, and Adequacy

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INTRODUCTION

The prevalence of peritoneal dialysis (PD) continues to grow steadily worldwide. It is estimated that more than 272,000 patients worldwide are treated with PD, accounting for about 11% of the total global dialysis population.1 Patients on PD can have numerous fluid exchanges through a permanent indwelling silicone-based catheter. The exchange of PD fluid involves three important steps: filling, dwelling, and draining. Sterile dialysate provided in plastic bags is instilled into the peritoneal cavity with each exchange. The peritoneal membrane and surrounding capillaries function as a semipermeable membrane, which allows removal of waste and fluid. The removal of waste from the blood occurs by diffusion. Fluid is removed by a process called ultrafiltration (UF), in which an osmotic gradient generated by glucose or by another osmotic agent leads to water flux across the membrane.

PD can be prescribed up to 24 hours/day and 7 days/wk to patients in the form of continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD). In CCPD, patients receive treatment with an automated PD (APD) cycler, allowing for nighttime exchanges followed by a long dwell called a “last fill” that remains in the peritoneum during the daytime. There is significant geographic variation in the use of PD cyclers, driven in part by local resources and reimbursement policies. For example, in lower-resource settings, the overall PD uptake, prevalence, and cycler use are reduced compared with countries where reimbursement is greater.2 CAPD is the preferred dialysis modality in low- and middle-income countries as it is cost-effective and does not require more expensive equipment such as automated PD cyclers.3

ADVANTAGES AND LIMITATIONS OF PERITONEAL DIALYSIS

PD can be offered to many patients with kidney failure barring a few absolute contraindications. These contraindications include abdominal hernias that cannot be corrected surgically, abdominal adhesions not amenable to adhesiolysis, recurrent intraabdominal infections, and large hiatal hernias. Furthermore, severe cognitive impairment is another contraindication, unless a helper or visiting health care worker is available.

Patients with residual kidney function (RKF) may have greater benefit from PD compared with anuric patients. PD prescriptions can be adjusted easily to ensure effective clearance when RKF declines. However, if adequate dialysis or UF cannot be achieved or maintained with PD, patients may need to be transferred to hemodialysis (HD).

PD offers numerous advantages to patients. First, PD can be initiated in an incremental manner, which allows incident patients to become comfortable in the early phases of their treatment while minimizing treatment burden. Second, PD allows for slow and gentle

removal of fluid without significant hemodynamic changes. Third, PD can preserve RKF better than HD.4 Fourth, PD does not require vascular access and, unlike HD, there is no blood-membrane contact, which has been suggested as a cause of accelerated decline in RKF.2 Observational data suggests that PD can effectively remove excess fluid in patients with refractory volume overload due to cardiorenal syndrome.5

PD patients have better self-reported quality of life than patients receiving other types of dialysis. PD offers flexibility in schedule and travel while reducing the frequency for hospital visits. In patients receiving kidney transplants, PD is associated with better 5-year overall patient survival and a lower risk of delayed graft function compared with patients previously treated with HD.[3]

There are, however, some important disadvantages of PD that must be considered by patients, caregivers, and practitioners. PD is usually offered in the home, where the burden of care for patients and family members can be overwhelming, especially among patients who are frail or unable to safely perform PD without daily assistance. PD also increases hyperglycemia risk, particularly when using highconcentration glucose-based solutions. There is also an increased risk of dyslipidemia along with volume overload. Volume overload risk can be reduced by prescribing high-dose diuretics in patients with RKF.

PRINCIPLES OF PERITONEAL DIALYSIS

The fundamental principles of solute and fluid transport across the peritoneal membrane in PD include diffusion, osmosis, and convection. The peritoneal membrane consists of two major layers, the mesothelial monolayer and submesothelial compact zone (Fig. 101.1A).

The compact zone contains peritoneal capillaries that allow for solute clearance and fluid removal. Over time, changes in the peritoneal membrane can occur, leading to neovascularization of capillaries and fibrosis, and ultimately to changes in membrane transport characteristics (Fig. 101.1B).

Three-Pore Model

Peritoneal membrane transport occurs through three distinct pores of varying sizes, in what is described as the three-pore model (Fig. 101.2). Small pores allow small-solute and fluid exchange between the plasma and peritoneal cavity through the capillary wall in spaces called interendothelial clefts. These clefts have a radius of 40 to 50 Å, preventing the movement of larger macromolecules such as immunoglobulins and other macromolecules.[6] Larger molecules can move between the plasma and peritoneal cavity via very large pores (radius ~250 Å) in the capillaries and postcapillary venules. Very large pores only account for 0.01% of the total capillary pores, and transport across these pores is mainly driven by hydrostatic pressure.[6] The smallest pore, also called aquaporin-1 (AQP-1, radius < 4 Å), is

Peritoneal Membrane Layers
Peritoneal
cavity
Mesothelial
monolayer
Submesothelial
compact zone

Deeper loose
adipose
connective
tissue
A
B

Fig. 101.1 (A) various layers of the peritoneal membrane. (B) Changes occurring over time with peritoneal dialysis in peritoneal membrane layers with the submesothelial compact zone increasing in thickness due to extracellular matrix expansion along with neovascularization of capillaries in the deep layers. (From Nessim SJ, Perl J, Bargman JM. The renin-angiotensin-aldosterone system in peritoneal dialysis: is what is good for the kidney also good for the peritoneum? Kidney Int 2010;78[1]:23–28.)

Three-Pore Model
Smallest pore Small pore
(water channel)
4 nm
<0.5 nm

Large pore
>15 nm

Peritoneal
membrane
Water

Small solute

Large molecule

Fig. 101.2 Three-Pore Model. Small pores (4 nm) represent the major pathway across the peritoneum through which small solutes move by diffusion and water by convection driven by hydrostatic, colloid osmotic, and crystalloid osmotic pressure differences. Across large pores (>15 nm), macromolecules move out slowly by convection from plasma to the peritoneal cavity. The smallest pores (<0.5 nm) are represented by aquaporins permeable to water but are impermeable to solutes. Water moves here exclusively by crystalloid osmotic pressure.

responsible for nearly 50% of osmotically driven water movement in PD[7] (Fig. 101.1).

Effective Peritoneal Surface Area

The effective peritoneal surface area represents an area of the peritoneum that is perfused by capillaries and remains in direct contact with dialysate. Peritoneal blood flow through the capillaries can vary depending on vasodilation and vasoconstriction but is estimated to be 50 to 100 mL/min.[8] Variations in peritoneal capillary vascular resistance can also influence the permeability-surface area product (PS), also known as the mass transfer area coefficient. For example, inflammation from peritonitis can potentiate capillary vasodilation, increasing the capillary surface area and in turn enhancing small solute PS. Although small solute clearance may be enhanced with an increase in capillary recruitment, the same cannot be said about fluid permeability. Alterations in peritoneal blood flow do not directly translate to changes in peritoneal fluid permeability. The peritoneal fluid permeability is also known as hydraulic conductance (LpS) and is dependent on the distribution and density of AQP-1 and small pores across the peritoneum.[9] LpS varies from individual to individual such that in some cases of peritonitis, there is an increase in the LpS, leading to increased fluid transport across all pores. The opening of large pores may increase the leakage of macromolecules such as albumin into the peritoneum from the plasma. Enhanced peritoneal absorption of fluid from the dialysate can occur with peritonitis, resulting in reduced fluid removal due to rapid dissipation of the osmotic gradient between peritoneum and plasma.

Changes in patient positioning and fill volume can have significant variation in the dialysate-peritoneal surface area. Most adult patients will tolerate a maximum fill volume of 2 to 2.5 L or an intraperitoneal hydrostatic pressure (IPP) of less than 18 cm of H_2O without much discomfort.[10] However, at higher pressures (≥18 cm of H_2O), patients normally highlight discomfort even in a supine position. IPP is highest when patients are sitting compared with standing and is lowest in the supine position. A common misconception is that IPP elevations could result in high transcapillary hydrostatic pressure gradients that may lead to an increased loss of fluid from the peritoneal cavity. However, approximately 80% of the change in IPP (ΔIPP) will transmit to large veins surrounding the peritoneal cavity, causing increased intracapillary hydrostatic pressure.[11,12] As a result, the transcapillary hydrostatic pressure gradient is reduced, and the impact of ΔIPP on fluid absorption is minimal.

Fluid Kinetics

In PD, small pores account for over 95% of all pores in the peritoneal membrane. Only 2% of all pores in the peritoneal membrane are AQP-1, but they account for about 50% of water transport that is driven by the osmotic gradient created by intraperitoneal hyperosmolar dialysate.[13] Glucose-based dialysate solutions generate water transport through both AQP-1 and small pores. On the other hand, colloid osmotic agents such as icodextrin remove fluid primarily through small pores (~90%). The movement of electrolyte-free water via AQP-1 results in a fall in dialysate concentration of sodium during the first 2 hours of the dialysate dwell, a process referred to as sodium sieving. As dwell duration extends beyond 2 hours, sodium diffuses from plasma to dialysate through the small pores along its concentration gradient, and the dialysate concentration of sodium approaches the level in plasma.

Computer models have simulated the variation in UF over a 12hour dwell time (Fig. 101.3A). The osmotic gradient is greatest in the initial phase of the dwell, resulting in a large initial UF volume that diminishes with time as the osmotic gradient is lost. As the osmotic gradient dissipates, fluid absorption occurs through small pores (60%–80%) and lymphatics (20%–40%) in the surrounding tissues. Fig. 101.4 demonstrates the partial flows in the peritoneal membrane modeled across the various fluid conductive pathways in the three-pore model for 3.86% glucose PD solution. In “rapid transporters” (high and high-average transporters), the osmotic gradient created by glucose dissipates rapidly with UF occurring early in the dwell and fluid reabsorption in the latter part of the dwell. Conversely, “slow transporters” have prolongation of the glucose osmotic gradient, and thus better and more prolonged UF. Glucose has a low osmotic efficiency (osmotic reflection coefficient $[\sigma] = 0.03$), indicating that the osmotic gradient is more rapidly lost compared with many other solutes. On the other hand, glucose has an osmotic efficiency of 100% across AQP-1 ($\sigma = 1$).[14] As a result of this increased efficiency across AQP-1, glucose exerts about a 30-fold increase in the transport of fluid through aquaporins and leads to movement of solute-free water across the membrane. Fig. 101.3B demonstrates that for 4.25% glucose solution, the dialysate concentration of sodium will drop from 132 mmol/L to

Ultrafiltration Volume as a Function
of Dwell Time and Glucose Concentration
800
600

UFV (mL)

400
200
0

3.86%
0

60 120 180 240 300 360 420 480 540 600 660 720

-200

2.27%

-400

1.36%

-600
-800

A

Time (min)

Dialysate Sodium Concentration as a Function
of Dwell Time
142
140
138
[Na] (mmol/L)

136
134
132
130
128
126
124
122
0

60

120

180

240

300 360

B

420

480 540

600 660

720

Time (min)

Fig. 101.3 (A) Ultrafiltration as a function of dwell time. Net ultrafiltration volume (UFV) as a function of dwell time for 3.86% (yellow line), 2.27% (green line), and 1.36% (blue line) glucose, computer simulated using the three-pore model of peritoneal transport. (B) Dialysate sodium as a function of dwell time. Dialysate sodium as a function of dwell time for 3.86% (yellow line), 2.27% (green line), and 1.36% (blue line) glucose, computer simulated according to the three-pore model of peritoneal transport.

123 mmol/L within 90 minutes, followed by a gradual increase toward the serum sodium concentration. On the other hand, icodextrin (see later) has an average molecular weight between 13 and 19 kDa with a higher osmotic efficiency ($\sigma \sim 0.5$) compared with glucose across the small pores and is inefficient across aquaporins.[15] This inefficiency of icodextrin across aquaporins results in minimal UF across these channels and explains why this solution does not result in sodium sieving (Fig. 101.5B). The important clinical implication is that the volume of ultrafiltrate induced by icodextrin will contain more sodium than the volume induced by a dextrose-based solution.

gradient. The primary osmotic agents used in PD fluids are glucose, amino acids, and icodextrin. Traditionally, solutions were prepared using a lactate-buffer instead of bicarbonate, as Ca^{2+} and Mg^{2+} may precipitate to form calcium carbonate and magnesium carbonate, respectively, at an elevated pH during storage. Commercially available solutions now include multichambered PD delivery systems that replace lactate with bicarbonate. In dialysis bags with multiple chambers, the glucose is stored under conditions of low pH (the buffer is in another chamber that is admixed before inflow), and the production of glucose degradation productions during sterilization or storage is delayed by this low pH (see biocompatible solutions).[16]

TYPES OF PERITONEAL DIALYSIS FLUID

Glucose-Containing Solutions

PD fluid is usually packaged in clear polyvinyl chloride bags containing lactate-buffered, tightly regulated electrolyte levels without much variation between manufacturers. The solutions are potassium free, which allows for easier clearance of potassium down a concentration

Glucose-based solutions are the primary osmotic agents used in the management of PD. Options include solutions of low concentration (1.36% or 1.5%), intermediate concentration (2.27% or 2.5%), and high concentration (3.86% or 4.5%). The approximates in osmolarities must be considered in patients being treated with icodextrin, or it must be ensured that the glucometer being used is compatible with use of icodextrin and does not read out maltose as glucose.[21]

Amino acid–based solutions are available as a 1.1% amino acid mixture that has a similar osmolality to 1.36% glucose solution.[22] Like icodextrin, these solutions have the theoretical benefit of reducing the overall glucose exposure for the peritoneal membrane. Amino acid–based solutions are used primarily to enhance nutrition, but the results have been disappointing.[23,24] These solutions are limited to one exchange per day, as the absorbed amino acids can lead to acidosis and increase plasma urea levels. The access to amino acid–based solutions is now limited to European countries and a few other countries in compassionate use programs.

Peritoneal Volume Flows as a
Function of Dwell Time

Flow (mL/min)

7
6

Small pores

5

Aquaporins

4

Large pores

3

Lymph flow

2
1
0
1 0

120

240

360

480

600

1123

720

2

Time (min)

Fig. 101.4 Peritoneal Volume Flows as a Function of Dwell Time. Peritoneal volume flows as a function of dwell time for 3.86% glucose partitioned among aquaporins, small pores, large pores, and lymphatic absorption. The small-pore volume flow is initially approximately 60%

of total volume flow and becomes negative after peak time (220 min). The aquaporin-mediated water flow becomes slightly negative after approximately 250 minutes. The large-pore volume flow is negligible and remains constant throughout the dwell, as does lymphatic absorption (0.3 mL/min). (Modified from Venturoli D, Rippe B. Validation by computer simulation of two indirect methods for quantification of free water transport in peritoneal dialysis. Perit Dial Int. 2005;25[1]:77–84.)

are 345 mOsm/L (low concentration), 395 mOsm/L (intermediate concentration), and 484 mOsm/L (high concentration). A very-lowconcentration solution (0.5%) is less readily available and can be offered to patients with hypotension or intravascular volume contraction. The 0.5% solution leads to water and electrolyte absorption from dialysate to plasma and can sometimes be used to avoid intravenous fluid resuscitation.

There are, however, important drawbacks associated with the chronic use of glucose-based solutions. These include hyperglycemia, dyslipidemia as a result of continuous glucose absorption, and declining osmotic gradient (σ = 0.03) over time (Fig. 101.3A). Additionally, heat sterilization of glucose can lead to the generation of glucose degradation products (GDPs) (~5.5), which could have detrimental effects on the peritoneal membrane.17 These reactive carbonyl compounds have also been shown to have toxic effects on various cells in vitro and in vivo.18 19

Non–Glucose-Based Solutions

Given the highlighted drawbacks of glucose-based solutions, alternative osmotic agents including amino acids and icodextrin are available.

Icodextrin is an isoosmolar glucose polymer (~280 mOsm/L) that is manufactured as a 7.5% solution with the same electrolyte constituents as glucose-based solutions. It has a molecular weight averaging between 13 and 19 kDa that generates UF by its oncotic effect.20 The large molecules greatly enhance the osmotic efficiency of this solution (σ = 0.5) compared with glucose solutions, leading to more sustained UF over a 12-hour period (Fig. 101.5A), and so icodextrin is preferred for long dwell exchanges (daytime dwell for patients on APD and overnight dwell for CAPD). Although icodextrin can be slowly absorbed into the plasma and metabolized to produce maltose, there have been no reported events of maltose toxicity. However, maltose can interact with glucose dehydrogenase pyrroloquinoline quinone assays used for capillary glucose measurement, leading to falsely elevated results for glucose. Therefore, alternative strategies for blood glucose monitoring

“Biocompatible” Solutions

The previously mentioned multicompartment systems are mixed just before instillation, thus addressing two potential limitations of traditional single-compartment lactate-buffered solutions. First, mixing just before instillation allows bicarbonate to be used as the buffer instead of lactate. The pH of lactate-buffered solutions is acidic (~5.5), whereas the pH of bicarbonate-buffered solutions is approximately neutral (~7.4),19 25-27 which may reduce infusion pain while still correcting metabolic acidosis.28 Second, the use of two compartments allows glucose to be stored at very low pH during heat sterilization, which protects it from caramelization and GDP formation. Experimental and observational data suggest that these solutions should reduce the patient’s exposure to GDPs and that this should lead to clinical benefit. However, clinical data has shown conflicting results in terms of overall benefits with the use of these “biocompatible” solutions. For example, one study demonstrated an improvement in RKF among patients receiving PD solutions with low GDP concentration.25 However, more recent randomized trials have not supported such findings.28 29 The balANZ study was a small randomized controlled trial (RCT) that suggested biocompatible solutions had lower incidence of peritonitis compared with conventional solutions.30 There have been other small RCTs with conflicting results with regards to peritonitis and RKF. Systematic reviews have also shown inconclusive findings, and as a result the overall benefit of biocompatible solutions remains unclear.26 27

In commercial PD solutions the concentration of Na^+, Cl , Ca^{2+}, and Mg^{2+} are provided at levels similar to their respective plasma concentrations.11 As a result, the diffusive capacity of these electrolytes is greatly reduced, and their transport across the peritoneal membrane is mostly dependent on convective transport (with UF). Computer simulations demonstrate that for an average patient with a plasma concentration of 140 mmol/L, approximately 10 mmol of Na^+ is removed with every 100 mL of UF volume produced.11 Na^+ concentration in the solution is usually 132 to 134 mmol/L, as higher concentrations would reduce the diffusive gradient for sodium removal from the plasma.

Similarly, Ca^{2+} transport is primarily driven by convective transport, a UF-dependent process. The concentration of Ca^{2+} in PD solutions usually ranges from 1.25 to 1.75 mmol/L. In reducing the risk of hypercalcemia in PD patients who commonly use calciumbased phosphate binders, a calcium concentration of 1.25 mmol/L in the dialysate is recommended to achieve a “calcium neutral” state,11 in which calcium is neither lost nor gained during a dwell.

In commercial solutions, the concentration of Ca^{2+} does not vary with glucose concentrations, and so solutions with 1.25 mmol/L of Ca^{2+} may be preferable for patients treated with calcium-based phosphate binders to reduce the risk of hypercalcemia. Net peritoneal calcium removal can be obtained by intermediate- and highconcentration solutions with a Ca^{2+} concentration of 1.25 mmol/L, Ultrafiltration volume (mL)

Ultrafiltration Profiles for PD
800
600
400
200

0
0

60

120

180

240

300

360

420

480

540

600 660 720

Time (min)

A

Sodium Sieving Curves for PD
142
140
138
[Na] (mmol/L)

136
134
132
130
128
126
124
122
0

60

120

180

240

300

B

360

420

480

540

600 660

720

Time (min)

Fig. 101.5 (A) Ultrafiltration (UF) profiles for peritoneal dialysis (PD). UF profile for 7.5% icodextrin (blue line), computer simulated according to the three-pore model in an average patient who is not naive to icodextrin, in comparison with the computer-simulated UF curve for 3.86% glucose (red line). (B) Sodium-sieving curves for PD. 7.5% icodextrin (blue line) and 3.86% glucose (red line) (see Fig. 101.3). Na, Sodium. (A, From Rippe B, Levin L. Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD. Kidney Int. 2000;57[6]:2546–2556.)

as convective transport results in 0.1 mmol of Ca^{2+} for every 100 mL of UF.11

The other important divalent cation in PD solutions is magnesium. The concentration of Mg^{2+} in manufactured solutions ranges from 0.25 to 0.75 mmol/L. In 1.5% (1.36%) glucose solutions, the concentration of Mg^{2+} at 0.25 mmol/L would maintain a net neutral magnesium level during the dwell,31 whereas net losses of Mg^{2+} would be seen with PD fluid with higher glucose concentrations due to larger convective flux driven by UF.

PERITONEAL ACCESS

Peritoneal Dialysis Catheters

A well-functioning PD catheter is critical for sustainable treatment with PD, because approximately 20% of PD withdrawal is due to catheter dysfunction.32 The Tenckhoff catheter is a Silastic tube with numerous holes along the intraperitoneal segment.33 Modern catheters typically have two Dacron (polyester) cuffs that limit catheter migration and reduce risks of pericatheter leaks and infection. The deep cuff is best placed in the rectus muscle of the abdominal wall, which allows the tissue ingrowth to encapsulate the catheter, reducing the risk of migration. On the other hand, the superficial cuff is best placed about 2 to 4 cm from the exit site. This functions as a barrier against the entry of bacteria into the subcutaneous tunnel.34

Catheters are available in coiled-tip and straight-tip types, with further variation existing in some catheters whereby there is a preformed bend in the intercuff segment called a “swan neck” (Fig. 101.6). Reported benefits of less inflow pain associated with coiled-tip variants due to better dispersion of dialysate fluid rather than a rapid jet flow with straight-tip variants remain hypothetical. Numerous studies comparing outcome and complication rates between the two cathetertip variants have produced conflicting results,35-37 and thus either is acceptable.

Insertion of Peritoneal Dialysis Catheters

PD catheters should be inserted under sterile conditions by a skilled operator. Laparoscopic insertion is the preferred method, as it allows the operator to incorporate interventions to enhance the overall success rate of functioning catheter. Operators can insert catheters with laparoscopically guided rectus sheath tunneling directed toward the pelvis,

Common Types of Peritoneal
Dialysis Catheter
Straight 1 cuff catheter

Straight 2 cuff catheter

2 cuff coil catheter

Swan neck catheter

Toronto Western catheter

Fig. 101.6 Various types of peritoneal dialysis catheter.

Fig. 101.7 Peritoneal Dialysis Catheter Inserted at the Bedside. Note the insertion in the left paramedian portion of the abdomen through which the catheter was inserted using a Seldinger technique (arrow).

which reduces the likelihood of catheter tip migration. Furthermore, laparoscopic insertion allows operators to visualize redundant omentum that may compromise catheter function; redundancy is reduced by suturing it to a nearby organ or upon itself in a procedure referred to as an omentopexy. Alternatively, percutaneous insertion using needle with guidewire and the assistance of ultrasound is a technique that can be performed at the bedside (Fig. 101.7). This technique uses a modified Seldinger technique and is useful in low-resource settings in patients who do not have abdominal hernias and previous surgical abdominal history.34

Before catheter insertion, patients should undergo a complete abdominal assessment to identify any prior surgical scars or hernias and to plan for the catheter exit site. It is important that the exit site be planned with the patient sitting rather than when lying on the table so as to account for any pannus that could obscure the site. Antibiotic prophylaxis should be given to patients before catheter insertion to reduce the risk of peritonitis.38 A single preoperative dose of a first- or second-generation cephalosporin is recommended depending on local resistance patterns and patient allergic history.

PERITONEAL DIALYSIS TECHNIQUES

Historically, transporter status guided prescriptive strategies for PD patients. For example, high transporters would have a rapid dissipation of their glucose gradient and theoretically were deemed best suited for APD. On the other hand, patients with low transporter status were deemed best suited for CAPD, allowing for dwells of longer duration in effort to maximize diffusive transport. Although theoretically these prescriptive strategies may maximize the efficiency of peritoneal transport, it is not a practical approach used in everyday practice. PD prescriptions should be individualized according to patient priorities and lifestyle rather than relying on transport kinetics. For instance, patients who have undergone recent abdominal surgery or have a history of hernias may be better suited for cycler-based APD therapy. This technique provides rapid exchanges for patients while maintaining adequate dialysis without significantly increasing IPP, in turn reducing the risk of leaks and other complications. Additionally, patients with daytime employment may find it challenging to perform exchanges during the day. Nightly APD followed by a long day-dwell allows flexibility in the daytime schedule for patients. Automated cyclers have evolved with newer technological features that allow for remote monitoring of inflow time, dwell time, and drain time along with drain volumes. Most APD machines are equipped with warmers that can warm fluid before inflow into the peritoneal cavity, reducing the episodes of discomfort and shivering that may occur with room temperature fluid.

In certain patients, low drain alarms may occur on the cycler, which affects the efficiency of an exchange. This can be overcome by increasing the residual intraperitoneal volume and proportionally decreasing subsequent fill volumes in a process called tidal peritoneal dialysis (TPD). For example, 70% TPD implies that, for a 2-L inflow volume, 1.4 L would be drained out, and the next inflow volume would also be 1.4 L, leaving a residual intraperitoneal volume of about 0.6 L repeated over the cycles until the final drain. TPD was initially developed to enhance the diffusive clearance of solutes, but results have been disappointing; TPD is now used primarily for the management of low drain alarms on the cycler and for those experiencing pain during the inflow and/or drain phase of the exchange.

Alternatively, patients can be managed with CAPD using a volume of 1.5 to 2.5 L of fluid with up to five exchanges daily depending on RKF. CAPD day-dwell times can range from 4 to 6 hours before dissipation of the glucose osmotic gradient. The overnight dwell for CAPD can last for a period of 10 to 12 hours, where icodextrin or a highconcentration glucose-containing solution can be used to sustain an osmotic gradient.

PD is also dependent on a functioning connection system that is safe and simple to use. There are three major types of connection systems used in PD. They include the “standard” or straight connecting system, the Y connecting system, and the double bag system. The standard connecting system has fallen out a favor due to higher rates of peritonitis and is now rarely used. The Y connecting system uses a Y-shaped tube that attaches to an extension tube from the patient’s catheter; the two other limbs of the system are connected to unused PD fluid and a sterile empty drain bag. This system uses a principle called "flush before fill," which is likely the underlying reason that peritonitis rates are lower with this system. Intraluminal microorganisms are flushed into the drain bag, avoiding intraperitoneal contamination.39 The original Y system developed in the 1980s has since evolved to the double-bag system, which is the most widely used connection system.40 In this system the solution bag and drain bags are already attached to the two limbs of the Y connector; patients now have to make one simple connection to extension tubing rather than three with the original system.40 The double-bag system is flushed for about 5 seconds and then a "frangible" (breakable) pin within the tubing is broken, allowing the spent dialysate from the peritoneal cavity to fill in the drain bag for up to 20 minutes. The limb to the drain bag is then clamped and the limb from the PD solution is opened to fill the peritoneal cavity. The time for exchange, accounting for the instillation and drainage, should not exceed 30 minutes provided that the PD catheter is functional. The initial volume (the first 1.6–1.8 L) from the peritoneal cavity usually drains rapidly, but this rate decreases as the residual intraperitoneal volume (sump volume) falls to less than 300 mL.

PERITONEAL SOLUTE TRANSPORT AND ULTRAFILTRATION

Small-Solute Removal

Most solutes typically removed by normal functioning kidneys are primarily removed by diffusive clearance in PD. The two methods commonly used in PD to assess solute clearance are the urea clearance normalized to total body water, expressed as Kt/V_{urea} (where Kt is the weekly clearance and V_{urea} is the volume of distribution of urea), and the peritoneal creatinine clearance standardized to body surface area ($1.73\ m^2$).

In determining Kt, daily clearance must first be established by the measurement of urea and creatinine with PD in using the dialysateplasma concentration ratios (D/P). The D/P_{urea} and $D/P_{creatinine}$ for either solute is done by measuring the concentration of the solute in the "used" dialysate and that in the plasma multiplied by the daily drain volume to provide the 24-hour clearance, providing the daily clearance. The weekly clearances can then be calculated by multiplying these values by 7.

Despite more contemporary studies showing little association between small-solute kinetics and patient outcomes, Kt/V_{urea} is still used as a marker of adequacy.41 42 However, some centers use peritoneal creatinine clearance as a marker of solute removal given the data for Kt/V_{urea} and the imprecision in determining V.

Large-Solute Removal

Large solutes are removed more slowly compared with small solutes with PD via convective clearance. Although surrogate markers for large-solute clearance can be measured using albumin, immunoglobulins, and α_2-macroglobulin, this is not common practice. These solutes move across the large pores very slowly, such that equilibration in the dialysate with the plasma does not occur with the typical dwell time that is used for PD. Nevertheless, removal of large solutes is time dependent, and so the long dwell is important for this process.

Ultrafiltration

The volume of UF achieved with PD can vary significantly from day to day. This variability stems from changes in the tonicity of the solution used and patient positioning along with common factors affecting drainage such as constipation, which may lead to elevations in residual intraperitoneal volume. Collecting fluid volumes over several days and using the average value improves the accuracy of estimated daily UF

BOX 101.1

Peritoneal Equilibration Test

1. Two liters (warm) 2.27% fluid are instilled for 10 min with the patient supine and rolling from side to side every 2 min.
2. Exactly 10 min after start of the infusion, 200 mL is drained into the bag. Draw 5 mL (discard); the next 5 mL is taken for creatinine and glucose determination.
3. After 2 h, new samples are collected as in step 2.
4. After 4 h exactly, collect drainage over 20 min. Note total bag weight. Subtract empty bag weight. Take samples (after mixing) for creatinine and glucose.
5. Glucose D/D0 (ratio of dialysate glucose at 4 h and at time zero) and creatinine D/P (ratio of dialysate and serum creatinine at 4 h) are plotted versus time (see Fig. 101.8). Record the total drain volume.

The night bag (8–12 h) must be 1.36% or 2.27% glucose, drained for 20 min with patient sitting upright.

volume. If UF volumes remain low, then patients should be evaluated for ultrafiltration failure (UFF) by using a high-concentration solution (3.86%/4.25%). A UF volume of less than 400 mL after a 4-hour dwell with high-concentration solution is consistent with UFF. Additionally, UF volumes can also be evaluated using the PET (see later). In determining intraperitoneal volume as a function of time, iodine-125 (^{125}I)–human serum albumin (HSA) can be used as a more accurate measurement of fluid kinetics in PD,43 although this is rarely done in clinical practice.

ASSESSING PERITONEAL MEMBRANE FUNCTION

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) provides an estimation of small-solute transport and UF capacity44 by using equilibration ratios between the dialysate and plasma (D/P) for various solutes across the peritoneal membrane. These include urea (D/Purea), creatinine (D/Pcreatinine), and sodium (D/Psodium). The procedure is summarized in Box 101.1 and traditionally involves the instillation of 2 L of an intermediate (2.27% or 2.5%) glucose-based solution; more recently, some centers have used 4.25% solutions. As the fluid is instilled over a period of about 10 minutes, the patient is encouraged to roll from side to side while in a supine position. This allows the infused fluid to be well distributed in the peritoneal cavity, particularly in the paracolic gutters.

After the fill is completed, dialysate samples are taken three times: at time zero, 2 hours postfill, and 4 hours postfill. At the end of the 4-hour dwell, the dialysate drained is measured to calculate the total UF. During the test, the concentrations of glucose, creatinine, urea, and sodium are noted in three dialysate samples and the plasma. These values are used to determine D/P ratios; glucose is expressed differently as the glucose concentration in the 4-hour dialysate relative to that at time zero (D/D0 glucose). The D/Pcreatinine and D/D0 glucose values are used to categorize patients into one of four different transporter categories: slow, slow average, fast average, or fast (Fig. 101.8). Although transport characteristics may change with time due to alterations in peritoneal membrane, nearly 70% of patients have stable transport status 1 year post-PET and about 50% of patients at 2 years post-PET.

Alternatives to the traditional PET include the mini-PET and the double-mini PET. The mini-PET provides a quicker method to assess small-solute and free water transport. It uses a high-concentration (3.86% or 4.25%) glucose-based solution that is infused intraperitoneally and dwells for 1 hour.45 The concentration of sodium is measured in the drained dialysate sample; free water transport across the

1.1

1.1

1.0

1.0

0.9

0.9

0.8

0.8

Creatinine (D/P)

Glucose (D/D0)

Interpretation of Peritoneal Equilibrium Test Results

0.7
0.6

0.61

0.5

0.49

0.4

0.38

0.3

0.26

0.2
0
0

2
Time (h)

4

0.81

0.7

0.65

0.6

0.50

0.5
0.4

0.34

0.3
0.2

0.12

0.1

1.03

0.1
Fast
Fast average
Slow average
Slow

0
0

2
Time (h)

4

Fig. 101.8 Interpretation of Peritoneal Equilibration Test Results. Changes in solute concentration during a peritoneal equilibration test allow classification into different transport types. D/D0, Ratio of dialysate glucose at 4 hours and at time zero) D/P, ratio of dialysate and serum creatinine at 4 hours. (Modified from Twardowski ZJ, Nolph KD, Khanna R. Limitations of the peritoneal equilibration test. Nephrol Dial Transplant. 1995;10[11]:2160–2161.)

membrane is determined indirectly. The double-mini PET test is used to evaluate the free transport of water and osmotic conductance of glucose (OCG) across differing concentrations of solutions. The test is conducted by performing two consecutive mini-PETs46: the first uses a low-concentration (1.36% or 1.5%) glucose, and the second uses a high-concentration (3.86% or 4.25%) glucose solution. The doublemini PET can be used to calculate the OCG without computer modeling by using the differences in drain volume between the low- and high-concentration solutions. In theory, it could be used to identify early signs of UFF in PD patients, but further data are needed.

It isn’t clear that the PET has to be routinely performed in all PD patients. As discussed earlier, the transport status has historically been used to dictate the PD prescription, but more recently the choice of CAPD versus cycler is primarily driven by patient preference and finances. We no longer routinely perform the PET in our PD patients.

If a PET is done, this should occur no sooner than a month after catheter insertion, as the inflammation from the procedure can affect transport status. Similarly, a PET should not be done in a patient with current or recent peritonitis.

DOSE AND ADEQUACY OF PERITONEAL DIALYSIS

The use of absolute targets for Kt/Vurea to determine the adequacy of PD remains controversial. Historically, clinical practice guidelines recommended weekly Kt/Vurea of 2.0, but recent studies have failed to demonstrate a clinical benefit of Kt/Vurea values of greater than 1.7. Rather, a better survival advantage is associated with high RKF compared with a higher peritoneal solute clearance with higher Kt/Vurea 41

Based on this emerging data, current clinical practice guidelines have evolved and now recommend that patients with a RKF of more than 100 mL/day have a minimal delivered total (peritoneal and renal) dose of small-solute clearance with a weekly Kt/Vurea of 1.7.47

Residual Kidney Function

RKF and its preservation has been associated with numerous benefits, including lower relative risk of death in dialysis patients.41 48 Observational data has demonstrated that RKF is better preserved in patients on PD compared with HD.49 RKF can easily be assessed by performing a 24-hour urine collection with assessment of the urea and creatinine concentrations along with the total urine volume. Because renal creatinine clearance may result in an overestimation of glomerular filtration rate (GFR) due to its tubular secretion, GFR can be more accurately estimated by averaging the renal creatinine and urea clearances respectively. However, if a 24-hour urine collection is impractical, the serum creatinine can be used as a surrogate marker of RKF. If serum creatinine is stable in the absence of changes in muscle mass or recent changes to the PD prescription, it can be assumed that RKF is preserved.4

PRINCIPLES AND PRACTICE OF INCREMENTAL DIALYSIS

The adoption of incremental PD has numerous benefits to patients and the health care system. It allows patients time to become comfortable with the therapy, and the prescription is enhanced to promote appropriate small-solute clearance if there is a decline in RKF. Simply put, as RKF declines, the dose of PD will need to increase. Longitudinal observational data has demonstrated that in comparison to standard PD prescriptions, survival rates in PD patients were similar, but the rates of hospitalizations and cost to the health system were much less in the incremental group. Incremental PD also reduces the reliance on Kt/Vurea and redirects more attention to clinical assessments and other biochemical data to determine adequacy. Incremental PD has some disadvantages that include a reluctance of patients to increase the dialysis dose when a decrease in RKF suggests that this is necessary. Delays in adjusting the PD prescription to achieve effective solute clearance can result in uremia in patients. Therefore, patients and caregivers should be informed about the principles of incremental PD before starting this type of treatment so that prescription changes are better accepted when they are warranted. However, in our experience, the RKF does not usually suddenly decline in a stable outpatient unless there has been some notable intercurrent event. Therefore, the concern that a patient on an incremental prescription may suddenly become underdialyzed due to a sudden drop in RKF is unwarranted.

Prescribing Incremental Peritoneal Dialysis

In adopting the principles of incremental PD, clinicians should individualize prescriptions to patient needs while focusing on clinical symptoms in conjunction with laboratory investigations. For example, a patient who prefers to do manual exchange therapy can be started on CAPD with 1 to 2 exchanges per day at 1.5-L fill volumes with each exchange. Depending on patient comfort, fill volumes can be increased incrementally up to maximum of 2.5 L with each exchange. If a patient needs more solute clearance, then additional daytime exchanges can be incorporated if a maximal tolerated fill volume has been achieved. On the other hand, for patients receiving cycler-based therapy, nocturnal intermittent peritoneal dialysis (NIPD) is an initial preferred option. NIPD may be more attractive to patients with reduced flexibility in daytime schedules and can be provided initially with two to three exchanges overnight with volumes of 1.5 L with each exchange. If there is a gradual decline in RKF, then the fill volumes could be increased in 20% to 30% increments up to a maximum patient tolerance, or a value not exceeding 2.5 L, in order to improve solute clearance. If more solute clearance is still needed, then the number of exchanges on the cycler can gradually be increased followed by the addition of a daytime dwell.

Fluid Balance

Patients on PD have significant day-to-day variation in their fluid balance, which requires changes in the PD prescription and diuretic dosing in those with significant RKF. Maintaining euvolemia is an important predictor of outcomes in PD patients, but hypervolemia is quite common in this population.50 Observational data have revealed that among 639 prevalent patients who had been on PD for at least 2 years, more than 70% had hypervolemia.51 The reasons for hypervolemia are multifactorial and include loss of RKF, increased dietary intake of salt and fluid, nonadherence to dialysis, and inadequate prescription (low-concentration solution leading to rapid dissipation of osmotic gradient in a fast transporter). Hypervolemia can exacerbate hypertension in PD patients and may lead to left ventricular hypertrophy. As patients remain on PD for longer periods, their antihypertensive regimen (number of agents and their doses) often increases over time. In patients with hypervolemia, clinical assessment (in conjunction with a mini-PET or double mini-PET test if required; see earlier) is used to determine whether UFF is the underlying cause for volume overload.

Management of Fluid Overload

In treating fluid overload, a stepwise approach should be considered for all PD patients. First, patients must be encouraged to reduce dietary intake of sodium to less than 2 g/day. Second, if RKF is more than 100 mL/day and volume overload persists, then a loop diuretic such as furosemide can be increased to 320 to 400 mg/day in divided doses52; a thiazide-like diuretic such as metolazone can be added to enhance urinary volumes. Increased doses of diuretics serve to promote natriuresis and do not augment renal clearance of solutes. Last, if volume overload remains despite dietary modifications and increased diuretic dosing, then volume removal can be enhanced with peritoneal UF by increased glucose concentration of PD solutions. Icodextrin can be used for longer dwells, particularly for daytime dwells with APD, as this increases UF and reduces extracellular volume.53 The rate of UF with icodextrin is much slower compared with glucose solutions with maximal UF occurring about 10 hours into the dwell. Therefore, icodextrin should not be used for the management of acute volume overload, where hypertonic solutions with faster UF profile rates are preferred.

Nutrition

The importance of good nutrition while on PD may be neglected, leading to poor patient outcomes. PD initially leads to weight gain in patients in the absence of volume overload. This weight gain is due to increase in caloric intake from peritoneal glucose reabsorption. Peritoneal glucose reabsorption leads to daily average of 400 to 600 kcal/day, which may lead to metabolic syndrome in nearly half of all prevalent PD patients.54 However, despite glucose reabsorption, patients may still have energy malnutrition as a result of uremic wasting syndrome. Furthermore, as RKF declines, protein-energy malnutrition and wasting increases due to impairment in protein metabolism in the presence of uremia.55 The suggested daily energy target for PD patients is at least 35 kcal/kg/day, with about 10% to 30% of this target being derived from the glucose-based PD solutions. Considering protein losses with PD (5–7 g/day, 80% of which is albumin), the recommended dietary daily protein target should be more than 1.2 g protein/kg/day.

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SELF-ASSESSMENT QUESTIONS

1. In PD, the fraction of AQP-mediated water flow is much higher for glucose than for ICO as osmotic agent. Why?
A. Glucose will induce more initial vasodilation and recruitment of exchange vessel surface area than ICO.
B. The glucose molecules are smaller than the ICO molecules and therefore are relatively “inefficient” as osmotic agents in small pores but relatively more efficient across AQP.
C. Glucose, but not ICO, will regularly induce an increase in the number of AQPs.
D. Glucose, but not ICO, can increase the peritoneal capillary filtration coefficient.
E. Oncotic agents such as ICO cannot pull fluid across AQP at all.
2. Which PD catheter has a superior clinical outcome?
A. The Toronto Western catheter
B. The Swan neck catheter
C. The straight one-cuff (original) Tenckhoff catheter
D. The straight two-cuff (original) Tenckhoff catheter
E. None of these catheters shows significant clinical superiority

3. Long-term changes in peritoneal transport parameters usually involve:
A. increases in PETcreat and marked increases in the peritoneal UF coefficient.
B. reductions in PETcreat and increases in the peritoneal UF coefficient.
C. increases in PETcreat combined with no or only moderate increases in the UF coefficient.
D. increases in large-solute transport together with increases in UF coefficient.
E. increases in large-solute transport combined with reductions in the UF coefficient.
4. Glucose-based dialysis fluids for PD that are low in GDPs have which of the following advantages?
A. They prevent peritoneal fibrosis and encapsulating peritoneal sclerosis.
B. They preserve residual renal function.
C. They prevent increases in small-solute transport over treatment time.

D. They produce higher concentrations of the dialysate effluent marker CA-125.
E. They increase peritoneal UF capacity.

5. Which of the following is true about icodextrin as a high molecular weight osmotic agent?
A. ICO is monodispersed.
B. ICO is polydispersed, but with 100% of the molecules being larger than 3 kDa.
C. ICO is polydispersed, but with 80% of the molecules being larger than 3 kDa.

D. ICO is polydispersed, but with 50% of the molecules being larger than 3 kDa.
E. ICO is polydispersed, but with 30% of the molecules being larger than 3 kDa.

6. Net fluid reabsorption from the peritoneal cavity occurs via lymphatic reabsorption plus backfiltration through:
A. small pores.
B. AQP-1.
C. large pores.
D. larges pores + AQP-1.
E. small pores + large pores.

REFERENCES

1. Li PK, Chow KM, Van de Luijtgaarden MW, et al. Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol. 2017;13(2):90–103.
2. Lysaght MJ, Vonesh EF, Gotch F, et al. The influence of dialysis treatment modality on the decline of remaining renal function. ASAIO (Am Soc Artif Intern Organs) Trans. 1991;37(4):598–604.
3. Tang M, Li T, Liu H. A comparison of transplant outcomes in peritoneal and hemodialysis patients: a meta-analysis. Blood Purif. 2016;42(2):170–176.
4. Auguste BL, Bargman JM. Incremental peritoneal dialysis: new ideas about an old approach. Semin Dial. 2018;31(5):445–448.
5. Auguste BL, Agarwal A, Ibrahim AZ, et al. A single-center retrospective study on the initiation of peritoneal dialysis in patients with cardiorenal syndrome and subsequent hospitalizations. Can J Kidney Health Dis. 2020;7:2054358120979239.
6. Rippe B. A three-pore model of peritoneal transport. Perit Dial Int. 1993;13(suppl 2):S35–S38.
7. Ni J, Verbavatz JM, Rippe A, et al. Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. Kidney Int. 2006;69(9):1518–1525.
8. Solass W, Horvath P, Struller F, et al. Functional vascular anatomy of the peritoneum in health and disease. Pleura Peritoneum. 2016;1(3):145–158.
9. Leypoldt JK. Evaluation of peritoneal membrane permeability. Adv Ren Replace Ther. 1995;2(3):265–273.
10. Fischbach M, Dheu C. Hydrostatic intraperitoneal pressure: an objective tool for analyzing individual tolerance of intraperitoneal volume. Perit Dial Int. 2005;25(4):338–339.
11. Rippe B, Venturoli D, Simonsen O, de Arteaga J. Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit Dial Int. 2004;24(1):10–27.
12. Imholz AL, Koomen GC, Voorn WJ, Struijk DG, Arisz L, Krediet RT. Dayto-day variability of fluid and solute transport in upright and recumbent positions during CAPD. Nephrol Dial Transplant. 1998;13(1):146–153.
13. Rippe B, Stelin G, Haraldsson B. Computer simulations of peritoneal fluid transport in CAPD. Kidney Int. 1991;40(2):315–325.
14. Devuyst O, Rippe B. Water transport across the peritoneal membrane. Kidney Int. 2014;85(4):750–758.
15. Rippe B, Levin L. Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD. Kidney Int. 2000;57(6):2546–2556.
16. Drugs.com. Extraneal Prices, Coupons and Patient Assistance Programs. https://www.drugs.com/price-guide/extraneal#:~:text=The%20cost%20for%20Extraneal%20intraperitoneal,on%20the%20pharmacy%20you%20visit.
17. Kjellstrand P, Erixon M, Wieslander A, Linden T, Martinson E. Temperature: the single most important factor for degradation of glucose fluids during storage. Perit Dial Int. 2004;24(4):385–391.
18. Wieslander AP, Nordin MK, Kjellstrand PT, Boberg UC. Toxicity of peritoneal dialysis fluids on cultured fibroblasts, L-929. Kidney Int. 1991;40(1):77–79.
19. Rippe B, Simonsen O, Heimburger O, et al. Long-term clinical effects of a peritoneal dialysis fluid with less glucose degradation products. Kidney Int. 2001;59(1):348–357.
20. Mistry CD, Gokal R, Peers E. A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis. Kidney Int. 1994;46(2):496–503.
21. Oyibo SO, Pritchard GM, McLay L, et al. Blood glucose overestimation in diabetic patients on continuous ambulatory peritoneal dialysis for endstage renal disease. Diabet Med. 2002;19(8):693–696.
22. Kopple JD, Bernard D, Messana J, et al. Treatment of malnourished CAPD patients with an amino acid based dialysate. Kidney Int. 1995;47(4):1148–1157.
23. Asola M, Virtanen K, Nagren K, et al. Amino-acid-based peritoneal

dialysis solution improves amino-acid transport into skeletal muscle. Kidney Int Suppl. 2008;(108):S131–S136.

24. Li FK, Chan LY, Woo JC, et al. A 3-year, prospective, randomized, controlled study on amino acid dialysate in patients on CAPD. Am J Kidney Dis. 2003;42(1):173–183.
25. Williams JD, Topley N, Craig KJ, et al. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int. 2004;66(1):408–418.
26. Cho Y, Johnson DW, Craig JC, Strippoli GF, Badve SV, Wiggins KJ. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2014;(3):CD007554.
27. Cho Y, Badve SV, Hawley CM, Wiggins K, Johnson DW. Biocompatible peritoneal dialysis fluids: clinical outcomes. Int J Nephrol. 2012;2012:812609.
28. Mactier RA, Sprosen TS, Gokal R, et al. Bicarbonate and bicarbonate/lactate peritoneal dialysis solutions for the treatment of infusion pain. Kidney Int. 1998;53(4):1061–1067.
29. Fan SL, Pile T, Punzalan S, Raftery MJ, Yaqoob MM. Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function. Kidney Int. 2008;73(2):200–206.
30. Johnson DW, Brown FG, Clarke M, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol. 2012;23(6):1097–1107.
31. Hutchison AJ, Merchant M, Boulton HF, Hinchcliffe R, Gokal R. Calcium and magnesium mass transfer in peritoneal dialysis patients using 1.25 mmol/L calcium, 0.25 mmol/L magnesium dialysis fluid. Perit Dial Int. 1993;13(3):219–223.
32. Workeneh B, Guffey D, Minard CG, Mitch WE. Causes for withdrawal in an urban peritoneal dialysis program. Int J Nephrol. 2015;2015:652953.
33. Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. Trans Am Soc Artif Intern Organs. 1968;14:181–187.
34. Crabtree JH, Chow KM. Peritoneal dialysis catheter insertion. Semin Nephrol. 2017;37(1):17–29.
35. Ouyang CJ, Huang FX, Yang QQ, et al. Comparing the incidence of catheter-related complications with straight and coiled Tenckhoff catheters in peritoneal dialysis patients-a single-center prospective randomized trial. Perit Dial Int. 2015;35(4):443–449.
36. Hagen SM, Lafranca JA, I.J JN, Dor FJ. A systematic review and meta-analysis of the influence of peritoneal dialysis catheter type on complication rate and catheter survival. Kidney Int. 2014;85(4):920–932.
37. Nielsen PK, Hemmingsen C, Friis SU, Ladefoged J, Olgaard K. Comparison of straight and curled Tenckhoff peritoneal dialysis catheters implanted by percutaneous technique: a prospective randomized study. Perit Dial Int. 1995;15(1):18–21.
38. Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection recommendations: 2017 update. Perit Dial Int. 2017;37(2):141–154.
39. Daly CD, Campbell MK, MacLeod AM, et al. Do the Y-set and double-bag systems reduce the incidence of CAPD peritonitis? A systematic review of randomized controlled trials. Nephrol Dial Transplant. 2001;16(2):341–347.
40. Buoncristiani U. Birth and evolution of the “Y” set. ASAIO J. 1996;42(1):8–11.
41. Bargman JM, Thorpe KE, Churchill DN, Group CPDS. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001;12(10):2158–2162.
42. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13(5):1307–1320.
43. Olszowska A, Waniewski J, Stachowska-Pietka J, Garcia-Lopez E, Lindholm B, Wankowicz Z. Long peritoneal dialysis dwells with icodextrin: kinetics of transperitoneal fluid and polyglucose transport.

Front Physiol. 2019;10:1326.
44. Twardowski ZJ, Nolph KD, Khanna R. Limitations of the peritoneal equilibration test. Nephrol Dial Transplant. 1995;10(11):2160–2161.
45. La Milia V, Di Filippo S, Crepaldi M, et al. Mini-peritoneal equilibration test: a simple and fast method to assess free water and small solute transport across the peritoneal membrane. Kidney Int. 2005;68(2):840–846.

46. La Milia V, Limardo M, Virga G, Crepaldi M, Locatelli F. Simultaneous measurement of peritoneal glucose and free water osmotic conductances. Kidney Int. 2007;72(5):643–650.
47. Peritoneal Dialysis Adequacy Work G. Clinical practice guidelines for peritoneal dialysis adequacy. Am J Kidney Dis. 2006;48(suppl 1): S98–S129.
48. Marron B, Remon C, Perez-Fontan M, Quiros P, Ortiz A. Benefits of preserving residual renal function in peritoneal dialysis. Kidney Int Suppl. 2008;(108):S42–S51.
49. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1996;7(2):198–207.
50. Lo WK, Bargman JM, Burkart J, et al. Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. Perit Dial Int. 2006;26(5):520–522.

51. Van Biesen W, Williams JD, Covic AC, et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. PLoS One. 2011;6(2):e17148.
52. Krediet RT. Preservation of residual kidney function and urine volume in patients on dialysis. Clin J Am Soc Nephrol. 2017;12(3):377–379.
53. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol. 2003;14(9):2338–2344.
54. Fortes PC, de Moraes TP, Mendes JG, Stinghen AE, Ribeiro SC, PecoitsFilho R. Insulin resistance and glucose homeostasis in peritoneal dialysis. Perit Dial Int. 2009;29(suppl 2):S145–S148.
55. Demirci MS, Demirci C, Ozdogan O, et al. Relations between malnutrition-inflammation-atherosclerosis and volume status. The usefulness of bioimpedance analysis in peritoneal dialysis patients. Nephrol Dial Transplant. 2011;26(5):1708–1716.

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Complications of Peritoneal Dialysis

Simon J. Davies, Martin E. Wilkie

CATHETER MALFUNCTION

Optimal Timing and Placement of the Peritoneal Dialysis Catheter

next few cycles. We no longer recommend the use of an endoscopic brush because of safety concerns.

If the radiograph shows the catheter to be malpositioned, an attempt should be made to reposition the catheter tip into the pelvis (Fig. 102.1). This can be done under radiologic guidance with a sterile guidewire inserted into the catheter; alternatively, the catheter can be repositioned at laparotomy or with the laparoscope. Sometimes the catheter becomes wrapped in omentum, suggested usually by complete inflow and outflow failure. This requires a partial omentectomy or an omental hitch, a surgical procedure in which the omentum is temporarily held away from the catheter by a dissolvable suture (omentopexy). The value of laparoscopy in this context is that it can provide a diagnosis as to the cause of catheter flow failure and provide a solution (e.g., by repositioning the catheter, removing an omental wrap, or performing a limited omentectomy).

Catheter dysfunction adversely affects patient outcome by preventing commencement of the chosen dialysis modality, as well as by disrupting training schedules and increasing health care costs. Published literature does not demonstrate that one insertion technique is better than another, although a recent meta-analysis suggested an advantage of the laparoscopic compared with the open surgical insertion technique.[1] It is clear that the enthusiasm and experience of the operator are key determinants of catheter outcome,[2] and international guidelines describe the optimal conditions for catheter insertion.[3] Timing is also important; patients randomized to the late start arm of the Initiating Dialysis Early and Late (IDEAL) study (estimated glomerular filtration rate [eGFR] 5–7 mL/min/1.73 m^2) were less likely to start kidney replacement on peritoneal dialysis (PD) than those starting early (eGFR 10–14 mL/min/1.73 m^2), despite PD being their preferred treatment.[4] Early catheter problems are more difficult to manage in the absence of residual kidney function. Our practice is to place catheters once the GFR falls below 10 mL/min/1.73 m^2, aiming to start dialysis when the GFR is 7 to 8 mL/min/1.73 m^2. However, this is individualized according to patient symptoms and whether fluid retention is a particular problem. Some centers use an approach where the external part of the catheter is buried in the subcutaneous tissue at the time of implantation (known as the Moncrief technique) so that it can be exteriorized at the time it is required. This approach means that the catheter can be placed several months prior to be needed. For optimized catheter function, it is necessary that each center audit its success with catheter placement against internationally agreed-upon standards as part of local quality improvement.[2,3]

The most common reason for outflow failure is constipation, although causes of inflow failure discussed previously should also be considered. Loading of the bowel with fecal material is often obvious on a plain radiograph, but treatment for constipation should be initiated without recourse to this investigation because it is so common. Constipation should be treated with oral laxatives or an enema. Subsequently, bowel action should be kept regular by increasing the fiber in the diet and, if necessary, adding a mild laxative. Slow outflow can be a problem in patients using automated peritoneal dialysis (APD), resulting in excessive machine alarms. This can be managed by switching to tidal APD and using a relatively large residual volume (e.g., 25% to 50% of the fill volume). Recently, concerns have been raised about the risk for excessive intraperitoneal dialysate volume that might occur during tidal PD;

as a precaution, cycler algorithms have been altered to incorporate a complete drain into the treatment schedule.

Catheter Function: Inflow

Fibrin in the Dialysate

A 2-L bag of dialysate should normally take 15 minutes or less to run into the peritoneal cavity. If inflow has stopped or significantly slowed, mechanical causes should be suspected. After checking to ensure that the tubing and catheter are not kinked, that all clamps or rollers are open to the inflow position, and that any frangible seal is fully broken, the catheter should be flushed vigorously with 20 mL of heparinized saline. If the catheter is cleared, heparin should be added (500 U/L) to the next few cycles because the cause of the blockage is often a fibrin plug. Should the catheter remain blocked, a plain abdominal radiograph is required. If this shows that the catheter is in a satisfactory position in the deep pelvis, an attempt to restore patency should be made with a thrombolytic agent (urokinase 5000 U or tissue plasminogen activator [tPA] 2 mg in 40 mL of normal saline),[5] which can be instilled into the PD catheter for approximately 1 hour before being withdrawn. If inflow is restored, heparin should be added to the dialysate for the

The mesothelial cells of the peritoneal membrane have a range of physiologic functions, including the production of fibrinolytic agents such as tPA. This process is disrupted during peritonitis when the appearance of fibrin in the dialysate is common. If fibrin causes restriction of dialysate flow, heparin (500 U/L) should be added to each bag. A small number of patients have fibrin formation in the absence of peritonitis. Immediately on drainage the bag may appear cloudy, but on standing the fibrin will aggregate and the fluid becomes clear. The first time this happens, a sample must be sent to the microbiology laboratory to exclude infection. If the results of this testing prove negative, the patient can be reassured.

Catheter Function: Outflow

FLUID LEAKS

Fluid leaks occur in which dialysate leaks out of the peritoneal cavity, which can be either visible externally or not. It is recommended that after PD catheter surgery, patients be allowed to heal sufficiently before use (1–2 weeks) to minimize this risk. If the catheter must be used early, low volumes should be used (start with 1 L) in the supine position (e.g., APD with a dry day), with the patient instructed not to mobilize while dialysate is in the peritoneal cavity during the first 2 weeks after catheter insertion. Although PD catheters can be used successfully as the primary approach to manage late-presenting patients or for acute kidney injury, the incidence of leaks is higher under these conditions unless precautions are taken.[6,7]

Curled
catheter
tip

Connector

External Leaks

On occasion, fluid may leak from the exit site or even the incision used to insert the catheter into the peritoneal cavity. A leak of dialysate, which is confirmed by measuring glucose concentration in the leaking fluid, is a risk factor for infection. It is important that PD catheters be adequately immobilized if used for early-start PD to reduce the risk for tugging and leak.

Internal Leaks

Isolated edema of the abdominal wall suggests an internal leak from the peritoneal cavity, either spontaneously or in association with a surgical hernia. In contrast, genital edema suggests an inguinal hernia or patent processus vaginalis. On occasion, both can be present. The site of the leak can be visualized on computed tomography (CT) scanning after intraperitoneal instillation of contrast material or on magnetic resonance imaging without the use of contrast. It may be necessary for the patient to stand or perform other maneuvers to increase intraabdominal pressure before the leak is demonstrated (Fig. 102.2A). An alternative diagnostic test is to perform scintigraphy after injection of a compound such as technetium 99m–labeled diethylenetriaminepentaacetic acid (99mTc-DTPA; see Fig. 102.2B). A surgical repair will be required if a major leak is visualized and should always be considered when there is a hernia. Most leaks, however, will heal after resting or with APD, using dry days, or temporary HD.

Hydrothorax

Fig. 102.1 Catheter Malposition. Plain radiograph of the abdomen with curled catheter (arrows) misplaced in the upper left abdomen.

A pleural effusion can occur with generalized fluid overload or local lung disease, but it is occasionally caused by a leakage of dialysate

R

A

L

B

Fig. 102.2 Inguinal Hernia During Peritoneal Dialysis. (A) Computed tomography scan after intraperitoneal injection of contrast material in a male patient showing dialysate flowing into a right inguinal hernia. (B) Peritoneal scintigram of a male patient on peritoneal

dialysis showing bilateral inguinal hernias. The left hernia extends into the scrotum; the right hernia is less extensive. (From Tintillier M, Coche E, Malaise J, et al. Peritoneal dialysis and an inguinal hernia. Lancet. 2003;362:1893.)

A

B

Fig. 102.3 Hydrothorax in Peritoneal Dialysis. (A) Chest radiograph showing a right-sided pleural effusion with partial collapse of the right lung caused by a diaphragmatic leak. (B) Scintigram in a peritoneal dialysis patient showing isotope in the right hemithorax (arrows) confirming a right pleural effusion.

through the diaphragm (Fig. 102.3A). This occurs more commonly on the right side. A leak is most simply indicated by aspirating a sample of the effusion and demonstrating that its glucose concentration is higher than the patient’s blood glucose concentration, which can be confirmed by scintigraphy after intraperitoneal instillation of isotope, usually ^{99m}Tc-DTPA (see Fig. 102.3B). If one can be confident that the pleural effusion is not caused by the PD, then PD can be continued while the effusion is investigated and managed. Although there are reports that repairing pleural leaks allows subsequent PD, the best advice is to transfer the patient to HD unless there are very strong reasons not to do so.

PAIN RELATED TO PERITONEAL DIALYSIS

Inflow Pain

Soon after starting PD, patients may experience pain during fluid inflow, and occasionally pleuritic pain affects the shoulders, possibly because of diaphragmatic irritation, which usually resolves over the following days. Slowing the rate of fluid inflow will often reduce the symptoms, and peritonitis should be excluded and treated. A small number of individuals have persistent inflow pain, and the use of bicarbonate-lactate–buffered dialysate at physiologic pH improves symptoms in such patients.[8]

Outflow Pain

Some patients have discomfort or pain when the fluid is drained out, which can be experienced in the genital area or rectum and is commonly a result of pelvic irritation related to the catheter tip. This emptying sensation is abolished when the next cycle runs in and is best treated by leaving a small residual volume of fluid in the peritoneal cavity at the end of the drain (e.g., by using tidal APD). In tidal APD, a residual volume is left in the peritoneal cavity at the end of each dialysis cycle (e.g., 20% of the drain volume). To reduce the risk for intraperitoneal volume overload, the treatment algorithm includes at least one complete drain during and at the end of treatment.

Blood-Stained Dialysate

Blood-stained dialysate is uncommon. It is rarely serious but causes considerable alarm to the patient. There is sometimes a clear history of trauma to the abdomen or of unexpected strain. A range of rare conditions are associated with this complication[9]; a few female patients relate the episode to their time of ovulation or menstruation. The treatment is to flush the abdomen with a few cycles of dialysate containing heparin (500 U/L) to minimize the chances of clotting in the catheter. The problem usually resolves spontaneously and often is visible only in one outflow. It is unusual for the blood-stained dialysate to be associated with infection, although it is wise to have the fluid cultured. Routine use of antibiotics is not necessary.

INFECTIOUS COMPLICATIONS

Peritonitis

There are wide variations in peritonitis rates both between and within countries. Reducing peritonitis rates requires a multifaceted, multidisciplinary approach based on the use of preventive measures around the time of catheter insertion, the use of modern disconnect systems, exit site management, and education of patients and health care professionals.10 This should be supported by regular local audit of peritonitis rates including causative organisms and local sensitivities, which is increasingly important because of the emergence of resistant organisms and the requirement to use antibiotics effectively. Root cause analysis (e.g., inquiring about breaches in sterile technique) should be performed after each episode of PD peritonitis, with retraining as appropriate. Guidelines for the diagnosis and management of PD peritonitis are published by the International Society for Peritoneal Dialysis in adults and children (ISPD; https://www.ispd.org) (Box 102.1).10 11 The Peritoneal Dialysis Practice and Outcomes Study has provided information on the variation in peritonitis rates between countries and center practices that are associated with lower rates. The findings included advantages for APD use and longer training periods and corroborated the use of antibiotic prophylaxis for catheter insertion and topical application to prevent exit site infection.12

Diagnosis of Peritonitis

Peritonitis should be suspected in any patient who develops abdominal pain or a cloudy bag when PD fluid is drained; patients with these symptoms should be advised to contact their dialysis center immediately. Fever may be present but is not a universal feature. Samples of the dialysate should be taken for cell count and microbiologic examination. The diagnosis is confirmed by finding more than 100 white blood cells (WBCs) per microliter (1 × 107/L), which should be more

Antibiotic Regimens for Bacterial Peritoneal Dialysis Peritonitis

BOX 102.1

Relevant International Society for Peritoneal Dialysis (ISPD) Guidelines

TABLE 102.1

Cardiovascular and Metabolic
- ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients
- Part I: Assessment and Management of Various Cardiovascular Risk Factors
- Part II: Management of Various Cardiovascular Complications
- Encapsulating Peritoneal Sclerosis
- Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis: Position Paper for ISPD

Culture

Antibiotic

Gram positive: based on sensitivities
Coagulase-negative staphylococci
Staphylococcus aureusa
Enterococci
Other streptococci
Gram-negative bacilli or mixed bacterial growth

Vancomycin or other appropriate antibiotic
Treat for 14 days
Treat for 21 days: screen for carriage
Treat for 21 days
Treat for 14 days
Continue gram-negative coverage based on sensitivities
Consider switching to third- or fourth-generation cephalosporins
Two antibiotics based on sensitivity
Treat for 21–28 days
Treat for 21 days
For mixed gram-negative or gramnegative + gram-positive, consider metronidazole and ampicillin/vancomycin

Infections
- ISPD Catheter-Related Infections Recommendations: 2017 Update
- ISPD Peritonitis Guideline Recommendations: 2022 Update on Prevention and Treatment

All guidelines available at ISPD.org

than 50% neutrophils. A Gram stain of the spun deposit should be performed to help identify the type of causative organism, although initial treatment will usually be empiric pending culture and sensitivity results. Various culture techniques have been proposed, but WBC lysis and inoculation into blood culture media is often helpful in increasing the yield of a positive growth.

The dialysate leukocyte count will be affected by dwell length, and this needs to be considered in APD patients. In short dwells, the count will be lower, and under these circumstances, if the proportion of cells that are neutrophils exceeds 50%, empiric treatment of peritonitis should be commenced. Conversely, if the patient has had a dry abdomen during the day, the initial drain on connection may be cloudy.

This will clear within one or two cycles, and most of the cells found will be mononuclear leukocytes.

Treatment of Peritonitis

The empiric treatment of peritonitis will vary according to center and should be developed in close collaboration with the local microbiology service, taking into account sensitivity patterns and infection control policy. Initial regimens must cover both gram-positive and gram-negative organisms; the latest ISPD guidelines give examples of appropriate antibiotics and their doses, including vancomycin, cephalosporins, and aminoglycosides. Antibiotic regimens are adjusted as soon as culture results are available, usually after about 48 hours.10

The preferred route of administration is intraperitoneal (IP) unless the patient has features of systemic sepsis. IP gentamicin can be administered as daily intermittent dosing at a dose of 0.6 mg/kg/day (aiming to maintain the trough serum concentration of <2 mg/L); IP vancomycin also can be administered intermittently every 5 to 7 days, at a dose of 15 to 30 mg/kg, aiming to maintain the serum vancomycin level above 15 µg/mL. IP cephalosporin can be administered either continuously (in each exchange) or on a daily intermittent basis.10

Dosage regimens will depend on whether the patient is on continuous APD (CAPD) or APD. For CAPD, the antibiotic is administered as a loading dose in the first bag and then as a maintenance dose in subsequent bags. The intermittent IP dose can be given in the day dwell of APD patients; however, APD results in a higher peritoneal clearance of antibiotics than CAPD, and therefore extrapolation of data from CAPD to APD may result in underdosing.

Once the culture result is available, the regimen should be modified accordingly (Table 102.1). If the organism is methicillin-resistant

Pseudomonasa or
Stenotrophomonas spp.
Other gram-negative bacilli

Suggested antibiotic regimens when dialysate fluid culture is available.
Except for culture-negative episodes, empiric treatment is stopped once the sensitivities are known. All antibiotic regimens should be adjusted for local microbiologic practices.
aExamine for exit site or catheter tunnel infection.
From Li PK-T, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2016;36:481–508.

Staphylococcus aureus (MRSA), vancomycin will be continued as part of the regimen. If the culture is negative, empiric therapy should be continued for 2 weeks, assuming there is a clinical response. If a gram-negative organism is identified, the subsequent management will depend on the sensitivity (Fig. 102.4). The isolation of multiple organisms with or without anaerobes strongly suggests perforation of the small or large intestine or biliary system. Metronidazole should be added to the regimen to cover anaerobic organisms, antibiotic therapy augmented to intravenous administration, and prompt surgical review obtained with necessary imaging (CT scan if appropriate).

A wide variety of antibiotics other than those cited have been used with success, and these are documented in the ISPD 2016 guideline.10 A commonly used strategy is to include an oral quinolone, such as ciprofloxacin. There is debate surrounding the role of aminoglycosides, the advantages being simplicity of use and good coverage for gram-negative organisms; however, there are concerns regarding ototoxicity and nephrotoxicity, the former of which is irreversible. Reports regarding the impact of these agents on residual kidney function are inconsistent, but serious episodes of peritonitis tend to adversely affect residual kidney function. It is advisable to avoid recurrent or protracted courses of aminoglycosides, with an early switch to alternative agents (e.g., third-generation cephalosporins) if they are used as empiric first-line treatment. There is evidence for the use of concomitant N-acetylcysteine, which should be considered to prevent the ototoxicity.13 Current recommendations are that for gram-positive organisms, therapy should be for 14 days except in the case of S. aureus, for which 21 days is suggested. For culture-negative episodes, 14 days of therapy should suffice. The same is true in the case of single-organism gram-negative peritonitis.

Overview of the Management of Peritonitis

Clinical suspicion of peritonitis

Repeat on next
exchange if
symptoms persist

Check dialysate white blood cell count

>100 cells per mm 3

<100 cells per mm 3

positive
Gram stain

negative

negative

Commence empiric antibiotics
(e.g., cefazolin, cefalothin, aminoglycoside,
depending on residual renal function and
result of Gram stain)

Culture result

Refine antibiotics
(see Table 102.1)

Multiple or
anaerobic organisms

Despite appropriate antibiotics
symptoms worsen or persist

Resolution

Catheter removal 6 laparotomy

Fig. 102.4 Management of peritonitis.

Many patients can be treated successfully as outpatients. It is extremely important, however, that they be followed either in the clinic or by telephone. In most patients, clinical resolution (as judged by the clearing of the bags) starts within 48 hours. If there is no improvement within 96 hours despite use of the correct antibiotic, as judged by sensitivity tests, the fluid must be retested by cell count, Gram stain, and culture. The ISPD recommends that the catheter be removed if there is no improvement in 5 days; however, in a severe infection this should be done earlier, and in a more indolent case, the period of observation can be longer. A specific recommendation is that the catheter should be removed where a Pseudomonas or S. aureus peritonitis occurs in conjunction with an exit site or tunnel infection.10 In addition, the possibility of intraabdominal or gynecologic disease or the presence of unusual organisms such as mycobacteria should be considered. Under these circumstances, a minilaparotomy should be performed to exclude intraabdominal disease, and if mycobacterial infection is suspected, a peritoneal biopsy specimen should be obtained for culture.

Fungal Peritonitis

If peritonitis is caused by yeasts or fungi, the peritoneal catheter should be removed promptly. This should be combined with treatment with an appropriate antifungal for at least 2 weeks after catheter removal. Fungal peritonitis is a serious complication of PD, commonly requiring hospitalization and transfer to hemodialysis (HD), with a high associated mortality. It is essential to review the appropriate antifungal agent with the local microbiologic team; options are described in some detail in the 2016 peritonitis update from the ISPD.10 Amphotericin B should not be given intraperitoneally because it causes chemical peritonitis and pain. Appropriate antifungal therapy should be continued for at least 2 weeks after catheter removal.

Relapsing Peritonitis

Relapsing peritonitis is defined as infection caused by the same organism as the original infection occurring within 4 weeks, whereas recurrent peritonitis is defined as a different organism within 4 weeks of completion of an appropriate course of antibiotics. In general, the advice is to treat as for a primary infection but to try to establish an underlying cause. For example, recurrence of S. aureus infection should trigger a search for pericatheter infection. If enterococci or gram-negative organisms are the cause of a relapse, the possibility of intraabdominal disease or an abscess should be considered (although these organisms are frequently waterborne). If a patient has other gastrointestinal symptoms, such as change in bowel habit, appropriate investigation should be conducted. Some organisms (including coagulase-negative staphylococci) produce biofilm that can lead to a relapse of the infection. Consideration should be given to changing the PD catheter once the infection has been treated; of course, the catheter will need to be removed if the infection does not respond to treatment. Current practice in most units is to allow up to 3 weeks of treatment before a new catheter is inserted and to bridge with hemodialysis if required.

Culture-Negative Peritonitis

Culture-negative peritonitis is associated with increased risk for treatment failure. Commonly, the cause relates to the sampling technique or the microbiologic approach; alternatively, concurrent antibiotic use may be responsible. It is important to be aware of the possibility of

ESIs caused by Pseudomonas spp. are particularly difficult to treat and often require prolonged therapy with two antibiotics.

Treatment is recommended for a minimum of 2 weeks, extended to 3 weeks in Pseudomonas infections. In gram-positive infections, if there is no improvement within 7 days, ultrasound of the catheter tunnel should be performed because a collection of fluid around the catheter signifies a tunnel infection. If complete healing does not take place after 4 weeks of therapy, further measures should be considered, such as exteriorizing and shaving the outer cuff, because it may be involved in the infection. If the infection persists or relapses, catheter removal must be considered because there is a high risk that the ESI will lead to peritonitis. It is important that the new exit site be formed in a different part of the anterior abdominal wall.

Fig. 102.5 Exit Site Infection. Severe exit site infection that has exposed the outer cuff of the catheter.

fastidious organisms (e.g., atypical mycobacteria, suspicious of contaminated water sources, or yeasts). In addition, other causes of peritoneal inflammation may be responsible; these include the presence of an intraabdominal malignancy or surgical pathology or eosinophilic reactions (e.g., in the case of vancomycin allergy or some fungal infections). An eosinophilic or allergic peritonitis can be diagnosed from the nature of the effluent cell type and requires specific action such as avoiding the causative agent if identifiable, although this usually resolves with time. Chylous effluent is a rare finding in PD; the cause is often unclear, but if recurrent, conditions affecting lymphatic drainage should be considered.

Exit Site Infection

Exit site infection (ESI) is an important complication of long-term PD. The diagnosis is suspected on clinical grounds, usually by the presence of marked erythema or discharge from the exit site (Fig. 102.5). A scoring system for exit sites has been developed to determine the likelihood of infection and grade its severity, with points assigned for crusting, swelling, pain, and discharge according to severity; if the discharge is purulent, this mandates treatment.14 Extension of the infection into the tunnel may be assessed either clinically or by ultrasound. The most common infecting organism is S. aureus. There is now substantial evidence for the use of prophylactic topical antibiotics at the exit site, the strongest being for mupirocin for the prevention of ESI caused by S. aureus,12 14 which we recommend in our practice. There is also evidence for the use of topical gentamicin, although there were some reports of an increase in ESI caused by Enterobacteriaceae, Pseudomonas spp., and probably nontuberculous mycobacteria after a change of prophylactic protocol from topical mupirocin to gentamicin.10

All suspected infected exit sites should be swabbed; routine swabbing of healthy exit sites should be avoided, and incidental bacterial growth does not require treatment. Unless there is prior evidence that the patient carries MRSA or Pseudomonas, initial treatment should be with an antibiotic effective against S. aureus—such as a penicillinase-resistant penicillin (e.g., cloxacillin, dicloxacillin, or flucloxacillin; it is important to be aware of the risk for associated hepatotoxicity with the latter) or a first-generation cephalosporin if the patient is allergic to penicillin. In most patients, the drug can be given orally, but if the individual is systemically ill, the antibiotics should be administered intravenously until clinical improvement occurs. Hospitalization, parenteral antibiotics, and often urgent catheter removal are required if there is evidence of spread into the tunnel. If the infection is with MRSA, eradication should be attempted with systemic vancomycin, as for peritonitis. Should the culture grow a gram-negative organism, ciprofloxacin (500–750 mg once daily orally) will be effective empiric treatment in most patients.

MEMBRANE DYSFUNCTION AND INSUFFICIENT ULTRAFILTRATION

Recognition and Significance of Membrane Dysfunction

There are two complementary approaches to recognizing membrane dysfunction as the cause of insufficient ultrafiltration (UF). The first is based solely on the net fluid removal (termed ultrafiltration capacity) from a standard 4-hour peritoneal equilibration test (PET). The conduct and interpretation of the PET are further discussed in Chapter 101. Account should be taken of the overfill of dialysis bags by the manufacturers, which can be as much as 200 mL. A net UF capacity below 400 mL with a hypertonic exchange (3.86% glucose/4.25% dextrose) is indicative of an inadequate membrane,15 bearing in mind that this may not be clinically relevant in a patient with well-preserved residual kidney function. If a middle-strength glucose solution is used (2.27%), the equivalent value is 100 mL (again excluding overfill). The main limitation of this approach is that it relies on a single measurement of UF capacity, which is subject to significant error (coefficient of variation is up to 25%) and does not identify the cause. The second approach to recognizing UF failure is more holistic in that it considers patient factors that affect fluid status (e.g., comorbid conditions) and an acceptable glucose exposure required to maintain adequate hydration. Many clinicians now take the view that regular use of hypertonic solutions is not acceptable unless the life expectancy is shorter than the likely time to development of severe injury and its complications, unusual before 5 years.

Insufficient UF is a significant cause of technique failure16; it results in low UF, which in turn increases the risk for mortality in anuric patients17 18 and is also a risk factor for encapsulating peritoneal sclerosis (EPS).19 Although it is impossible to set a fluid removal goal that applies to all patients, the European Automated Peritoneal Dialysis Outcomes Study (EAPOS) found that anuric patients who did not reach an UF target of more than 750 mL/day had less efficient membranes (specifically lower osmotic conductance; see later) and higher mortality.18 Patients whose total fluid removal is less than 1 L/day because of poor UF should have their membrane function assessed.

Establishing the Causes of Membrane Dysfunction

Failure of the membrane to ultrafiltrate sufficiently needs to be distinguished from other causes of inadequate peritoneal fluid removal, such as catheter dysfunction, leak, or excessive fluid reabsorption.14 The latter can occur if the intraperitoneal cavity pressure is too high, suspected if the UF falls after an increase in dialysate volume. If there is doubt, a fall in the dialysate sodium concentration by more than 5 mmol/L at 1 hour into a PET using 3.86% glucose is an indicator of preserved sodium sieving (see later), suggesting that UF is preserved.

There are two main causes of UF failure: a fast peritoneal solute transfer rate (PSTR) or a low intrinsic membrane UF efficiency, despite a preserved osmotic gradient, termed reduced osmotic conductance. Both can exist at the start of PD or can be acquired with time on therapy, although it is rare for a patient to develop reduced osmotic conductance without also developing a fast PSTR.

Fast PSTR–Related Membrane Dysfunction: Diagnosis and Management

With the 4-hour PET, a dialysate–plasma creatinine ratio greater than average (typically 0.64) could contribute to poor UF. This is because more rapid diffusion of small solute across the membrane leads to earlier dissipation of the osmotic gradient driving UF. Furthermore, once the gradient is lost, membranes with a larger diffusive area will reabsorb fluid more rapidly. A higher than average PSTR is associated with increased mortality, technique failure, and hospitalization,20 21 whereas this association is ameliorated when APD is used.20 22 Thus, both theoretically and empirically, the short exchanges used in APD prescription are associated with better outcomes in fast PSTR–associated insufficient UF. Prevention of fluid reabsorption during the long day or night exchange is also required in these patients, and this can be achieved by use of icodextrin (polyglucose solution), which also improves the fluid status23 and ultrafiltration, reduces episodes of fluid overload and possibly survival.24 25 The main determinant of fast PSTR is increased intraperitoneal inflammation, which is independent of systemic inflammation.26 Only the latter is an independent predictor of mortality.

Low Osmotic Conductance–Related Membrane Dysfunction: Diagnosis and Management

This problem should be suspected if UF insufficiency is suspected or there is reduced UF capacity as described earlier. Osmotic conductance is a measure of the efficiency of the peritoneal membrane to ultrafiltrate for a given osmotic agent, typically glucose. Reduced osmotic conductance can be demonstrated quite easily in the clinic. Sodium sieving is the consequence of free water entering the peritoneal cavity via the transcellular endothelial aquaporin pathway, resulting in a drop resulting from dilution in the dialysate sodium concentration; it is independent of the sodium-coupled UF that occurs across endothelial tight junctions. Thus, the absence of a fall in the dialysate sodium concentration 1 hour after using a high glucose exchange indicates the lack of sodium sieving, which implies reduced free water UF. A sodium dip of less than 5 mmol/L is indicative of this type of membrane dysfunction and is associated with worse outcome on PD, including the risk of EPS.15 The two causes so far identified are reduced aquaporin function, possibly constitutive and thus present at the start of treatment, and progressive fibrosis of the membrane as a result of acquired membrane injury. There is no specific treatment, so clinical effort should focus on prevention (see next section) and timely switch to HD or transplantation.

CHANGES IN PERITONEAL STRUCTURE AND FUNCTION

It is widely assumed that acquired changes in membrane function, a combination of a fast PSTR, and loss of osmotic conductance are related to structural changes in the peritoneal membrane.27 There is accumulating evidence that continuous exposure to dialysis solution components and repeated episodes of bacterial peritonitis are the main drivers of this process (Fig. 102.6). The relationship between structure and function is becoming clearer: increased PSTR is likely to reflect a greater vascular surface area, whereas loss of osmotic conductance requires an additional mechanism that is associated with progressive membrane fibrosis and an increased risk for EPS. The submesothelial

M
M

Fig. 102.6 Peritonitis. Scanning electron micrograph of the peritoneum from a patient receiving peritoneal dialysis who has peritonitis. The small round cells (arrows) are phagocytes, which are widely distributed among the mesothelial cells (M). (Magnification, ×1800.)

collagenous zone shows progressive increase in thickness with time on PD (Figs. 102.7 and 102.8), and this is associated with progressive changes to the structure of small venules ranging from subtle thickening of the subendothelial matrix to complete obliteration of vessels (Fig. 102.9).[28,29] This process is accompanied by a reduction in sodium sieving, implying reduced free water transport, but no change in aquaporin expression, suggesting that the fibrosis is the main cause of UF failure.[30]

Preventing Membrane Injury

The main clinical factors associated with more rapid and severe membrane injury are early loss of residual kidney function, recurrent or severe peritonitis, and the earlier use of higher glucose–containing solutions (often associated with loss of diuresis but an independent risk factor).[31] Hypertonic solutions may induce injury because of direct glucose toxicity; glucose degradation products (GDPs) manifest as a result of the sterilization process; or both. The prevention of membrane injury should focus on all of these drivers and include (1) preservation of residual kidney function by avoiding both volume depletion and the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; (2) use of loop diuretics to maintain urine volume and delay use of hypertonic exchanges; (3) use of icodextrin in the long exchange; (4) avoidance of peritonitis; and (5) use of low-GDP neutral pH solutions.[32] The balANZ study shows that the increase in PSTR over the first 2 years of PD is prevented by use of ultralow-GDP dialysis fluid. More importantly, this study showed that achievement of less UF, lower use of hypertonic glucose, and in particular low-GDP solutions early in the course of PD, now confirmed in meta-analyses of several trials is associated with preservation of residual kidney function.[24,33] This, combined with trial evidence that fluid status is stable in patients with residual kidney function,[34] supports the main strategy clinicians should adopt in preserving the membrane: prescribing to maintain adequate but not excessive UF, which will only drive thirst and increase the risk for volume depletion.

Encapsulating Peritoneal Sclerosis

A minority of patients on PD develop EPS, in which the bowel is enveloped in a thick cocoon of fibrous tissue, causing intestinal obstruction (Fig. 102.10).[19] It is variable in severity but may be life-threatening, causing death from malnutrition or intraabdominal catastrophe; but with experienced management by a multidisciplinary team, overall

Peritoneal Membrane Thickening in Peritoneal Dialysis
2000

Membrane thickness (μm)

Normal vs all: P = .00001
HD vs PD: P = .0049
PD: P = .0049
1000

0
Normal Undialyzed
CKD

49-72
73-96
97+
months months
months
PD

Fig. 102.7 Peritoneal Membrane Thickening in Peritoneal Dialysis (PD). The thickness of the submesothelial collagenous zone of the peritoneal membrane in normal individuals, in undialyzed patients with advanced chronic kidney disease (CKD), patients with uremia, in patients receiving hemodialysis (HD), and in those who have received PD for different periods. Membrane thickness is significantly increased in all uremic and dialysis patients compared with normal individuals. Membrane thickness increases significantly with duration of PD and is increased in PD patients as a group compared with HD patients.

A

HD

0-24
months

100μm

25-48
months

B

100μm

Fig. 102.8 Morphologic Changes in the Parietal Peritoneal Membrane. (A) Normal. (B) A patient who has been on peritoneal dialysis for 10 years. Note the marked thickening of the submesothelial compact zone (arrows). (Toluidine blue stain.)

survival compares well with that of matched controls. Diagnosis of this syndrome requires both clinical signs and symptoms of bowel obstruction leading to weight loss and malnutrition (with or without features of systemic inflammation) combined with either typical features on imaging (CT scanning) or confirmation of fibrous cocooning at laparotomy. Although UF failure is a risk factor for EPS (especially when there is also loss of osmotic conductance), EPS appears to be a different pathologic process that predominantly affects the visceral membrane, is usually associated with another trigger (e.g., severe peritonitis or interruption of PD), and frequently has a systemic inflammatory phase (biopsy material more often shows inflammation and fibrinous exudates).

The single most important risk factor for EPS is time on PD; at 5 years the incidence is 2% to 3%, whereas by 10 years, this rises to 6% to 20%.19 Recent reports from Japan35 and the Netherlands suggest that the incidence of EPS is decreasing, possibly because of a better understanding of the management of risk factors. There is increasing evidence that surgical treatment (extensive adhesion lysis and excision of the peritoneum while avoiding enterotomy) is most effective, especially when there are obstructive symptoms. This should be undertaken by an experienced surgical team, which can achieve cure rates of 70% to 80%. Parenteral nutrition can be used as a preparation for surgery and occasionally as a long-term solution. In about 50% of patients, symptoms are less severe and gradually resolve. There is no

A

10µm

B

10µm

Fig. 102.9 Blood Vessels in the Parietal Peritoneum: Transverse Sections of Peritoneal Arterioles. (A) Normal. (B) Vasculopathy in a patient on peritoneal dialysis; the vascular lumen (arrows) is occluded by connective tissue containing fine calcific stippling (arrows)

Fig. 102.10 Encapsulating Peritoneal Sclerosis. Abdominal computed tomography scan from a patient with encapsulating peritoneal sclerosis. Red arrows indicate thickened parietal peritoneum with calcification; yellow arrows indicate thickened visceral peritoneum forming a cocoon containing loops of bowel.

role for screening with CT scanning, but this is helpful in diagnosis. Most commonly, EPS develops after transfer from PD to either HD or transplantation; but if it develops in a patient on PD, the consensus is that PD should be stopped to avoid continued exposure to nonphysiologic dialysis solutions. Other strategies, such as continued irrigation, dual-modality treatment with PD and HD, and use of antifibrotic drugs such as tamoxifen, are practiced, but an evidence base for such management is lacking.

NUTRITIONAL AND METABOLIC COMPLICATIONS

Undernutrition

Cross-sectional surveys of patients receiving PD show that about 40% have evidence of mild and 8% severe protein-calorie depletion as judged by the subjective global assessment of nutritional state. Malnutrition is a risk factor for morbidity and mortality of patients on PD and often associated with systemic inflammation. The assessment and management of malnutrition are discussed further in Chapter 90. One obvious contributing factor is protein loss through the peritoneum, which averages 8 g/day. Protein loss is proportional to effective membrane area and so is most marked during peritonitis and in patients with fast peritoneal transport. The ensuing hypoalbuminemia exacerbates the extravascular extracellular fluid expansion in these patients.[36] Therefore, it has been recommended that PD patients should consume daily at least 1.2 to 1.3 g of protein per kilogram of body weight. In practice, many patients take only about 0.8 g/kg/day, and nitrogen balance is maintained partly as a result of calories from dialysate. However, especially once patients are anuric, there is a progressive loss in lean body mass.[34] Despite concerns about the increased prevalence of hypoalbuminemia among peritoneal dialysis patients, the association with mortality is not worse than for HD patients.[37] PD patients have abnormal eating behavior with smaller meals, slow eating, and impaired gastric emptying, which causes nausea, especially in patients with diabetes. This is worst when using more hypertonic glucose and least severe with icodextrin. Amino acid–based dialysate improves nitrogen balance in malnourished patients, but the long-term nutritional benefit is marginal.[38]

Acid-Base Status

Correction of acidosis is best achieved by use of dialysate with higher levels of potential buffer,39 but if necessary, oral bicarbonate may be added. There is evidence that correction of acidosis, by whatever means, to within the upper half of the normal range for serum bicarbonate reduces protein catabolism, resulting in weight gain and increased midarm muscle circumference.38 The use of amino acid–containing dialysate fluid can worsen acid-base status, requiring close monitoring.

Lipids and Obesity

PD results in significant daily glucose absorption, which may range from 80 to 200 g/day (300–800 kcal). Therefore, PD patients tend to develop features of metabolic syndrome, including central obesity, hyperglycemia, dyslipidemia, and hyperinsulinemia; they may even develop frank diabetes, although there is no evidence that this or worsening obesity is more common than in HD patients.40 These problems can be reduced by use of icodextrin and amino acid solutions in place of glucose with better glycemic control in diabetics.41
Blood glucose monitoring in diabetic patients using icodextrin must

not use glucose dehydrogenase pyrroloquinoline quinone test strips because this will lead to falsely high estimates and risk for severe hypoglycemia.

Despite these concerns, there is no evidence to suggest that PD should be avoided in obese patients even though the survival advantage seen in HD associated with a higher body mass index is not seen with PD.[42]

SELF-ASSESSMENT QUESTIONS

1. Regarding catheter function, which of the following statements are false?
A. Introducing the routine use of laparoscopic technique for catheter insertion will improve early catheter survival more than carefully audited standard methods used by an experienced surgeon.
B. Slow catheter drainage is most commonly a result of constipation.
C. Pain on draining in (“inflow pain”) is best solved by use of tidal PD.
D. Pain on draining out is best solved in APD patients by use of tidal PD.
E. Poor drainage associated with edema in the genital area indicates an inguinal hernia or patent processus vaginalis.
2. Regarding peritonitis and infection, which of the following statements are false?
A. Treatment of suspected peritonitis should always commence with antibiotics covering both gram-positive and gram-negative organisms and antifungal prophylaxis.
B. Fungal peritonitis usually can be successfully treated with intraperitoneal agents without requiring catheter removal.
C. Redness and pain at the exit site always should be treated immediately with oral antibiotics.

D. Prophylactic use of mupirocin or gentamicin at the exit site has been shown to reduce the chances of peritonitis.
E. Culture of more than one organism in a patient with peritonitis should raise serious concerns of a perforated viscus and lead to minilaparotomy and catheter removal.
3. Regarding ultrafiltration insufficiency, which of the following statements are false?
A. Membrane function should be fully assessed if the ultrafiltration capacity is less than 100 mL on a 4-hour middle-strength glucose 2.27% (dextrose 2.5%) exchange.
B. There should be a minimum target of 1 L UF per day regardless of residual kidney function.
C. Fast peritoneal solute transfer rate contributes to poor UF, but this can be addressed by use of APD and icodextrin.
D. Routine computed tomography scanning to look for progressive membrane thickening and calcification is the best way to screen for EPS.
E. Progressive loss of osmotic conductance (a 1-hour sodium dip <5 mmol/L using a glucose 3.86% exchange) is thought to represent increasing fibrotic damage, may predispose to EPS, and is a reason for switching to hemodialysis.

REFERENCES

1. Shrestha BM, Shrestha D, Kumar A, Shrestha A, Boyes SA, Wilkie ME. Advanced laparoscopic peritoneal dialysis catheter insertion: systematic review and meta-analysis. Perit Dial Int. 2018;38(3):163–171.
2. Goh BL, Ganeshadeva Yudisthra M, Lim TO. Establishing learning curve for Tenckhoff catheter insertion by interventional nephrologist using CUSUM analysis: how many procedures and in which situation? Semin Dial. 2009;22:199–203.
3. Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. Perit Dial Int. 2019;39(5):414–436.
4. Johnson DW, Wong MG, Cooper BA, et al. Effect of timing of dialysis commencement on clinical outcomes of patients with planned initiation of peritoneal dialysis in the ideal trial. Perit Dial Int. 2012;32:595–604.
5. Shea M, Hmiel SP, Beck AM. Use of tissue plasminogen activator for thrombolysis in occluded peritoneal dialysis catheters in children. Adv Perit Dial. 2001;17:249–252.
6. Povlsen JV, Ivarsen P. How to start the late referred ESRD patient urgently on chronic APD. Nephrol Dial Transplant. 2006;21(suppl 2):ii56–ii59.
7. Cullis B, Al-Hwiesh A, Kilonzo K, et al. ISPD guidelines for peritoneal dialysis in acute kidney injury: 2020 update (adults). Perit Dial Int. 2021;41(1):15–31.
8. Mactier RA, Sprosen TS, Gokal R, et al. Bicarbonate and bicarbonate/lactate peritoneal dialysis solutions for the treatment of infusion pain. Kidney Int. 1998;53:1061–1067.
9. Lew SQ. Hemoperitoneum: bloody peritoneal dialysate in ESRD patients receiving peritoneal dialysis. Perit Dial Int. 2007;27:226–233.
10. Li PK-T, Chow MC, Cho Y, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Perit Dial Int. 2022;42(2):110–153.
11. Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32:S32–S86.
12. Perl J, Fuller DS, Bieber BA, et al. Peritoneal dialysis-related infection rates and outcomes: results from the peritoneal dialysis outcomes and practice patterns study (PDOPPS). Am J Kidney Dis. 2020;76(1):42–53.
13. Tokgoz B, Ucar C, Kocyigit I, et al. Protective effect of N-acetylcysteine from drug-induced ototoxicity in uraemic patients with CAPD peritonitis. Nephrol Dial Transplant. 2011;26:4073–4078.
14. Szeto CC, Li P, Johnson DW, et al. ISPD Catheter-related infections recommendations: 2017 update. Perit Dial Int. 2017;37(2):141–154.
15. Morelle J, Stachowska-Pietka J, Öberg C, et al. ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention. Perit Dial Int. 2021. 896860820982218.
16. Davies SJ, Phillips L, Griffiths AM, et al. What really happens to people on long-term peritoneal dialysis? Kidney Int. 1998;54:2207–2217.
17. Jansen MA, Termorshuizen F, Korevaar JC, et al. Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 2005;68:1199–1205.
18. Brown EA, Davies SJ, Rutherford P, et al. Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. J Am Soc Nephrol. 2003;14:2948–2957.
19. Brown EA, Bargman J, van Biesen W, et al. Length of time on peritoneal dialysis and encapsulating peritoneal sclerosis - position Paper for ISPD: 2017 update. Perit Dial Int. 2017;37(4):362–374.
20. Mehrotra R, Ravel V, Streja E, et al. Peritoneal equilibration test and patient outcomes. Clin J Am Soc Nephrol. 2015;10:1990–2001.
21. Brimble KS, Walker M, Margetts PJ, et al. Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. J Am Soc Nephrol. 2006;17:2591–2598.

22. Johnson DW, Hawley CM, Mcdonald SP, et al. Superior survival

of high transporters treated with automated versus continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant. 2010;25:1973–1979.

23. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol. 2003;14:2338–2344.

24. Htay H, Johnson DW, Wiggins KJ, et al. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2018;10(10):CD007554.

25. Goossen K, Becker M, Marshall MR, et al. Icodextrin versus glucose solutions for the once-daily long dwell in peritoneal dialysis: an enriched systematic review and meta-analysis of randomized controlled trials. Am J Kidney Dis. 2020;75(6):830–846.

26. Lambie M, Chess J, Donovan KL, et al. Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. J Am Soc Nephrol. 2013;24:2071–2080.

27. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. Kidney Int. 2004;66:2437–2445.

28. Williams JD, Craig KJ, Topley N, et al. Morphologic changes in the peritoneal membrane of patients with renal disease. J Am Soc Nephrol. 2002;13:470–479.

29. Honda K, Nitta K, Horita S, et al. Morphological changes in the peritoneal vasculature of patients on CAPD with ultrafiltration failure. Nephron. 1996;72:171–176.

30. Morelle J, Sow A, Hautem N, et al. Interstitial fibrosis restricts osmotic water transport in encapsulating peritoneal sclerosis. J Am Soc Nephrol. 2015;26:2521–2533.

31. Lambie ML, John B, Mushahar L, et al. The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis is made. Kidney Int. 2010;78:611–618.

32. Davies SJ, Mushahar L, Yu Z, et al. Determinants of peritoneal membrane function over time. Semin Nephrol. 2011;31:172–182.

33. Johnson DW, Brown FG, Clarke M, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol. 2012;23:1097–1107.

34. Tan BK, Yu Z, Fang W, et al. Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. Kidney Int. 2016;89:487–497.

35. Nakayama M, Miyazaki M, Honda K, et al. Encapsulating peritoneal sclerosis in the era of a multi-disciplinary approach based on biocompatible solutions: the NEXT-PD study. Perit Dial Int. 2014;34:766–774.

36. John B, Tan BK, Dainty S, et al. Plasma volume, albumin, and fluid status in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2010;5:1463–1470.

37. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. Am J Kidney Dis. 2011;58:418–428.

38. Li FK, Chan LYY, Woo JCY, et al. A 3-year, prospective, randomized, controlled study on amino acid dialysate in patients on CAPD. Am J Kidney Dis. 2003;42:173–183.

39. Mujais S. Acid-base profile in patients on PD. Kidney Int Suppl. 2003:S26–S36.

40. Mehrotra R, Devuyst O, Davies SJ, et al. The current state of peritoneal dialysis. J Am Soc Nephrol. 2016;27:3238–3252.

41. Li PKT, Culleton BF, Ariza A, et al. Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. J Am Soc Nephrol. 2013;24:1889–1900.

42. Ahmadi S-F, Zahmatkesh G, Streja E, et al. Association of body mass index with mortality in peritoneal dialysis patients: a systematic review and meta-analysis. Perit Dial Int. 2015;36:315–325.

103
c0103

Extracorporeal Therapies for Drug Overdose and Poisoning

Nigel Suren Kanagasundaram, Andrew Lewington, Etienne Macedo

p0010 Whether intentional or accidental, poisoning and drug overdose are common medical emergencies that account for around 160,000 presentations annually in the United Kingdom and many more consultations with primary care and National Health Service (NHS) advice services.1 Most exposures do not require hospitalization, with around 66% of US cases in 2019 being managed in a non–health care facility, usually at the site of the incident.2 Overall exposure-related mortality remains relatively low, with 1411 exposure-related fatalities recorded in around 2.15 million exposures in this same US report.2 However, poisoning is a significant cause of death in young people.3

p0015

The spectrum of agents ingested is wide, ranging from overdose of prescribed and nonprescribed medicinal drugs to poisoning with nonpharmacologic substances and recreational drugs. The pattern of toxin ingestion has changed over the years and varies according to geographic location. Frequently implicated agents in industrialized societies include analgesics (acetaminophen, opioids, and salicylates), antidepressants, sedatives, and antipsychotics. Pesticides are a frequent cause of poisoning in low- and middle-resource countries.3 Legislation has been used to reduce the availability of potential toxins; for instance, paraquat has not been sold in the United Kingdom since July 2008. Similarly, UK legislation limiting pack size of paracetamol (acetaminophen) in 1998 was followed by a significant reduction in the number of deaths from paracetamol overdose.4

p0020

Effective management of poisoning depends on hemodynamic, respiratory, and other supportive care, prevention of further poison absorption (through oral activated charcoal in specific patients), neutralization of toxicity (e.g., with intravenous N-acetylcysteine after significant acetaminophen overdose or digoxin immune Fab [Digibind]), and enhancement of endogenous toxin elimination (e.g., through urinary alkalinization). These aspects of management are well described by resources such as Toxbase in the United Kingdom (https://www.toxbase.org) and via the American Association of Poison Control Centers (https://www.aapcc.org). Other local and regional poison information services are linked through the website of the European Association of Poisons Centres and Clinical Toxicologists (https://www.eapcct.org).

p0025

Extracorporeal treatment (ERCT) for poison elimination includes kidney replacement therapy (KRT) and other modalities such as hemoperfusion and therapeutic plasma exchange. However, ERCT is only occasionally needed to manage poisoning and overdose; in the United States in 2019, only around 3400 patients were treated, mostly with hemodialysis (HD) or continuous KRT (CKRT).2 Only 21 patients were recorded as receiving hemoperfusion, reflecting a long-term decline explained partly by the increasing rarity of theophylline and barbiturate overdose (historically, the main indications for this technique) but also by the increased use of high-efficiency, highflux HD, allowing removal of toxins previously regarded as being nondialyzable.5 6

ERCT has long been used to manage poisoning,5 but common practices are often not supported by high-quality evidence, at least partly because of the practical and ethical barriers to randomized controlled p0030 trials.5 Despite these barriers the EXTRIP (Extracorporeal Treatments in Poisoning) consensus group (https://www.extrip-workgroup.org)6 has created several useful resources for clinicians endorsed by various national and international stakeholder societies.

WHEN SHOULD EXTRACORPOREAL REMOVAL BE CONSIDERED?

s0010

p0035 ERCT is most commonly used for lithium, toxic alcohol, and salicylate ingestions7; other potential indications are shown in Table 103.1. Extracorporeal elimination should be considered when it is evident that other treatments (e.g., activated charcoal, specific antidotes) will not reduce poison levels below toxic thresholds. It is therefore important to understand the general principles underpinning the use of ERCT to make decisions about management of poisonings, particularly for those for which no consensus or evidence base exists.

p0040 Extracorporeal removal is appropriate for only a small proportion of poisonings. The potential advantages of therapy must be balanced with the risks that are generic to all forms of ERCT (e.g., acute transfer to a specialist center, vascular access, anticoagulation8,9) and those specific to its use in poisoning (discussed later under individual treatment modalities). Factors that help determine the potential value of extracorporeal removal are summarized in Box 103.1. It should be noted that effective clearance by ERCT does not necessarily prevent ongoing end organ toxicity5 or death, as may occur in cases of paraquat poisoning.10

Molecular Weight

s0015

p0045 Most ingested poisons have a molecular weight (MW) in the 100 to 1000 Da range and so are amenable to removal by HD,11 which is the modality of choice for clearance of small solutes. Higher flux membranes extend the range of dialyzable solutes up to approximately 10,000 Da, particularly if performed for long hours, and allow removal of toxins such as theophylline and carbamazepine, for which hemoperfusion might historically have been indicated.11 Molecules toward the upper end of this range and up to about 40 kDa are more effectively removed using modalities with a significant convective component such as hemofiltration (HF) or hemodiafiltration (HDF). Even larger solutes may be removed by non-KRT, such as plasma exchange or one of the albumin dialysis techniques used for liver support.

Protein Binding

s0020

p0050 Diffusive and convective modalities (HD, HF, HDF; either intermittent or continuous) are generally unsuitable for removing poisons with protein binding greater than 80%.11 However, certain toxins (e.g.,

t0010

Poisonings for Which Extracorporeal Removal May Be Indicated[a]
TABLE 103.1

Agent	Preferred Modality	Other, Acceptable Modalities
Acetaminophen	IHD	IHP, CKRT, Ex
Long-acting barbiturates	IHD	HP, CKRT
Carbamazepine	IHD	IHP, CKRT
Ethylene glycol	IHD	CKRT
Lithium	IHD	CKRT[a]
Metformin	IHD	CKRT[a]
Methanol	IHD	CKRT
Phenytoin	IHD	IHP
Salicylates	IHD	IHP, CKRT, Ex
Thallium	IHD	IHP, CKRT
Theophylline	IHD	HP, CKRT, Ex
Valproate	IHD	IHP, CKRT

Other agents that may be amenable to removal by extracorporeal techniques include β-blockers, meprobamate, deferoxamine, aminoglycosides (with high flux membranes), pentoxifylline, sodium edetate, Amanita phalloides toxin, and paraquat.

[a] After initial treatment, both IHD and CKRT are equally acceptable.

CKRT, Continuous kidney replacement therapy; Ex, exchange transfusion in neonates; IHD, intermittent hemodialysis; IHP, intermittent hemoperfusion.

See EXTRIP. Blood Purification in Toxicology: Reviewing the Evidence and Providing Recommendations. http://www.extrip-workgroup.org/

Factors Affecting Toxin Removal by Extracorporeal Therapy

BOX 103.1
b0010

- Molecular weight
- Protein binding
- Volume of distribution
- Solute compartmentalization
- Contribution of extracorporeal toxin removal relative to endogenous clearance

salicylate, valproate) are highly protein bound under normal circumstances but saturate protein-binding sites during poisoning, leading to high (and therefore dialyzable) serum concentrations of free agent.5 In addition, easy dissociation of protein-toxin complexes may allow significant diffusive removal, as with phenytoin.5 Agents with very high (>90%) protein binding and that are not amenable to diffusive or convective elimination may be removed by plasma exchange (e.g., l-thyroxine and cisplatin).11
p0055
The interplay between MW and protein binding and their impact on modality choice are shown in Fig. 103.1

s0025 Volume of Distribution

p0060 The efficacy of toxin removal is also influenced by the theoretical volume of distribution (VD). Substances confined to the bloodstream will have a low VD (~0.07 L/kg body weight); those distributed in the extracellular space, a VD of approximately 0.2 L/kg; and those confined to total body water, approximately 0.6 L/kg. Higher distribution volumes are often found in substances with avid tissue binding, lipophilicity, or sequestration. As VD increases, more solute must be removed for achievement of a particular blood level. The ideal solute for extracorporeal removal would therefore have a low distribution volume and would be located within a single, well-mixed compartment that

is directly accessible by ERCT. There are exceptions: carbamazepine, metformin, and thallium all have high distribution volumes but are amenable to extracorporeal removal.11

Solute Compartmentalization

s0030
Solutes are often distributed across one or more body compartments p0065 that may not be directly accessible by ERCT (Fig. 103.2). If there is any resistance to solute movement between the accessible proximal and the remote compartments, disequilibrium will develop during ERCT, reducing the overall efficiency of toxin removal, and potentially leading to a large postsession rebound in toxin blood levels. Potentially toxic posttreatment levels may be missed if the immediate postdialysis blood level is used to estimate elimination (Fig. 103.3). After ERCT for lithium poisoning, for example, it is recommended that levels be rechecked after 6 to 12 hours to detect clinically significant rebound.12 Vigilance for rapidly rising levels is also important if ongoing toxin

absorption is suspected and may require earlier and more frequent monitoring.

High clearance techniques (i.e., intermittent HD or HDF) rapidly p0070 reduce blood solute levels but are more likely to result in intercompartmental disequilibrium. Extending sessions beyond 4 hours can ameliorate rebound, but intermittent HD and the diffusive component of intermittent HDF are inherently inefficient processes that depend on the solute concentration presented to the dialyzer. Most solute removal will therefore occur at the start of dialysis, so any gains in solute removal will be disproportionately lower as dialysis time extends. Increasing treatment frequency can mitigate the risk for significant rebound to toxic blood levels.

Compartmentalization need not preclude HD-/HDF-mediated p0075 toxin removal, but the total body burden of highly compartmentalized toxins (e.g., digoxin; tricyclic antidepressants [TCAs]) cannot be effectively reduced by HD even though blood levels are rapidly reduced. Therefore, ERCT is not recommended in digoxin or TCA poisonings6 despite occasional reports of successful clearance of TCAs with dialysis.5

Contribution of Extracorporeal Toxin Relative to Endogenous Clearance

s0035

Even toxins that may be readily cleared by ERCT may not require such p0080 treatment if endogenous clearance rates are high. It is proposed that ERCT is justified if it increases total body clearance by at least 30%13 or if endogenous clearance is less than 4 mL/min/kg body weight.14 Unfortunately, these thresholds can be difficult to estimate at the bedside, although an indication of endogenous clearance rates is available for some drugs (see https://www.medicines.org.uk/emc/), and estimates of dialyzer clearances can be obtained from product inserts. For HF, an estimate of clearance can be provided by the ultrafiltration rate. Maximal clearances for ERCT are approximately 240 mL/min (for intermittent HD/HF/hemoperfusion), 50 mL/min (for CKRTs and plasma exchange), and 10 mL/min (for exchange transfusion).11

However, endogenous elimination in the setting of poisoning may p0085 be markedly lower than in health. High endogenous clearances of approximately 2000 mL/min (e.g., for cocaine, labetalol, toluene, and verapamil)11 would appear to obviate the need for ERCT. However, if these elimination routes are limited by end organ dysfunction (e.g., by kidney or liver failure), ERCT may be life-saving.

p0090

These considerations are summarized in Fig. 103.4

TREATMENT MODALITIES

s0040

The range of ERCT used for toxin elimination with parameters p0095 that might be manipulated to enhance toxin clearances is shown

The Impact of Molecular Weight and Protein
Binding on Modality Choice
PE

1,000,000

Molecular weight (Da)

100,000

HF

HP

HD

10,000
1,000
100
10
1
0%

f0010

20%

40%

60%

80%

100%

Protein binding
Fig. 103.1 Impact of Molecular Weight and Protein Binding on Modality Choice. Circles indicate for which poisons a specific modality might be most useful. The decline in use of hemoperfusion in many parts of the world means that it may be unavailable as a treatment option. In these circumstances, plasma exchange, which is widely available, may be used. HD, Hemodialysis; HF, hemofiltration; HP, hemoperfusion; PE, plasma exchange. (From Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. Semin Dial. 2014;27[4]:362–370.)

Development of Intercompartmental
Solute Disequilibrium

Postdialysis Solute Rebound
to Toxic Levels

Only blood directly exposed
to dialyzer is cleared
Start

Proximal
compartment

Remote
compartment

Blood solute
concentration

End

End + 60 min

Toxic blood
level

Dialyzer

f0015

Solute disequilibrium results
from incomplete diffusion
between the two compartments

Fig. 103.2 Intercompartmental Solute Disequilibrium. Access of dialyzer to toxin is limited by disequilibrium, which retains toxin in the remote compartment.

in Box 103.2. Generic considerations, including the basics of physical process, nomenclature, and vascular access (and its care) are detailed elsewhere.[8,9]

s0045

Intermittent Hemodialysis, Hemofiltration, and Hemodiafiltration

p0100 Diffusion against a steep concentration gradient (as in intermittent HD) encourages the rapid removal of smaller solutes, including most poisons, unless there is significant protein binding. Clearances can be enhanced by increasing dialyzer efficiency (indicated by the KoA, the urea mass transfer area coefficient) or membrane surface area. Larger

Time

f0020

Fig. 103.3 Postdialysis Rebound. Falling solute concentration during dialysis with rapid postdialysis rebound to toxic levels.

solute removal can be enhanced by increasing dialyzer flux (Kuf) when intermittent HD is used (for toxins with MW between 500 Da and 10,000 Da, such as deferoxamine and aminoglycosides) or by introducing convective removal (with HF or HDF), which can allow removal of toxins up to approximately 40,000 Da.

Intermittent HD is usually the first-choice extracorporeal modality p0105 because of its common availability, the rapidity of toxin removal, and the low MW of common poisons. The role of other kidney replacement modalities is less clear because of a lack of published data.

Peritoneal Dialysis

s0050

Peritoneal dialysis (PD) is not an “extracorporeal” technique per se p0110 and is rarely used to treat poisoning because of the comparatively slow rate of clearance, the risks associated with acute PD catheter insertion, and the widespread availability of other modalities, at least in the

Stepwise Approach to Initiation of Extracorporeal
Therapies in Poisoning
Toxic blood levels (if a threshold of toxicity can be defined)
Serious clinical manifestations despite optimal support
Delayed action possible (e.g., ethylene glycol,
methanol, paraquat)

Anticipated benefits of extracorporeal
therapy outweigh risks?
Yes
Alternative therapy available
and effective (e.g., antidote)?
No

No

Yes

No extracorporeal therapy*

Yes

VD o1-2 L/kg body weight?
OR
Endogenous clearance o4 mL/min/kg
body weight?
No
Protein binding of toxin

80%-95%

o80%

o95%
Plasma exchange†

Hemoperfusion

o40 kDa
Molecular weight of toxin

o10 kDa

10-40 kDa

f0025

Hemofiltration‡

Hemodialysis

Fig. 103.4 Stepwise Approach to the Initiation of ERCT for Enhanced Elimination in Poisoned Patients.
*Unless other indication (e.g., acute kidney injury [AKI], such as from acetaminophen overdose; severe metabolic acidosis; severe liver failure; hypothermia; hyperthermia). Choice of technique will depend on the indication (e.g., one of the kidney replacement therapies for AKI). †Or albumin dialysis if available. ‡Or hemodialysis with high cut-off membrane, if available (pore size cut-off ~65 kDa). VD, Solute volume of distribution.
(Modified from Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach

for the management of
poisoning with extracorporeal treatments. Semin Dial. 2014;27[4]:362–370.)

industrialized world. It may have a role in the treatment of poisoning in childhood because its lower clearance may be sufficient for the smaller solute distribution volumes in children and because of technical challenges associated with HD in very young children.

s0055 Continuous Kidney Replacement Therapy

p0115 CKRT may be used when intermittent HD is not immediately available or when more rapid solute removal would be compromised by significant intercompartmental disequilibrium. For small-solute clearances, continuous HF and continuous HD have near kinetic equivalence. Full saturation of dialysate effluent in continuous HD, because of its slow flow rates, gives a small-solute concentration similar to both the ultrafiltrate from HF and plasma water as it leaves the hollow-fiber device.

CKRT gives better solute clearances when applied over the course of several days, but elimination is not as rapid as with intermittent HD. Delivered small-solute clearances of CKRT can be maximized by combining diffusion and convection in continuous HDF. If it is logistically possible, an ideal combination may be initial use of intermittent HD for rapid reduction of toxin levels, with continuous therapy then used to ameliorate any postdialysis rebound when this is anticipated.

Although small-solute clearances are similar in continuous HF and p0120
continuous HD, the former should be used in preference to remove larger toxins.

Because HF and HD modalities are often applied for drug elimination p0125
in the absence of kidney dysfunction or serious electrolyte disturbance, careful monitoring for evolving biochemical abnormalities is required.

BOX 103.2 Practical Considerations in Prescribing Extracorporeal Therapy for Poisonings

b0015

Intermittent Hemodialysis

- Maximize Qb and dialyzer membrane surface area
- Aim for Qb/Qd ratio of 2.5:1 or greater (although diminishing benefits gained from increasing Qd beyond ~600 mL/min)[33]
- Maximize treatment times to at least 4 hours
- Use high-flux (Kuf), high-efficiency (KoA) dialyzer, particularly if middle molecular weight solutes (>1000 Da) are to be cleared

Intermittent Hemofiltration/Filtrative Component of Intermittent Hemodiafiltration

- Aim for postdilution fluid replacement to maximize efficiency with high-flux membrane
- Maximize Quf according to filtration fraction

Continuous Kidney Replacement Therapies[a]

- Aim for high convective clearances (i.e., postdilutional CVVH with high-flux membrane) for larger solutes (>1000 Da)
- Aim for high diffusive clearances (i.e., CVVHD) for small solutes (≤1000 Da)
- For CVVH, maximize Quf according to filtration fraction[b]
- For CVVHD, CVVHDF, maximize Qd up to at least 2.5 L/h[c] for small solutes
- For larger solutes (e.g., of an equivalent size to β_2-microglobulin; MW 11,800), there may be little gain from a Qd >1.5 L/h[34]

Hemoperfusion

- Limit Qb to ~100 to 250 mL/min (see section on hemoperfusion)
- Change cartridge every 3 to 4 hours
- Consider benefits of charcoal vs. resin cartridges depending on poison[15]

Plasma Exchange

- Aim for two plasma volume exchanges per day
- Modify replacement fluid according to poison (see text for details)

[a] Aiming for conventional effluent flow rates (i.e., 25 mL/kg/h) [36] for support of the patient with acute kidney injury may fail to maximize potential poison clearances.

[b] The chief risk with postdilutional fluid replacement is hemoconcentration. This can be minimized by keeping the filtration fraction (FF) at 50% or less. The minimum Qb to achieve this can be calculated from the formula[35]: Minimum Qb = Quf/(0.5 × [1 − Hematocrit]). Alternatively, the maximum Quf would solve as: Quf = Qb × 05 × (1 − Hematocrit). In addition, transmembrane pressures should be kept <400 mm Hg to help prevent membrane fiber rupture.

[c] For small solutes at Qb 150 mL/min, there appears to be a direct linear relationship between increasing clearances and Qd to flow rates of at least 2.5 L/h.[34] It would therefore seem reasonable to maximize Qd as machine hardware, dialyzer specifications, and practicalities (fluid availability, nursing workload) allow.

CVVH, Continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; MW, molecular weight; Qb, extracorporeal blood flow; Qd, dialysate flow; Quf, ultrafiltration rate.

From Bouchard J, Roberts DM, Roy L, et al. Principles and operational parameters to optimize poison removal with extracorporeal treatments. Semin Dial. 2014;27(4):371–380.

Hypokalemia can be corrected by adjusting the dialysate or replacement fluid composition and by supplementation. Hypophosphatemia can be addressed with standard supplements. At least for intermittent

HD, the risk of developing metabolic alkalosis can be attenuated in patients with normal kidney function and baseline serum bicarbonate by using a dialysate bicarbonate concentration at the lower end of the

f0030
Fig. 103.5 Charcoal hemoperfusion cartridge.

Extracorporeal Circuit for Hemoperfusion
Blood flow rate
200-300 mL/min

Heparin
≥2000 U/h

Blood
pump
Doublelumen
venous
catheter

A
V

Heparin
infusion

Charcoal
hemoperfusion
cartridge
Air detector

f0035
Fig. 103.6 Extracorporeal circuit for hemoperfusion.

deliverable range. Because the bicarbonate concentration of premanufactured replacement or dialysate fluid in CKRT cannot be manipulated, intermittent HD against a low bicarbonate dialysate may be preferable if severe metabolic alkalosis is present.

Hemoperfusion

s0060
The technique involves the extracorporeal circulation of blood p0130 through a hemoperfusion cartridge (Fig. 103.5) containing an adsorbent material such as activated charcoal or a resin. Hemoperfusion removes substances that bind to the adsorbent material. It is effective at removing uncharged molecules through competitive binding, especially those that are significantly plasma protein bound and lipophilic, although those toxins exceeding about 5000 to 10,000 Da are less well removed.15 As with other modalities, the decision to start hemoperfusion should be based on its likely proportional contribution to total toxin elimination, as well as the availability of potentially safer techniques such as long-hour, high-flux dialysis (see later).

Other than the cartridge and the lack of dialysate and other replacement p0135 fluid circuits, the disposables and hardware for hemoperfusion are the same as those used for intermittent HD (Fig. 103.6). Blood flow should be limited to approximately 100 to 250 mL/min to minimize the risk of hemolysis during passage through the cartridge.16

Standard anticoagulation protocols may be insufficient for hemoperfusion p0140 because heparin is also adsorbed. A larger initial bolus and maintenance dose of unfractionated heparin is usually required (e.g., ≥2000 U/h), with adjustments guided by regular monitoring of clotting times during the procedure. The manufacturer’s instructions should be reviewed carefully because some cartridges require priming with dextrose solution to prevent hypoglycemia. Other complications

p0145

p0150

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p0160

include hypocalcemia, hypophosphatemia, charcoal embolization, leukopenia, thrombocytopenia (usually uncomplicated and selflimiting), pyrogenic reactions, and adsorption of coagulation factors.15

The charcoal sorbent particles may be coated with a polymer or other substance to increase biocompatibility and reduce the risk of embolization. Pretreatment of cartridges with albumin, plasma, or heparin to improve biocompatibility and reduce removal of endogenous molecules is of uncertain benefit.15

Saturation of the adsorbent material limits the duration of treatment with any individual hemoperfusion cartridge. It is usually recommended that cartridges are changed approximately every 3 to 4 hours, but treatments of this length are usually adequate for a significant lowering of toxin blood levels.15

If a toxin is equally removed by intermittent HD and hemoperfusion, intermittent HD should be used preferentially because it is less risky and also allows correction of fluid balance, electrolyte status, and other metabolic abnormalities.

Decreasing familiarity with hemoperfusion and increasing scarcity of the requisite cartridges, coupled with the ready availability of alternative treatment (long-hour, high-flux kidney support), will likely continue to reduce its application, although the modality remains a more used option in China, India, and elsewhere.15

s0065 Other Modalities

p0165 Hybrid modalities, such as sustained low-efficiency dialysis, have theoretical appeal for management of poisoning and overdose but require further evaluation.

p0170

There are a few reports of the use of plasma exchange and the molecular adsorbent recirculating system in poisoning. In principle, both should be useful for toxins that are strongly protein bound but not lipid soluble, are tissue bound, or have a large VD outside the blood compartment.17 Plasma exchange is most commonly used in Amanita phalloides poisoning but may also prevent limb loss in snake envenomation and reduce toxic levels of biologic therapeutic agents (e.g., monoclonal antibodies).17 Plasma exchange can clear the red cell fragments and free hemoglobin that result from poisoning with sodium chlorate or other agents that can cause hemolysis. The replacement fluid used in plasma exchange warrants some consideration because the plasma free fraction of toxins that are highly albumin bound may rebound after treatment if insufficient albumin is administered.17 Some toxins have a greater affinity for other plasma proteins such as α1-acid glycoprotein than for albumin (e.g., dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine), arguing for the use of plasma-based rather than albumin-based replacement in these situations.17 Plasma replacement may be preferable where there is a significant coagulopathy, such as in certain instances of snake envenomation.17 One to two plasma volume exchanges per day is likely to be sufficient until toxic manifestations and tissue release have subsided.17

p0175

Exchange transfusion may be useful in neonates and small children who have been poisoned with toxins that have a low volume of distribution (e.g., theophylline, salicylates).11

s0070

EXTRACORPOREAL THERAPY FOR SPECIFIC DRUGS AND POISONS

s0075 Alcohols

p0180 Ethylene glycol (MW 62 Da) and methanol (MW 32 Da) can be found in antifreeze, deicing solutions, and windshield cleaning fluid. The ingestion of as little as 1 g/kg body weight of either methanol or ethylene glycol is potentially lethal. Toxicity results from the metabolism of ethylene glycol and methanol by alcohol dehydrogenase to glycolic acid and formic acid, respectively, and may result in optic nerve damage, seizures, coma, and ultimately death. Poisoning should be suspected in any patient presenting with nausea, vomiting, abdominal pain, impaired consciousness, severe metabolic acidosis, and acute kidney injury (AKI).

Early recognition of ethylene glycol or methanol poisoning may allow treatment with ethanol or fomepizole to inhibit hepatic alcohol dehydrogenase. Fomepizole has now replaced ethanol as first-line therapy because the former has more predictable pharmacokinetics than ethanol, has a safer side effect profile, shortens ICU and hospital stays, and decreases need for HD, at least in patients poisoned with ethylene glycol.18,19

Clinicians often have to make treatment decisions based on clinical suspicion and without serum drug levels. Fomepizole should be prescribed if there is a clear history of ethylene glycol and/or methanol ingestion, if the osmol gap is greater than 10 mOsm/kg, or the ethylene glycol/methanol blood level is greater than 20 mg/dL (3.2 mmol/L for ethylene glycol and 6.2 mmol/L for methanol). Fomepizole is administered as a loading dose of 15 mg/kg intravenously (IV). This is followed by 10 mg/kg every 12 hours for 4 doses and then 15 mg/kg every 12 hours until the pH is normal and the serum concentration of ethylene glycol and methanol is less than 20 mg/dL (or <10 mg/dL in the presence of end organ damage). Patients who have ingested methanol also should receive folinic acid 50 mg IV every 6 hours to enhance the metabolism of formic acid. Administration of thiamine 100 mg IV or pyridoxine 50 mg IV should be considered in patients with poor nutritional status after ethylene glycol ingestion.

If fomepizole is not available, ethanol can be used. It is a competitive inhibitor of antidiuretic hormone (ADH), as ADH has greater affinity for ethanol than for methanol or ethylene glycol. Ethanol 10% can be administered as a loading dose of 10 mL/kg over 60 minutes to avoid side effects, such as hypotension, respiratory depression, and excessive somnolence. A maintenance infusion should be started at 1 mL/kg/h, aiming to maintain an ethanol concentration of around 100 mg/dL, but an ethanol concentration as low as 20 mg/dL can effectively inhibit the metabolism of methanol or ethylene glycol. Ethanol should be administered until no ethylene glycol or methanol is detectable in the blood. Intravenous sodium bicarbonate should be considered to help correct any associated metabolic acidosis.

HD is considered for treatment of alcohol poisonings to expedite removal of the alcohol and its metabolites. Ethylene glycol and methanol have low MWs, limited protein binding, single-compartment kinetics, and a limited volume of distribution and thus are efficiently cleared by dialysis. Immediate HD is recommended in the presence of severe metabolic acidosis (pH 7.15) regardless of drug level, or if serum concentration is greater than 50 mg/dL (8.1 mmol/L for ethylene glycol and 15.6 mmol/L for methanol) with pH less than 7.3. If no levels are available, HD can also be indicated in the setting of coma seizures or the presence of end organ damage such as AKI or visual disturbance. Because fomepizole is removed by HD, a maintenance infusion of 1 to 1.5 mg/kg/h should be prescribed for the duration of the HD session after administration of the loading dose. Similarly, ethanol doses should be doubled during the dialysis session.

To achieve optimal clearance, the dialyzer should have a large surface area (>1.5 m2) and the blood flow rate should be greater than 300 mL/min. Bicarbonate buffer should be used, and serum concentrations of ethylene glycol and methanol should be measured 2 hours after the treatment to take account of rebound. HD should continue until the pH has normalized and the concentration of ethylene glycol or methanol is less than 25 mg/dL (<4.0 mmol/L for ethylene glycol and <7.8 mmol/L for methanol). Based on their half-life, it is recommended to start with 8 hours for intermittent HD or 18 hours for continuous modalities if there is no knowledge of the starting concentration or

p0185

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p0200

p0205

rate of removal of methanol or ethylene glycol. Regardless, acid-base status should be monitored after HD to detect recurrence of poisoning, which may prompt the reinitiation of HD. Patients who have ingested large quantities of ethylene glycol and methanol may require further HD treatment.

p0210

The EXTRIP workgroup recommends intermittent HD as the modality of choice; continuous modalities are acceptable if intermittent HD is not available, although they are not as effective at removing methanol.20

s0080 β-Blockers

p0215 β-Blocker overdose will manifest with bradycardia and hypotension and may also include altered mental state, seizures, bronchospasm, hypoglycemia, and cardiogenic shock. Extracorporeal removal is rarely required unless patients have not improved despite maximal medical therapy. β-Blockers have different physicochemical properties and pharmacokinetics that will affect their removal by ERCT. Specifically, ERCT is only effective for hydrophilic, minimally protein-bound drugs such as atenolol, sotalol, nadolol, and acebutolol. Propranolol, carvedilol, labetalol, timolol, and metoprolol are not or minimally removed. Recently, the EXTRIP workgroup recommended against using ERCT for patients severely poisoned with propranolol and offered no recommendation for ERCT in patients severely poisoned with atenolol or sotalol because of apparent balance of risks and benefits, except for impaired kidney function in which ERCT was suggested. Indications for ERCT in patients with impaired kidney function include refractory bradycardia and hypotension for atenolol or sotalol poisoning, and recurrent torsades de pointes for sotalol.20 Intermittent HD is recommended in hemodynamically stable patients. CKRT may be considered in patients who are hemodynamically unstable.

s0085 Lithium

p0220 Severe lithium poisoning may manifest with arrhythmias, hypotension, confusion, coma, or seizures. Lithium is a small (MW 7 Da) monovalent cation with properties similar to those of sodium. It is administered as either lithium citrate (liquid formulation) or lithium carbonate (solid formulation) and almost completely absorbed, with peak concentrations occurring in 30 minutes to 2 hours with immediate release capsules or 4 to 5 hours with modified-release preparations.

p0225

Mild lithium toxicity can be present with levels between 1.5 and 2.5 mEq/L and moderate toxicity when greater than 2.5 mEq/L and severe toxicity when greater than 3.5 mEq/L.21 However, clinical manifestations are both variable and dependent on the specific pattern of poisoning.22 The delayed symptoms in patients with acute lithium poisoning are due to the slow diffusion of lithium to the brain; thus lithium concentrations are only rough correlates of the potential risk of toxicity and should be interpreted based on history, clinical findings, and kidney function.

p0230

In patient with preserved kidney function, intravenous hydration should be provided with isotonic saline at a rate depending on the patient’s fluid status and cardiac function. In patients with lithiuminduced nephrogenic diabetes insipidus, sodium levels need to be closely monitored during intravenous hydration to prevent hypernatremia and potentially deteriorating neurologic symptoms. Hemodialysis is recommended if the serum lithium concentration is greater than 4 mmol/L, or greater than 2.5 mmol/L in a patient with central nervous system (CNS) manifestations of toxicity, such as altered mental status and seizures.12 The protein binding of lithium is negligible, and it is easily removed by HD. High-efficiency HD can achieve a lithium clearance of 180 mL/min—superior to that achieved by native kidney function, which is limited by significant proximal tubular reabsorption. However, impairment of kidney function is often present in lithium toxicity due to lithium's chronic nephrotoxic effects. Lithium equilibrates relatively slowly between the extracellular and intracellular compartments; thus postdialysis rebound may be significant,21 and extended or frequent HD treatment may be needed to minimize its effect. Postdialysis lithium rebound occurs can be pronounced after high-efficiency techniques, reaching 0.5 to 1.0 mEq/L after 6 to 12 hours. Rebound from ongoing absorption can occur in poisonings from extended-release formulations or patients with decreased gastrointestinal motility and may be associated with recurrence of symptoms or clinical deterioration. Serum lithium levels should be checked at 6 hours after dialysis to guide further therapy, and, if the level remains below 1 mEq/L, a second treatment may not be necessary. CKRT may complement intermittent HD by helping mitigate the effect of the postdialysis rebound.

Metformin

s0090

Metformin (MW 166 Da) is the most commonly prescribed oral anti- p0235 diabetic drug. It inhibits gluconeogenesis, facilitates cellular glucose uptake by muscle and adipose cells, and decreases insulin resistance in patients with type 2 diabetes. Metformin toxicity is associated with mortality of 30%, and its management can be challenging. A recent literature review noted that metformin poisoning was the most common toxicologic indication for ERCT.23 Symptoms include tachypnea, nausea, abdominal pain, tachycardia, hypotension, and, in the setting of AKI, severe lactic acidosis. Metformin has negligible plasma protein binding and a volume of distribution ranging from 63 to 276 L (1–5 L/kg), but the limiting factor for its extracorporeal elimination is the relatively large volume of distribution. Metformin is excreted, unmetabolized, via transporters in the proximal tubules of the kidneys and may accumulate in acute and chronic kidney disease.24 Metforminassociated lactic acidosis (MALA) occurs due to inhibition of hepatic gluconeogenesis from lactate and enhanced conversion of glucose to lactate in the small intestine. The mortality from MALA is high, and treatment options are limited. Medical management involves supportive measures and the intravenous administration of sodium bicarbonate. ERCT is recommended in patients who are unresponsive to medical management.22 As metformin is almost exclusively eliminated by the kidneys, the presence of impaired kidney function will increase the likelihood of severe and more prolonged toxicity. Liver failure can impair lactate clearance, and its presence should also lower the threshold for dialysis support. Extracorporeal removal can be beneficial in metformin toxicity by not only removing the drug but also by delivering a more rapid, predictable, and safe correction of acidemia than can be achieved with bicarbonate therapy, and correction of electrolyte abnormalities and supportive therapy if kidney function is impaired. Both intermittent HD and CKRT can provide effective extracorporeal removal, but a rebound after extracorporeal removal can result in a marked resurgence of lactic acidosis after therapy is discontinued. Close monitoring of the acid-base status is recommended, and extended duration or repeat session may be needed if severe metabolic acidosis (pH ≤7.0) is persistent or serum lactate concentration is greater than 20 mmol/L.

Salicylates

s0095

Aspirin remains a commonly used analgesic and widely prescribed p0240 antiplatelet therapy; despite improvements in supportive care, poisoning by salicylates (MW 180 Da) remains an important cause of poisoning-related mortality.

p0245 Aspirin is rapidly absorbed in the stomach, with peak blood concentrations usually reached within 1 hour. At therapeutic levels, 90% of salicylate is protein bound and therefore limited to the vascular space, being metabolized in the liver to salicyluric acid, which is less toxic and more rapidly excreted by the kidney. The clinical manifestations of salicylate overdose include fever, sweating, tinnitus, epigastric pain, nausea, vomiting, diarrhea, vertigo, and blurring of vision. Severe overdoses may progress to depression of mental state, noncardiogenic pulmonary edema, and death. Salicylate intoxication initially results in hyperventilation and respiratory alkalosis. This is followed by metabolic acidosis secondary to the accumulation of lactic acid and ketoacids. Therefore, patients may present with either respiratory alkalosis or mixed respiratory alkalosis–metabolic acidosis. Diagnosis is based on the presenting history and clinical examination and confirmed with plasma salicylate levels.

p0250

Increased salicylate tissue penetration and toxicity can occur with only small decreases in pH because of increased concentration of nonionized salicylate. Intravenous sodium bicarbonate should be given to decrease tissue penetration and facilitate the excretion of salicylate through the kidneys unless the patient has oliguric AKI, pulmonary edema, or cerebral edema.

p0255

Despite being highly protein bound, saturation of protein binding in significant poisoning and its limited volume of distribution makes it amenable to removal by dialysis. ERCT is recommended in patients with severe salicylate poisoning reflected by altered mental state, acute respiratory distress syndrome, and failure to respond to medical management irrespective of salicylate levels. ERCT is also indicated, regardless of signs and symptoms, at levels greater than 100 mg/dL (>7.2 mmol/L). Lower thresholds are applied for patients with AKI. Intermittent HD has advantages compared with hemoperfusion because the former allows rapid correction of associated electrolyte abnormalities and acidemia. CKRT provides lower salicylate clearance than HD and should be implemented only if intermittent modalities are not available.23

s0100 Theophylline

p0260 β2 agonists have gradually replaced theophylline in the treatment of lung disease over the past 20 years. Still, new therapeutic uses are emerging, and it remains a potential toxin. Methylxanthine (MW 180 Da) overdose manifests with nausea, vomiting, diarrhea, gastrointestinal hemorrhage, hypokalemia, seizures, arrhythmias, and hypotension. Overdose may be acute or chronic. Theophylline is readily cleared by either HD or hemoperfusion because of its low volume of distribution and minimal protein binding. ERCT is recommended for severe acute theophylline poisoning (theophylline level > 100 mg/L [>555 µmol/L], or the presence of seizures, life-threatening arrhythmias, shock, or failure of standard therapy). In chronic poisoning, extracorporeal removal is suggested if theophylline levels are greater than 60 mg/L (>333 µmol/L) or greater than 50 mg/L (>278 µmol/L) in a patient older than 60 years. Maximal theophylline clearance can be achieved with charcoal hemoperfusion. However, with the advent of new highefficiency filters and higher achievable blood flow rates, the clearances achievable with HD now rival those with hemoperfusion and are associated with fewer side effects. Continuous venovenous HF can be used but requires a longer treatment duration than with hemoperfusion.24

s0105 Valproate Acid

p0265 Valproate acid (VPA) is commonly used to treat epilepsy and bipolar disorder and to prevent migraine. VPA has a low molecular weight (144 Da), has a small volume of distribution (0.1–0.5 L/kg) and saturable plasma protein binding. At therapeutic concentrations, VPA is 94% protein bound, but it decreases to as low as 15% as concentrations rise to more than 1000 mg/dL, leading to greater clinical toxicity. Overdose may manifest with mild confusion, lethargy, nausea, vomiting, tachycardia, hypotension, metabolic acidosis, and electrolyte disturbances (hyponatremia and hypocalcemia). VPA concentrations can be helpful in determining the severity of intoxication; mild if less than 400 mg/L, moderate if between 450 and 850 mg/L, and severe if more than 850 mg/L. In addition to electrolyte abnormalities (hypernatremia, hypocalcemia), evidence of impaired mitochondrial function can be present, including metabolic acidosis, hyperlactatemia, and hyperammonemia.

ERCT is recommended for severe overdose (VPA level >1300 mg/L p0270 [>9000 µmol/L], cerebral edema, or shock). ERCT can be considered for VPA concentrations greater than 900 mg/L (>6250 µmol/L), coma or respiratory depression requiring ventilation, acute hyperammonemia, or pH less than 7.1. HD is preferred to hemoperfusion because it clears the unbound drug and also reverses associated metabolic abnormalities.25

Tricyclic Antidepressant Drugs

s0110

ERCT is not likely to have any clinical benefit for patients who have p0275 experienced an overdose with TCA drugs.26

Thallium

s0115

Thallium salts were once used in the treatment of ringworm. Poisoning p0280 continues to be reported where it is used as a rodenticide and a contaminant of herbal and illicit drug products.27 It is absorbed extensively through almost all routes of exposure and is widely distributed across multiple body compartments. Thallium is a small molecule (MW 204 Da) and does not bind to protein, but the efficacy of extracorporeal removal is limited by its large volume of distribution.

Toxicity is caused by thallium replacing potassium as a stimulator p0285 or inhibitor of a variety of intracellular electrochemical and enzymatic processes. ECTR removes around 3% of total body stores over 6 hours, with hemoperfusion seeming to be the most efficient modality. PD and plasmapheresis do not appear to deliver significance clearances. Based on a recent literature review, the EXTRIP workgroup strongly recommended extracorporeal removal for treatment of thallium poisoning, given the absence of alternative treatments.27 Intermittent HD is preferable, but hemoperfusion and CKRT are valid alternatives.

Barbiturates

s0120

The use of barbiturates in clinical practice has largely been replaced by p0290 benzodiazepines because of the lower risk from overdose and an available antidote to reverse toxicity. Nonetheless, barbiturate overdose is still a significant cause of fatal poisoning, especially phenobarbital, which is still used clinically and in veterinary practice.

Barbiturates mainly act on the CNS, and symptoms of a moderate p0295 overdose typically include sluggishness, lack of coordination, slow speech, faulty judgment, and drowsiness. Shallow respiration and coma occur in severe poisoning. It is recommended that ERCT be restricted to cases of severe, long-acting barbiturate poisoning with clinical features including prolonged coma, respiratory depression requiring ventilation, shock, and a failure to treat effectively with multiple-dose activated charcoal. ERCT improves barbiturate elimination and will be most beneficial if it is initiated early, ideally within 24 hours of exposure. Intermittent HD is the preferred modality: it is equivalent to hemoperfusion and superior to CVVH, which is in turn superior to PD.28

Acetaminophen/Paracetamol

s0125

Acute ingestions of acetaminophen (MW 46 Da) can still be lethal p0300
even when patients are treated early, within 8 hours of ingestion, and
despite the availability of the antidote, N-acetylcysteine (NAC). In
massive ingestions (>500 mg/kg), patients can present with an altered
level of consciousness and metabolic acidosis with elevated lactate
concentrations. Acetaminophen concentrations should be checked after
4 hours after ingestion or earlier in the case of massive ingestions.

p0305

There is a paucity of high-quality evidence for extracorporeal removal of acetaminophen, although it may have a role in the rare cases when N-acetylcysteine has not been effective. Patients with severe poisoning can also develop AKI even without liver dysfunction as a result of local production of the toxic by-product, N-acetylp-benzoquinone imine, by kidney prostaglandin synthetases. Thus, patients with acetaminophen-associated AKI may develop indications for ERCT other than acute toxin removal. Intermittent HD is the preferred modality.29

s0130 Carbamazepine

p0310 Carbamazepine is currently used to treat bipolar disorder, neuropathic pain, hyperactivity, and seizure disorder. It has a low molecular weight (236 Da), a structure similar to that of TCAs, and is highly bound to both albumin and α1-acid glycoprotein (70%–80%). It is metabolized in the liver, and only 1% to 3% of the drug is excreted unchanged in the urine. The therapeutic range is 4 to 12 mg/L, with toxicity usually occurring at more than 40 mg/L. Symptoms are mainly neurologic and include movement disorders, altered mental status, and seizures. Respiratory depression and cardiovascular symptoms can occur in severe overdose.

p0315

As the drug is moderately well dialyzed, extracorporeal removal is suggested in severe carbamazepine poisoning (as evidenced by coma,

respiratory depression requiring ventilation, or carbamazepine levels that do not respond to standard therapy with activated charcoal). Intermittent HD is the favored modality. If HD is not available, hemoperfusion or CKRT can be considered.30

Phenytoin

s0135

Phenytoin (MW 252 Da) has a large volume of distribution and is p0320 extensively protein bound (90%) but dissociates easily and is amenable to extracorporeal removal. However, phenytoin poisoning rarely causes permanent organ damage or death, so extracorporeal removal is recommended only in very severe poisoning that has been resistant to standard therapy.31 Enteral absorption of phenytoin is slow and unpredictable, so vigilance should be maintained for the delayed effects of poisoning. Extracorporeal removal should be reserved for patients with severe poisoning or prolonged coma, aiming to reduce morbidity and resource use rather than decrease mortality.

Digoxin

s0140

Digoxin (MW 781 Da) has variable absorption from the gut depend- p0325 ing on the size of the ingestion. Although it is 20% to 30% protein bound, it also has a large volume of distribution and an effective antidote (digoxin immune Fab), so extracorporeal removal is not useful for managing overdose.32

SELF-ASSESSMENT QUESTIONS

o0010 1. Which one of the following statements is true regarding ethylene glycol toxicity?

o0015

A. Ethylene glycol is metabolized to glycolic acid.

o0020

B. Ethylene glycol is metabolized to formic acid.
o0025
C. Ethylene glycol is metabolized by alcohol hydrogenase.
o0030
D. Urinalysis demonstrates uric acid crystals.
o0035
E. Ethylene glycol toxicity is associated with a normal anion gap.
o0040 2. Which one of the following is not associated with a raised osmolar gap?
o0045
A. Ethylene glycol intoxication
o0050
B. Methanol intoxication
o0055
C. Isopropanol intoxication
o0060
D. Diabetic ketoacidosis
o0065
E. Acute kidney injury
o0070 3. Intermittent HD is not effective for removal of which of the following in overdose?
A. Lithium
o0075

B. Ethylene glycol
C. Metoprolol
D. Carvedilol
E. Methanol
4. Which one of the following statements is true?
A. Hemoperfusion remains the first-choice treatment for removal of theophyllines.
B. If endogenous clearance rates of toxins are less than 10 mL/min/kg body weight, ERCT should be considered.
C. Highly protein-bound toxins are not suitable for ERCT.
D. When continuous venovenous hemofiltration is used solely for poison removal, conventional doses for patients with AKI should be used.
E. Toxin rebound after intermittent HD may be mitigated by frequent scheduling of treatment or adjunctive therapy with one of the continuous renal replacement therapies.

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REFERENCES

1. Gordon L, Jackson G, Eddleston M. Service NPI. National Poisons Information Service Report 2014/15. London: Public Health England; 2015.
2. Mowry JB, Spyker DA, Brooks DE, et al. 2014 annual report of the American association of poison control centers’ national poison data system (NPDS): 32nd annual report. Clin Toxicol. 2015;53(10):962–1147.
3. Bradberry S, Vale A. Epidemiology and clinical presentation. Clin Med. 2008;8(1):86–88. quiz 104–105.
4. Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ. 2013;346:f403.
5. Ghannoum M, Nolin TD, Lavergne V, et al. Blood purification in toxicology: nephrology’s ugly duckling. Adv Chronic Kidney Dis. 2011;18(3):160–166.
6. EXTRIP. Blood Purification in Toxicology: Reviewing the Evidence and Providing Recommendations. http://www.extrip-workgroup.org/.
7. Ghannoum M, Lavergne V, Gosselin S, et al. Practice trends in the use of extracorporeal treatments for poisoning in four countries. Semin Dial. 2016;29(1):71–80.
8. Kanagasundaram NS. Renal replacement therapy in acute kidney injury: an overview. Br J Hosp Med. 2007;68(6):292–297.
9. Luo Y, Kanagasundaram NS. Microbial control in renal support for acute kidney injury. Semin Dial. 2011;24(2):203–207.
10. Hampson EC, Pond SM. Failure of haemoperfusion and haemodialysis to prevent death in paraquat poisoning. A retrospective review of 42 patients. Med Toxicol Adverse Drug Exp. 1988;3(1):64–71.
11. Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. Semin Dial. 2014;27(4):362–370.
12. Decker BS, Goldfarb DS, Dargan PI, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2015;10(5):875–887.
13. Maher JF, Schreiner GE. The dialysis of poisons and drugs. Trans Am Soc Artif Intern Organs. 1968;14:440–453.
14. Fertel BS, Nelson LS, Goldfarb DS. Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. J Intensive Care Med. 2010;25(3):139–148.
15. Ghannoum M, Bouchard J, Nolin TD, et al. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. Semin Dial. 2014;27(4):350–361.
16. Rahman MH, Haqqie SS, McGoldrick MD. Acute hemolysis with acute renal failure in a patient with valproic acid poisoning treated with charcoal hemoperfusion. Hemodial Int. 2006;10(3):256–259.
17. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25(3):83–177.
18. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for toxic alcohols Study group. N Engl J Med. 1999;340(11):832–838.
19. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of methanol poisoning. N Engl J Med. 2001;344(6):424–429.

20. Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43(2):461–472.
21. Clendeninn NJ, Pond SM, Kaysen G, et al. Potential pitfalls in the evaluation of the usefulness of hemodialysis for the removal of lithium. J Toxicol Clin Toxicol. 1982;19(4):341–352.
22. Calello DP, Liu KD, Wiegand TJ, et al. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from

the extracorporeal treatments in poisoning workgroup. Crit Care Med. 2015;43(8):1716–1730.
23. Juurlink DN, Gosselin S, Kielstein JT, et al. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP Workgroup. Ann Emerg Med. 2015;66(2):165–181.
24. Ghannoum M, Wiegand TJ, Liu KD, et al. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2015;53(4):215–229.
25. Ghannoum M, Laliberte M, Nolin TD, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2015;53(5):454–465.
26. Yates C, Galvao T, Sowinski KM, et al. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. Semin Dial. 2014;27(4):381–389.
27. Ghannoum M, Nolin TD, Goldfarb DS, et al. Extracorporeal treatment for thallium poisoning: recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2012;7(10):1682–1690.
28. Mactier R, Laliberte M, Mardini J, et al. Extracorporeal treatment for barbiturate poisoning: recommendations from the EXTRIP Workgroup. Am J Kidney Dis. 2014;64(3):347–358.
29. Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. Clin Toxicol. 2014;52(8):856–867.
30. Ghannoum M, Yates C, Galvao TF, et al. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2014;52(10):993–1004.
31. Anseeuw K, Mowry JB, Burdmann EA, et al. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP (extracorporeal treatments in poisoning) workgroup. Am J Kidney Dis. 2016;67(2):187–197.
32. Mowry JB, Burdmann EA, Anseeuw K, et al. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup. Clin Toxicol. 2016;54(2):103–114.
33. Bouchard J, Roberts DM, Roy L, et al. Principles and operational parameters to optimize poison removal with extracorporeal treatments. Semin Dial. 2014;27(4):371–380.
34. Brunet S, Leblanc M, Geadah D, et al. Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. Am J Kidney Dis. 1999;34(3):486–492.
35. Kanagasundaram NS. Complications of Maintenance Haemodialysis and How to Avoid Them. In: Harber M, ed. Practical Nephrology. Springer London; 2014:685–703.
36. Kanagasundaram S, Ashley C, Bhojani, et al. UK Kidney Association Clinical Practice Guideline for Acute Kidney Injury (AKI); 2019.

104

Plasma Exchange

Jeremy Levy

p0010 Over the past 10 years, it has become clearer how best to use plasma exchange (plasmapheresis) in the management of kidney disease, but the quality of published data remains relatively poor, with less than 1% of relevant literature in the form of randomized controlled trials (RCTs). Plasma exchange came into widespread clinical use after early reports of beneficial effects in Goodpasture disease in the mid-1970s. It is used to remove many large-molecular-weight substances from plasma, including pathogenic antibodies, cryoglobulins, and lipoproteins. Newer techniques allow more selective removal of plasma components, such as double-filtration plasma exchange, cryofiltration, and immunoadsorption with or without immobilized ligands. The most common kidney indications are thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS), kidney transplantation (antibody-mediated rejection and for desensitization either for antiABO blood group antibodies or anti–human leukocyte antigen [HLA] antibodies), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, cryoglobulinemia, recurrent focal segmental glomerulosclerosis (FSGS), and anti–glomerular basement membrane (anti-GBM) antibody disease.

s0010

TECHNIQUES

p0015 Plasma exchange can be carried out either by centrifugal cell separators or (more commonly in dialysis units) with hollow-fiber plasma filters (membrane filtration) and standard hemodialysis (HD) equipment (Figs. 104.1 and 104.2). Centrifugal devices allow withdrawal of plasma from a bowl with either synchronous or intermittent return of blood cells to the patient.1 There is no upper limit to the molecular weight of proteins removed by this method. The bowls and circuits are single use and disposable and require relatively low blood flow rates (50–150 mL/min and can be as low as 5 mL/min for children) that can be delivered through large-bore peripheral cannulae. Platelets can be inadvertently removed by centrifugal devices, although this risk has reduced significantly with newer technologic approaches. Membrane plasma filtration uses highly permeable hollow fibers with membrane pores of 0.2 to 0.5 µm. Plasma readily passes through the membrane and the cells are simultaneously returned to the patient. All immunoglobulins will cross the membrane (immunoglobulin G [IgG] slightly more efficiently than immunoglobulin M [IgM]), and molecules up to 3 million Da are cleared. Hemolysis can occur if transmembrane pressures are too high (a rare complication). The blood flow rates required for membrane plasma filtration are higher than for centrifugal cell separators (100–300 mL/min) and require central venous access or a fistula. Membrane exchange takes slightly longer than centrifugal techniques for the same plasma volume removal. It has been suggested that the adsorptive properties of the membrane for cytokines and other biomolecules may account for some of the beneficial effects of plasma filtration. There have been occasional reports of mild adverse reactions

in patients taking angiotensin-converting enzyme inhibitors when plasma is filtered with ethylene vinyl alcohol or acrylic copolymer membranes. Reuse of plasma filters is not advised because of potential risks resulting from loss of filtration capacity and to staff from cleaning procedures, but performance data do not indicate a major loss of function during routine plasma exchange. For patients with severe kidney failure, sequential HD and plasma exchange can easily be performed with plasma filtration.

Vascular access is usually achieved using standard central venous p0020 catheters, but existing arteriovenous fistulas (AVFs) can be used if available. Sometimes plasma exchange can be done using large-bore, short intravenous (IV) cannulas placed in the antecubital fossa, especially with centrifugal devices. Single-needle access using an AVF is also relatively easy to accommodate, especially for centrifugal plasma exchange, in which the blood removal and return can be asynchronous, but also for membrane filtration. Anticoagulation must be carefully managed in patients at higher bleeding risk (e.g., thrombotic microangiopathy [TMA], recent or ongoing pulmonary hemorrhage, or a recent kidney biopsy). Citrate is used for anticoagulation with centrifugal plasma exchange and heparin for membrane plasma filtration; however, citrate is superior for patients at higher bleeding risk in view of its lack of systemic anticoagulation.1 When heparin is used, higher doses may be needed than in HD because of increased losses during the procedure (heparin is protein bound). Bolus doses of unfractionated heparin of 2000 to 5000 U are given initially and then 500 to 2000 U/h. Anticoagulant is administered prefilter. Increasingly low-molecularweight heparin (LMWH) is also used with a single bolus dose at initiation of exchange.

p0025 Both methods of plasma exchange require large volumes of colloid replacement. A single plasma volume exchange will lower plasma macromolecule levels by approximately 60%, and five exchanges over 5 to 10 days will clear 90% of the total body immunoglobulin (Fig. 104.3).1,2 For most patients, this is achieved by removing 50 mL of plasma per kilogram body weight at each procedure (~4 L for a 75-kg person). Daily plasma exchange more rapidly depletes total body load of immunoglobulins, but there is no good evidence that intensity of exchanges has a major effect on outcomes except in patients with HUS with poor prognostic markers (see later discussion). Indeed, alternate-day exchanges are of proven efficacy in ANCA-associated diseases. Replacement solely with crystalloid is contraindicated because of the need to maintain colloid oncotic pressure. Synthetic gelatin–based plasma expanders or hydroxyethyl starch (Hespan) can be used as part of a replacement regimen but have been reported to cause a coagulopathy in patients with sepsis and have a shorter half-life than human albumin, which is the main replacement fluid. The major disadvantage of albumin solutions is the lack of clotting factors, with the potential development of depletion coagulopathy after plasma exchange. Fresh-frozen plasma (FFP)

Hollow-Fiber Membrane Plasma Filtration

Centrifugal Cell Separation
Red cells for
return to patient

Colloid
replacement

Anticoagulant

Anticoagulant
Pump

Pump

Blood
Arterial

Arterial

Pump

Plasma

Hollow-fiber
plasma filter

Heater

Plasma

Plasma

Pump

Colloid
replacement

Cells
Venous
Plasma
collection

To
patient

A

To
patient

Venous

Heater

Pump

Plasma
collection

B

Protein A Immunoadsorption
Anticoagulant

Blood

Glycine
HCl

Pump

Arterial
Hollow-fiber
plasma filter

Pump

Pump

Plasma

Protein A
columns

To
patient

f0010

Venous

Heater

C

Pump
Eluted IgG

Fig. 104.1 Plasma Exchange and Immunoadsorption Techniques. Techniques include centrifugal cell separation (A), hollow-fiber membrane plasma filtration (B), and protein A immunoadsorption (C). IgG, Immunoglobulin G.

should be given, usually in addition to human albumin solution, in patients at particular risk for bleeding. If partial replacement is with FFP, this should be given late during the exchange so the constituents are not removed by the ongoing plasma exchange. However, almost all the serious complications of plasma exchange (hypotension, anaphylaxis, citrate-induced paresthesia, urticaria) have been reported in patients receiving FFP rather than albumin (see later discussion).1 3 Both human products carry a tiny risk for transmission of infectious diseases, especially viral. Standard regimens for plasma exchange are summarized in Table 104.1. Human albumin solution (4%–5%) should be used for all exchanges except in TMAs (in which plasma should provide the total exchange), and FFP should form part of the exchange when bleeding risk is high (ongoing pulmonary hemorrhage or within 48 hours of biopsy or surgery). If fibrinogen levels decrease to less than 1.25 to 1.5 g/L or prothrombin time (PT) is

increased 2 to 3 seconds above normal, FFP should be administered (Table 104.2).

Double-filtration plasma exchange (or cascade filtration) uses p0030 membrane filtration to separate cells from plasma and then a secondary plasma filtration (pore size 0.01–0.03 µm) to remove plasma solutes based on molecular size. Most albumin is therefore returned to the patient, together with lower molecular weight proteins, reducing the need for replacement fluids. Cryofiltration uses a similar principle but exposes the filtrate to 4°C during the procedure, with the aim of precipitating cryoproteins. These techniques are not widely available.

Selective and specific immunoadsorption techniques are available p0035 but rarely used. Protein A immunoadsorption has been used to remove immunoglobulin alone from plasma, without the need for replacement fluids and without depletion of clotting factors and complement (see Fig. 104.1C). Protein A selectively binds the Fc domains of efficacy has been equal to that of plasma exchange, although if used over the long term, immunoadsorption is much more cost-effective in single patients because replacement of albumin or plasma is not required. Specific ligands also have been immobilized onto columns for more specific removal of potentially pathogenic serum factors; ligands used include anti–human IgG, C1q, phenylalanine, hydrophobic amino acids, acetylcholine receptor, β-adrenoreceptor peptides, and blood group–related oligosaccharides. Immunoadsorption is not widely available because the initial column costs are high and few centers have much clinical experience. Costs of all other plasma exchange modalities are dominated by the costs of replacement albumin and plasma; equipment costs do not vary much among modalities, and all require skilled and trained nursing staff.

COMPLICATIONS

f0015
Fig. 104.2 A centrifugal cell separator in use for plasma exchange.

Clearance of Plasma Proteins
by Plasma Exchange
1.0
0.85
0.7
Fraction cleared

0.6
0.4
0.3
0.2
0.15
C4
Transferrin

f0020

IgG
IgM

0.11 0.26 0.43 0.57
0.80 0.96 1.11 1.27
Plasma volumes removed
Fig. 104.3 Clearance of Plasma Proteins by Plasma Exchange. Clearance from the intravascular compartment varies with the plasma volume exchanged and among individual proteins. IgG, Immunoglobulin G; IgM, immunoglobulin M. (Modified from Derksen RH, Schuurman HJ, Meyling FH, et al. The efficacy of plasma exchange in the removal of plasma components. J Lab Clin Med. 1984;104:346–354.)

immunoglobulin molecules, and the immunoadsorption columns can be repeatedly regenerated. Columns have been used for 1 year for a single patient on up to 30 occasions; however, the repeated acid stripping during regeneration reduces the efficacy of antibody binding. Selective immunoadsorption has been used to treat conditions in which autoantibodies are thought to be important and usually in place of plasma exchange (e.g., Goodpasture disease, rheumatoid arthritis, lupus, or systemic vasculitis) and to remove anti-ABO or anti–HLA antibodies in highly sensitized transplant recipients. In general, the reported

s0015

The complication rate of plasma exchange is not high.3 The Swedish p0040 registry reported no fatalities during 20,485 procedures and an overall adverse incidence rate of only 4.3% of all exchanges (0.9% for severe adverse events) of which 27% were paresthesias, 19% transient hypotension, 13% urticaria, and 8% nausea.4 The Canadian Apheresis Registry collected data on 144,432 apheresis procedures since 1981 and reported adverse events occurring in 12% of procedures (mostly minor) and overall in 40% of patients. Severe events occurred in only 0.4% of procedures. Three deaths were probably related directly to the procedure: one from a transfusion-related acute lung injury and two from complications from central venous catheters.5 An overall complication rate of 1.4% has been reported in more than 15,000 treatments in patients receiving albumin and 20% in patients receiving FFP.1 3 5 6 Plasma exchange by centrifugation had a lower risk for adverse events than by filtration.

Other complications directly attributable to plasma exchange p0045 include citrate-induced hypocalcemia (presenting with perioral tingling and paresthesias) and citrate-induced metabolic alkalosis. Citrate is usually present in FFP (up to 14% by volume) or is administered in the extracorporeal circuit as an anticoagulant; it binds free calcium in plasma. Symptomatic hypocalcemia can be averted by infusing 10 to 20 mL of 10% calcium gluconate during each plasma exchange. Alkalosis is rare and is caused by metabolism of citrate to bicarbonate and failure to excrete the latter in patients with kidney impairment.

Plasma exchange predictably increases the risk for bleeding by p0050 depleting coagulation factors in patients receiving albumin as sole replacement colloid. PT is increased by 30%, and partial thromboplastin time by 100% after a single plasma volume exchange. Patients at risk for bleeding (pulmonary hemorrhage, postbiopsy, postoperative) should receive FFP (300–600 mL) with replacement fluids.

Dilutional hypokalemia is avoided by replacing potassium according to daily blood testing. An increased incidence of infection secondary to hypogammaglobulinemia has not been confirmed in recent series.3–6 Sepsis related to IV access is the most common infectious complication of plasma exchange. Hypotension can occur for a variety of reasons related to extracorporeal circuits, sepsis, and allergic reactions.

Cascade filtration can lead to hemolysis (in up to 20% patients) but rarely necessitates transfusion.

MECHANISMS OF ACTION

s0020

The pathogenicity of autoantibodies in anti-GBM disease p0055 (Goodpasture disease) provided the impetus for development of plasma exchange therapy, but it is now clear that antibodies, although necessary, are not alone sufficient to cause the necrotizing glomerulonephritis (GN) in that disease. Plasma exchange, however, removes

TABLE 104.1

Practical Regimens for Plasma Exchange in Kidney Disease

Indication

Anti-GBM Disease

Small-Vessel
Vasculitis

Duration of
treatment

Daily, at least 14 days until
anti-GBM antibodies 20%
of baseline

Daily or alternate daily,
7–10 days depending
on clinical response

At least 7–10 days or
until clinical response

Exchange volume

50 mL/kg each treatment

As for anti-GBM disease

As for anti-GBM disease

Daily for at least 10
days initially, then
continuing less
frequently, often for
months
As for anti-GBM disease

Replacement fluid

Human albumin 5% (unless
bleeding risk)
20 mL 10% calcium
gluconate (occasionally
more), 3 mL 15% KCl if not
dialysis dependent, heparin
2000–5000 U bolus, then
500–2000/h (LMWH an
alternative with bolus only)
or citrate anticoagulation
See Chapter 25
FFP 5–8mL/kg at end of
exchange volume if
hemorrhage risk (kidney biopsy
in last 48h, lung hemorrhage,
platelets <40 ×109/L,
fibrinogen < 1.5g/L)

Immunoadsorption may be as effective

As for anti-GBM disease

As for anti-GBM disease

As for anti-GBM disease

As for anti-GBM disease

As for anti-GBM disease

As for anti-GBM disease

As for anti-GBM disease (may need more calcium because of increased volume of FFP-containing citrate)

See Chapter 26
As for anti-GBM disease
Immunoadsorption may be as effective

See Chapter 22
As for anti-GBM disease

See Chapter 30
As for anti-GBM disease; may need to include replacement immunoglobulins if continuing long term
Immunoadsorption may be as effective

See Chapter 30

Additions to replacement fluid

Immunosuppression
Variations

Cryoglobulinemia

Recurrent FSGS After Transplantation
HUS/TTP
Daily for 7–10 days or until platelet count 80–100 ×109/L (sometimes needed twice daily)
As for anti-GBM disease
FFP or cryo-poor FFP

FFP, Fresh-frozen plasma; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HUS, hemolytic-uremic syndrome; LMWH, low-molecular-weight heparin; TTP, thrombotic thrombocytopenic purpura.

t0015

TABLE 104.2

Investigations to Undertake Before Every Plasma Exchange Session

Investigation	Action to Take
Platelet count	Use plasma exchange with caution if platelet count < 40 × 109/L unless disease itself associated with thrombocytopenia (e.g., aHUS/TTP), and use FFP as part of replacement fluid.
Plasma fibrinogen	If <150 mg/dL, should use FFP as part of exchange fluid.
Prothrombin time	If prolonged more than 2–3 seconds, use FFP as part of exchange fluids.
Serum calcium	If <2.1 mmol/L (<8.4 mg/dL), increase amount being provided with replacement albumin/FFP.
Serum potassium	Can be highly variable depending on changing kidney function in addition to plasma exchange treatment; adjust potassium replacement according to serum potassium.

aHUS, Atypical hemolytic-uremic syndrome; FFP, fresh-frozen plasma; TTP, thrombotic thrombocytopenic purpura.

all large-molecular-weight substances from the plasma in addition to antibodies, including complement components, immune complexes, endotoxin, lipoproteins, and von Willebrand factor (vWF) multimers. In animal studies, for example, complement depletion abrogates antiGBM GN very effectively. Therefore, plasma exchange may have benefits in addition to clearance of autoantibodies.

p0060

The clearance of antibodies from patients is variable and depends on several factors, including the rate of equilibration of macromolecules between the intravascular and extravascular compartments. IgM antibodies are cleared more effectively than other classes of immunoglobulin because they are retained in the vascular compartment almost wholly. A rebound increase in antibody production will occur unless there is concomitant immunosuppression to prevent resynthesis.

p0065

Plasma exchange has been shown to remove immune complexes, which may have clinical significance in cryoglobulinemia and systemic

lupus, and fibrinogen and complement components. There is no good evidence that removal of cytokines has any clinical significance. Plasma exchange reduces plasma viscosity, with consequent improved blood flow in the microvasculature. There is also some evidence for improvement in monocyte/macrophage function, alteration in lymphocyte function, and sensitization of antibody-producing cells to immunesuppressive drugs after plasma exchange.

INDICATIONS FOR PLASMA EXCHANGE

s0025

p0070 Evidence to support specific indications for plasma exchange is variable in quality. Direct comparison among RCTs can be unsatisfactory because of variations in dose and frequency of plasma exchange and in immunosuppressive and other adjunctive therapy. The American Society for Apheresis (ASFA) reviewed all indications for plasma exchange most recently updated in 2016 and summarized available trial data.7 8 In this chapter, evidence from available RCTs is discussed alongside observational data. The indications are summarized in Tables 104.3 and 104.4

s0030

Anti–Glomerular Basement Membrane Antibody Disease (Goodpasture Disease)

p0075 Most patients can be depleted of pathogenic anti-GBM antibodies after 7 to 10 plasma volume exchanges if further antibody synthesis is inhibited by the concurrent use of cyclophosphamide and corticosteroids. Before plasmapheresis, the mortality from Goodpasture disease was higher than 90%, and only 11% of patients who were not dialysisdependent at presentation survived with preserved kidney function. The use of plasma exchange improved the outcome considerably: 70% to 90% of patients now survive. However, only 50% of survivors retain independent kidney function and 10% or less of those who are dialysis dependent at presentation. There has been only one small controlled trial of plasma exchange in the treatment of Goodpasture disease, which used a low intensity of plasma exchange.7 9 A total of 17 patients were randomized to receive corticosteroids and cyclophosphamide, with or without plasma exchange. Only 2 of the 8 who received plasma exchange developed end-stage kidney disease (ESKD) compared with 6 of the 9 who received drugs alone.

t0020

p0080 Long-term data from 71 patients with Goodpasture disease confirmed the benefit of a treatment regimen including plasma exchange because most patients with mild to moderate kidney failure retained independent kidney function over 10 to 25 years,10 and kidney recovery was possible even in some of those with the most severe kidney disease. Very similar results were identified in the largest reported series from China. Combining all the available published data for patients with Goodpasture disease, 76% of patients presenting with serum creatinine less than 5.5 to 6.8 mg/dL (500–600 µmol/L) will remain independent of dialysis if treated with plasma exchange, in contrast to only 8% of those who are dialysis dependent at presentation. Diffuse alveolar hemorrhage, which occurs in up to 50% of patients and can be life threatening, is an independent indication for plasma exchange regardless of kidney function.

Recommendation

s0035

p0085 All patients who are not dialysis dependent at presentation should receive intensive plasma exchange with daily 4-L exchanges initially for 14 days (regimen shown in Table 104.2). For dialysis-dependent patients, we recommend plasma exchange with immunosuppression only for those who have biopsy or clinical evidence of recent-onset disease. Pulmonary hemorrhage is an independent indication for plasma exchange. Treatment of Goodpasture disease is discussed further in Chapter 25

Conditions for Which There Is Strong Evidence for the Benefit of Plasma

TABLE 104.3

Exchange

RCTs (No.
Patients)

Controlled Trials Case Series
(No. Patients)
(No. Patients) Replacement Fluid Comments

ANCA-associated
systemic vasculitis

9 (652)

1 (26)

>22 (>347)

Albumin unless
pulmonary
hemorrhage or
need to prevent
coagulopathy

Anti-GBM antibody
disease

1 (17)

0

>10 (>587)

Albumin unless
pulmonary
hemorrhage or
need to prevent
coagulopathy

Cryoglobulinemia

1 (57)
1 (17) using
immunoadsorption
7 (301)

0

24 (302)

Albumin

2 (133)

>38 (>1541)

ABO-incompatible
kidney
transplantation

0

0

>21 (>750)

Antibody-mediated
kidney transplant
rejection

HLA desensitization
for transplantation
(in highly
sensitized
patients)

3 (61)

8 (342)

>37 (>727)

Plasma or cryo-poor
plasma
Albumin ± plasma
(compatible with
donor and recipient
or AB)
Albumin

0

5 (441)

29 (466)

Albumin

Indication

TTP

1153

Possible benefit only in dialysis-dependent
patients or those with most severe
kidney impairment.
Should consider daily exchanges in
fulminant cases or with pulmonary
hemorrhage.
Minimum course 14 days to remove
antibodies effectively. Especially
beneficial in nonoliguric patients
predialysis. Patients with creatinine
>5.5 mg/dL (500 µmol/L) unlikely to
benefit.
Long-term maintenance treatment needed
in some patients. Ensure blood warmer on
return lines or warm replacement fluids.
Daily, often with corticosteroids; the only
treatment that has improved mortality.
Used pretransplant to reduce titers of
antibodies and often continued for a few
days after surgery to allow successful
transplantation.
Daily or alternate day. Usually with
IVIG and sometimes enhanced
immunosuppression.
Always in combination with
immunosuppression and usually IVIG, and
continued until cross-match negative.
Usually five plasma exchanges are
needed to reduce Ab levels sufficiently.

ANCA, Antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HLA, human leukocyte antigen; IVIG, intravenous immunoglobulin; RCTs, randomized controlled trials; TTP, thrombotic thrombocytopenic purpura.

t0025

TABLE 104.4

Conditions for Which There Is Some Evidence for Plasma Exchange

Indication

RCTs (No. of Controlled Trials Case Series
Replacement
Patients)
(No. of Patients) (No. of Patients) Fluid
Comments

Catastrophic
antiphospholipid
antibody syndrome
Recurrent FSGS after
transplantation
Atypical hemolyticuremic syndrome
Myeloma

0

0

6 (109)

Plasma

0

3 (48)

77 (378)

Albumin

0

0

>10 (>200)

5 (182)

0

8 (102)

Plasma or cryopoor plasma
Albumin

Rapidly progressive
glomerulonephritis
(may include patients
with ANCA-associated
disease in older
literature)
Scleroderma

7 (196)

0

21 (295)

Albumin

0

3 (75)

7 (70)

Albumin

Systemic lupus (not nephritis)

1 (20)

1 (4)

14 (128)

Albumin

Should be done daily. Combination of plasma exchange or IVIG, heparin, and corticosteroids (from registry data) gives best outcomes.
Sometimes in combination with rituximab. May need long-term maintenance treatment.
Daily plasma exchange initially. Eculizumab is the preferred treatment if available.
Daily or alternate day for 7–10 exchanges. Despite negative randomized trial in 2005, plasma exchange might be considered if high light-chain load, severe kidney failure, and oliguria and light chains not depleted with urgent chemotherapy.
No good evidence for benefit in immune complex disease of any cause.
Small case series of benefit in crescentic IgA vasculitis (Henoch-Schonlein purpura) with RPGN.
No good evidence for benefit, but some patients have reported improvement.
For cerebritis, lupus-associated TTP, severe hemolysis, or pulmonary hemorrhage.

ANCA, Antineutrophil cytoplasmic antibody; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IVIG, intravenous immunoglobulin; RCTs, randomized controlled trials; RPGN, rapidly progressive glomerulonephritis; TTP, thrombotic thrombocytopenic purpura.

s0040 Small-Vessel Vasculitis

p0090 The majority of patients with rapidly progressive glomerulonephritis (RPGN), other than anti-GBM disease, have small-vessel vasculitis with ANCA detectable in their serum, and there is increasing evidence that these autoantibodies are pathogenic. Several trials of plasma exchange in non–anti-GBM RPGN have been reported.7 11
Most of the early trials included patients with a variety of diseases, used a low intensity of plasma exchange, and often excluded those with oligoanuria. These trials showed no overall benefit of plasma exchange in addition to conventional immunosuppression;

however, those patients with the most severe disease did seem to benefit. Two recent large RCTs have, however, added to the controversy. MEPEX (Methylprednisolone or Plasma Exchange in Severe ANCA-Associated Vasculitis) randomized 137 patients with ANCAassociated systemic vasculitis and serum creatinine greater than 5.5 mg/dL (500 µmol/L) to plasma exchange or IV methylprednisolone in addition to oral corticosteroids and cyclophosphamide.11 Sixtynine percent of patients recovered kidney function when treated with plasma exchange compared with 49% of those receiving IV methylprednisolone, and significantly more patients were dialysis independent at the trial endpoint, although this difference was not maintained at 3 years. MEPEX was the largest study in a meta-analysis of 387 patients, with creatinine levels ranging from 3.2 to 13.5 mg/dL. The addition of plasma exchange to standard immunosuppression in MEPEX was associated with reduced risk for ESKD or death.

The PEXIVAS trial randomized 352 patients with ANCA-associated vasculitis and estimated glomerular filtration rate (eGFR) less than 50 mL/min to plasma exchange (7 exchanges in 14 days) or no plasma exchange, and also low- or high-dose oral steroids.12 Overall, there was no difference in deaths or ESKD with or without plasma exchange (28.5% vs. 31%; hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.65–1.13) but a suggestion that plasma exchange might increase the chance of kidney recovery in those with the most severe kidney impairment at presentation, and a new meta-analysis including PEXIVAS is awaited.

Patients with both ANCA and anti-GBM antibodies (so-called p0095 double-positive patients) and RPGN do not respond well to plasma exchange and rarely, if ever, recover kidney function.13

Recommendation

s0045

We perform plasma exchange in patients with small-vessel vasculitis p0100 who present with severe kidney failure (serum creatinine > 5.5 mg/dL [~500 µmol/L] or dialysis dependent) or pulmonary hemorrhage. The regimen is shown in Table 104.2

Other Crescentic Glomerulonephritis

s0050

Crescent formation is a common histologic finding in several other p0105 patterns of GN, including postinfectious GN, GN associated with infective endocarditis, IgA nephropathy (IgAN), membranoproliferative glomerulonephritis (MPGN), and membranous nephropathy.

Such patients were often included in studies of treatment of RPGN, and plasma exchange has been used in the treatment of a number of these conditions. More than 400 patients with such diseases have been treated with plasma exchange with no good evidence for any benefit in crescentic GN not caused by anti-GBM disease or vasculitis.7 8 In crescentic IgAN, there are anecdotal reports of short-term benefit in patients with severe kidney impairment, but longer-term follow-up has proved disappointing. A single report showed some benefit of 5 to 10 plasma exchanges in preventing or reversing dialysis dependency in 12 patients with crescentic IgAN manifesting with RPGN, with measured decreases in circulating plasma IgA-IgG complexes.14

s0055 Recommendation

p0110 We offer plasma exchange in patients with IgAN and other GNs who have rapidly deteriorating kidney function and extensive fresh crescents in the biopsy specimen.

s0060 Focal Segmental Glomerulosclerosis

p0115 Plasma exchange, protein A immunoadsorption, and lipoprotein apheresis have been used to treat patients with primary FSGS or recurrent disease after transplantation. The results have been worse in primary disease with less than 40% of patients achieving either partial or complete remission,7,8,13 and we do not recommend plasma exchange in this setting. Plasma exchange for recurrent disease is discussed later and in Chapter 113.

s0065 Thrombotic Microangiopathies

p0120 In both HUS and TTP, endothelial activation leads to TMA but through distinct mechanisms.

s0070 Infection-Associated Hemolytic-Uremic Syndrome

p0125 Infections leading to HUS are most recognized after enteropathogenic Escherichia coli from Shiga toxin production (Stx-associated HUS) and after Streptococcus pneumoniae (pHUS). The prognosis is generally good, especially in childhood. Most children will recover extremely well with supportive care and management of fluid and electrolyte imbalance and hypertension. Two controlled trials of plasma infusion (at least 10 mL/kg/day) in childhood HUS complicated by dialysis-dependent kidney failure showed no clinical benefit (as determined by hypertension, kidney dysfunction, and proteinuria) in either short- or medium-term follow-up.15 There has been no study of plasma exchange in childhood Stx-associated HUS. Plasma exchange and infusion have not been subjected to any controlled trials in adult Stx-associated HUS, but uncontrolled observations suggest possible benefit.7,16 The 2011 outbreak of enterohemorrhagic and Stx-producing E. coli O104:H4 in Europe led to 855 confirmed cases of HUS, but despite severe illness in many patients, a retrospective analysis of 491 treated patients did not support any major benefit of plasma exchange in addition to intensive supportive care.17

s0075 Thrombotic Thrombocytopenic Purpura

p0130 Patients with TTP usually have a defective vWF cleaving protease (ADAMTS13), an enzyme that normally degrades large vWF multimers. The defect is typically because of an inherited deficiency or autoantibodies directed against the protease. Accumulation of vWF multimers leads to systemic platelet activation under conditions of high shear stress (the microcirculation) and thrombosis. The rationale for plasma infusion and plasma exchange in TTP is therefore to replenish vWF cleaving protease, to remove antibodies against the protease, and to remove the large vWF multimers from circulation. There are well-designed RCTs in the treatment of TTP.

p0135
The first prospective controlled trial compared plasma infusion with plasma exchange (1–1.5 plasma volumes at least seven times in the first 9 days).18 Of patients receiving plasma exchange, 47% had a platelet count exceeding 150 × 109 cells/L and no new neurologic features, compared with only 25% of those receiving plasma infusion over the first 2 weeks. At 6 months, survival was substantially better in those given plasma exchange (50% vs. 78%). More recent series using plasma exchange have reported mortality rates as low as 15%,7 and there may be an association of reduced early mortality with more intensive plasma exchange. Kidney impairment is not an independent predictor of poor outcome in TTP and does not in itself warrant more intensive therapy.

TTP may also be induced by drugs, including ticlopidine, clopi- p0140 dogrel, mitomycin C, cyclosporine, tacrolimus, gemcitabine, and quinine, and the evidence for benefit of plasma exchange in this context is poor, except for ticlopidine-induced TTP in which ADAMTS13 activity is severely depressed.7

Atypical Hemolytic Uremic Syndrome

s0080

The less common forms of HUS in which there is no clear diarrheal p0145 prodrome (atypical HUS [aHUS]) are commonly caused by mutations, polymorphisms, or acquired dysregulation of the complement pathway (including the development of autoantibodies), especially of factor H, factor I, and membrane cofactor protein, leading to uninhibited activation of complement. Other causes include infections or drugs that cause platelet or leukocyte activation and complement activation and consumption. Direct activation of endothelial cells also may be a cause. Plasma exchange and infusion have not been evaluated in controlled trials in aHUS, but uncontrolled series suggest benefit and current guidelines recommend early initiation of plasma exchange with FFP (see Chapter 30), both to remove potential complement inhibitors or autoantibody and to replace absent or defective complement regulators.7 The introduction of the complement inhibitor eculizumab, a humanized anti-C5 monoclonal antibody, has revolutionized the treatment of aHUS and should now be the mainstay of management after urgently excluding other diagnoses and can replace plasma exchange. If eculizumab is not available, plasma exchange should be continued. TMA after kidney transplantation has also responded to plasma exchange.

Recommendation

s0085

We use plasma exchange in all adults with TTP and perform all p0150 exchanges using FFP or cryo-poor FFP as the exchange fluid. In aHUS, we use plasma exchange until we can initiate eculizumab, which is the preferred treatment.

Systemic Lupus

s0090

Plasma exchange has been used extensively in patients with lupus. p0155 Most studies have included patients with diverse patterns of disease, often with only mild kidney involvement. A prospective RCT could show no benefit of plasma exchange over conventional immunosuppression for kidney, serologic, or clinical outcomes, both in the short and long term.19 However, patients with crescentic lupus nephritis and those with the most severe kidney dysfunction (dialysis dependency) were excluded. Anecdotal evidence suggests that plasma exchange may benefit patients with systemic lupus and crescentic GN, pulmonary hemorrhage, cerebral lupus, catastrophic antiphospholipid syndrome, severe antibody-induced hemolysis, lupus-associated TTP, or severe lupus unresponsive to conventional drugs or in patients for whom cytotoxic therapy has been withdrawn because of bone marrow suppression or other toxicity. Immunoadsorption may be more successful in the severe forms of lupus nephritis. A variety of techniques have been used, including standard protein A and anti-immunoglobulin absorption, and also phenylalanine, tryptophan, and dextran sulfate ligands, all of which bind immunoglobulin, rheumatoid factors, and immune complexes to varying degrees and all of which have been reported to induce remission in patients with severe disease after failure of conventional therapy.

Recommendation

s0095

We offer plasma exchange to lupus patients with rapidly progressive kidney failure and class IV lupus nephritis with crescents, to patients with severe neurologic involvement or severe hemolysis, to patients with myelosuppression who are thought unable to tolerate p0160 cyclophosphamide, and to those with catastrophic antiphospholipid syndrome or severe macrophage activation syndrome. The treatment of lupus is further discussed in Chapter 27

s0100 Cryoglobulinemia

p0165 In type I cryoglobulinemia, usually associated with myeloma or lymphoma, a monoclonal immunoglobulin causes hyperviscosity and cryoprecipitation. Such antibodies are easily removed by plasma exchange, often with immediate clinical benefit. Cytotoxic agents are used simultaneously to inhibit further paraprotein production. There are no controlled trials of plasma exchange, but symptoms are closely related to the presence of the cryoimmunoglobulin, and hence treatment with plasma exchange appears effective.7

p0170

Patients with type II (mixed essential) cryoglobulinemia develop a monoclonal antibody (usually IgM) with specificity for a second, usually polyclonal, immunoglobulin. Type II cryoglobulins occur most commonly in association with hepatitis C virus (HCV) infection and lymphoma. The resulting immune complexes can be deposited in the microcirculation and are particularly associated with an MPGN pattern of injury (see Chapter 22). Plasma exchange is effective at clearing the immune complexes, although the cryoglobulins often recur, and sustained benefit has not been clearly demonstrated. However, many of the acute features of cryoglobulinemia resolve with plasma exchange, particularly arthralgia, skin lesions, and digital necrosis, and patients with RPGN can recover kidney function. Concomitant treatment with rituximab may prevent resynthesis of the cryoproteins, although some patients require long-term intermittent plasma exchange to control symptoms. Patients with HCV-associated cryoglobulinemia should be treated with the newer antiviral agents, which are extremely effective in curing the viral infection, after which cryoglobulins usually disappear. A single RCT in 17 patients with HCV-associated cryoglobulinemia added immunoadsorption apheresis (with dextran sulfate) to antivirals and immunosuppression and showed significant clinical improvements, but this was from an era before the current antiviral agents.20

p0175

Cryofiltration apheresis (in which a normal plasma filter is used to separate plasma, which is then cooled to precipitate the cryoglobulin before return to the patient) selectively removes cryoglobulins, avoids large volumes of replacement fluids, and avoids deficiency of clotting factors, but needs to be combined with immunosuppression to prevent synthesis of further cryoglobulin. Few centers currently perform this technique, especially because of the widespread introduction of rituximab for cryoglobulinemia.

s0105 Recommendation

p0180 We offer plasma exchange (in addition to rituximab or antiviral treatments) to patients with cryoglobulinemia and rapidly progressive kidney failure, necrotic ulceration, and digital infarction and to patients with type 1 cryoglobulins and complications from hyperviscosity.

s0110 Myeloma

p0185 Plasma exchange almost certainly does not provide benefit in myeloma with either cast nephropathy or light-chain kidney toxicity, and the most important therapy seems to be urgent initiation of chemotherapy, especially thalidomide, lenalidomide, bortezomib, or newer agents. A large prospective RCT randomized 97 patients with myeloma and progressive acute kidney injury (creatinine > 200 μmol/L [2.3 mg/dL] with an increase of over 50 μmol/L over the previous 2 weeks despite conventional management) to receive plasma exchange (five to seven sessions of 50 mL/kg over 10 days) in addition to chemotherapy (vincristine, adriamycin, and dexamethasone [VAD] or melphalan and prednisolone).21 This study showed no benefit of plasma exchange on mortality or recovery of kidney function. However, patients had

a wide degree of kidney dysfunction, and relatively few had a kidney
biopsy performed to confirm cast nephropathy. A retrospective review
suggested that those with myeloma and high light-chain loads or severe
kidney failure may benefit if plasma exchange reduces light chains
rapidly.22 More recently a variety of studies in patients with kidney
disease and myeloma, especially using bortezomib-based regimens,
have shown significant improvements even in patients with dialysisrequiring
kidney failure but without plasma exchange. An RCT of
HD using novel membranes allowing the removal of large-molecularweight
substances and lengthy dialysis sessions (6–8 hours) failed to
show any benefit (for survival or recovery of kidney function) when
added to modern chemotherapy, which depleted light chains rapidly
in the absence of plasma removal.

Recommendation

s0115
We no longer use plasma exchange in patients with myeloma but p0190
ensure that effective chemotherapy is urgently initiated.

TRANSPLANTATION

s0120

Antibody-Mediated Rejection

s0125
A review of 157 patients included in five trials did not show any benefit p0195
of plasma exchange for the treatment of acute vascular rejection.7,8
At least 11 trials including more than 400 patients with more clearly
defined antibody-mediated rejection and case series of more than
700 patients have suggested that plasma exchange, combined with IV
immunoglobulin (IVIG) and/or rituximab, but sometimes antithymocyte globulin,
may reverse 55% to 100% of such rejection episodes.7

There is no convincing evidence that plasma exchange has any role p0200
in the treatment of chronic rejection.

Anti–Human Leukocyte Antigen Antibodies

s0130
Highly sensitized patients with preformed anti-HLA antibodies have p0205
been treated before and after transplantation with plasma exchange
or immunoadsorption to reduce cytotoxic antibody levels, often with
high-dose IVIG.7 Patients usually received intensive immunoadsorption or plasma
exchange before transplantation to ensure a current negative crossmatch
immediately before transplantation; some
received longer-term immunoadsorption or plasma exchange in combination with
immunosuppressive therapies in the months before
transplantation. Most recent studies have shown that donor-specific
antibody titers of less than 1 to 32 are often depleted completely with
preoperative plasma exchange, allowing successful kidney transplantation. Such
patients have an increased risk for antibody-mediated
rejection—approximately 40%—but despite this, 90% have 1-year
graft survival.

ABO-Incompatible Kidney Transplantation

s0135
Plasma exchange is widely used to remove natural anti-A or anti-B p0210
blood group antibodies from the recipient before living donor transplantation
from an ABO-incompatible donor. Various protocols are in
use, but all rely on depletion of specific antibody over 2 to 5 days before

transplantation by exchanging a single plasma volume for human albumin solution (in addition to routine immunosuppression, sometimes including rituximab and IVIG). Plasma exchange is sometimes continued for one or two sessions after transplantation or if antibodymediated rejection occurs.23 One-year graft survival rates of over 90% have been reported with such protocols, and although rejection episodes are more common than in ABO-compatible transplants, overall graft survival is similar. Subsequent return of ABO antibodies in the weeks after the kidney transplant does not usually cause rejection (a process termed accommodation and which is not fully explained).

Patients with increasingly high antibody titers are being treated in this way. Immunoadsorption using synthetic A- or B-oligosaccharide epitopes linked to Sepharose has been developed, which specifically remove anti-A or anti-B antibodies, but any clinical benefit remains uncertain and the costs are high.

s0140 Recurrent Focal Segmental Glomerulosclerosis

p0215 Plasma exchange, double-filtration plasma exchange, and protein A immunoadsorption have been used to treat nephrotic syndrome after transplantation in patients with recurrent FSGS.7 24 25 An incompletely defined circulating factor causing increased permeability of glomerular capillaries can be found in most patients with recurrent FSGS. There are no controlled trials of plasma treatments in recurrent FSGS, and most series are small. A meta-analysis and systematic review of 77 case reports including 378 patients demonstrated an overall remission rate of 71%, with 46.8% achieving a complete remission after plasma exchange.25 The study suggested that those with a more rapid relapse after transplantation and lower proteinuria were more likely to respond, with no difference between deceased and living

donors. Patients received a median of 12 plasma exchange sessions. All three apheresis modalities have been used prophylactically in patients deemed to be at high risk for recurrence, with variable success. Intriguingly, lipoprotein apheresis (LDL-A) has been shown in small case series to induce remission of proteinuria in both primary and recurrent FSGS, via unknown mechanisms. LDL absorption occurs using dextran sulfate cellulose columns which absorb and remove LDL, VLDL, and lipoprotein (a) from plasma. Treatments are undertaken weekly for 6 to 12 weeks, and in very small and selected series achieve remission rates of approximately 50%.26

Recommendations

s0145

We recommend plasma exchange for patients with recurrent FSGS, p0220 started early, initially daily for 7 to 10 days. If proteinuria is successfully reversed, this may need to be continued less frequently for several months. Management of recurrent FSGS is discussed further in Chapter 113 We recommend plasma exchange for acute antibody-mediated rejection together with enhanced immunosuppression.

SELF-ASSESSMENT QUESTIONS

o0010 1. A patient with anti–GBM disease, serum creatinine 250 μmol/L, and pulmonary hemorrhage is being treated with plasma exchange and immunosuppression. Which complication can occur as a direct result of the plasma exchange?

o0015
A. Hypernatremia
o0020
B. Hyperviscosity
o0025
C. Hypocalcemia
o0030
D. Pulmonary embolism
o0035
E. Thrombocytosis

o0040 2. A 52-year-old woman presented with acute kidney injury and evidence of hemolysis and thrombocytopenia. The results of investigations showed:

u0010 ✓ •✓ Hemoglobin: 86 g/L (115–165)
u0015 ✓ •✓ White blood cell count: 4.2 × 109/L (4.0–11.0)
u0020 ✓ •✓ Platelet count: 35 × 109/L (150–400)
u0025 ✓ •✓ Serum creatinine: 238 μmol/L (60–110)

The results of remaining investigations are awaited. Which one of these diagnoses should lead to urgent initiation of plasma exchange?

A. Atypical HUS
B. Infection-associated HUS
C. Myeloma
D. Scleroderma renal crisis
E. Systemic lupus

3. A 42-year-old man received a cadaveric kidney transplant under standard immunosuppression. Six weeks later, his kidney function deteriorated, an ultrasound scan was normal, and a kidney biopsy was performed. Which finding might lead to initiation of plasma exchange?

A. Antibody-mediated rejection
B. CD4+ staining on the biopsy
C. Cyclosporine-induced microangiopathy
D. Recurrent membranous nephropathy
E. T-cell–mediated cellular rejection

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REFERENCES

1. Kaplan AA. Therapeutic Plasma exchange: a technical and operational review. J Clin Apher. 2013;28:3–10.
2. Derksen RH, Schuurman HJ, Meyling FH, et al. The efficacy of plasma exchange in the removal of plasma components. J Lab Clin Med. 1984;104:346–354.
3. Mokrzycki MH, Balogun RA. Therapeutic apheresis: a review of complications and recommendations for prevention and management. J Clin Apher. 2011;26:243–248.
4. Norda R, Stegmayr BG. Swedish Apheresis Group. Therapeutic apheresis in Sweden. Transfus Apher Sci. 2003;9:159–166.
5. Rock G, Clark B, Sutton D, et al. The Canadian apheresis registry. Transfus Apher Sci. 2003;29:167–177.
6. Stegmayr B, Ptak J, Wikström B, et al. World apheresis registry 2003-2007 data. Transfus Apher Sci. 2008;39:247–254.
7. Szczepiorkowski ZW, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis. J Clin Apher. 2016;31:149–338.
8. Shaz BW, Linenberger ML, Bandarenko N, et al. Category IV indications for therapeutic apheresis: ASFA fourth special issue. J Clin Apher. 2007;22:176–180.
9. Johnson JP, Whitman W, Briggs WA, Wilson CB. Plasmapheresis and immunosuppressive agents in antibasement membrane antibody-induced Goodpasture’s syndrome. Am J Med. 1978;64:354–359.
10. Levy JB, Turner AN, Rees AJ, Pusey CD. Long term outcome of anti–glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001;134:1033–1042.
11. Walsh M, Casian A, Flossmann O, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment. Kidney Int. 2013;84(2):397–402.
12. Walsh M, Merkel P, Peh C-A, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Eng J med. 2020;382:622–631.
13. McAdoo S, Tanna A, Hruskova Z, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. Kidney Int. 2017;92(3):693–702.

14. Xie X, Lv J, Shi S, et al. Plasma exchange as an adjunctive therapy for crescentic IgA nephropathy. Am J Nephrol. 2016;44:141–149.
15. Rizzoni G, Claris-Appiani A, Edefonti A, et al. Plasma infusion for hemolytic uremic syndrome in children. J Pediatr. 1988;112:284–290.
16. Nguyen TC, Stegmayr B, Busund R, et al. Plasma therapies in thrombotic syndromes. Int J Artif Organs. 2005;28:459–465.
17. Keenswijk W, Raes A, De Clerck M, Vande Walle J. Is plasma exchange Efficacious in Shiga toxin-associated hemolytic uremic syndrome? A narrative review of current evidence. Ther Apher Dial. 2019;23(2):118–125.
18. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991;325:393–397.
19. Korbet SM, Lewis EJ, Schwartz MM, et al. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. Am J Kidney Dis. 2000;35:904–914.
20. Stefanutti C, Vivenzio A, Di Giacomo S, et al. Immunoadsorption apheresis and immunosuppressive drug therapy in the treatment of complicated HCV-related cryoglobulinemia. J Clin Apher. 2009;24:241–246.
21. Clark WF, Stewart AK, Rock GA, et al. Plasma exchange when myeloma presents as acute renal failure. Ann Intern Med. 2005;143:777–784.

22. Leung N, Gertz MA, Zeidenrust SR, et al. Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum light chains. Kidney Int. 2008;73:1282–1288.
23. Winters JL, Gloor JM, Pineda AA, et al. Plasma exchange conditioning for ABO-incompatible renal transplantation. J Clin Apher. 2004;19:79–85.
24. Dantal J, Bigot E, Bogers W, et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med. 1994;330:7–14.
25. Kashgary A, Sontrop JM, Li L, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. BMC Nephrol. 2016;17:104.
26. Raina R, Wang J, Sharma A, Chakraborty R. Extracorporeal therapies in the treatment of focal segmental glomerulosclerosis. Blood Purif. 2020;49:513–523.

SECTION XIX Transplantation

105

Immunologic Principles in Kidney Transplantation

Orhan Efe, Karl L. Womer, Leonardo V. Riella

s0010

INTRODUCTION

p0010 In 1954, Joseph Murray performed the first successful human kidney transplant between two identical twins. For decades now, kidney transplantation has been the standard of care for kidney failure patients. Maintenance of intact allograft function requires immunosuppression or immune tolerance in genetically nonidentical individuals. Thus, understanding of the immunologic principles remains cardinal in the management of kidney transplant patients (see Box 105.1 for graft terminology).

p0015

Protection against nonself antigens constitutes a paramount function of the immune system. After encountering a foreign antigen, the innate immune system responds by inducing antigen-nonspecific mechanisms such as phagocytosis and cytokine release. Afterwards, antigen-presenting cells (APC) of the innate immune system carry nonself peptides to T lymphocytes in the peripheral lymphoid organs to activate the adaptive immunity. B lymphocytes capture circulating foreign antigens through their B-cell receptors. Consequently, activation of T and B lymphocytes initiate antigen-specific responses that ultimately lead to direct cellular killing and antibody secretion, respectively.

p0020

Similar cascades of events provoke allorecognition and allograft rejection in transplant patients. Recipient’s naive T and B cells constitute a diverse repertoire of receptors for an enormous number of potential foreign antigens, including mismatched donor human leukocyte antigens (HLAs). Recognition of mismatched antigens instigates an immune response against the graft parenchyma and the vasculature, leading to allograft rejection (Fig. 105.1).

p0025

This chapter reviews the immunologic principles in kidney transplantation by dissecting the elements of the innate and the adaptive immune systems, the role of HLA in transplantation, and the pathophysiology of allorecognition and transplant rejection.

s0015

INNATE IMMUNE SYSTEM

p0030 Innate immunity is the frontline defense of the immune system that is activated by the entrance of foreign antigens such as microorganisms and tissue injury. Innate immunity occurs rapidly, with limited specificity and without memory. Innate responses are driven by cellular elements such as neutrophils, macrophages, dendritic cells (DCs), and natural killer (NK) cells, and by molecular components, such as pathogen-associated pattern recognition receptors (PRRs), complement proteins, and cytokines.

The innate response to an insult starts with local chemical signals. p0035 Invasion of a microorganism leads to leaking of certain microbial structures called pathogen-associated molecular patterns (PAMRP), such as lipoproteins and lipopolysaccharides. Alternatively, sterile tissue damage, such as because of ischemia, leads to release of endogenous molecules termed damage-associated molecular patterns (DAMP), such as adenosine triphosphate (ATP), calcium, uric acid, and DNA. PRRs of the innate system cells then recognize these molecular signals and their activation induces a cascade of events: (1) cytokine release for chemotaxis, (2) labeling of infected or damaged cells (opsonization), and (3) direct cellular killing. Toll-like receptors (TLRs) are the most well-known PRRs, which involve a family of receptors against microbial epitopes including bacteria, virus, and fungi. Similar insults could also activate the complement system through binding of complement factors to microbial proteins (lectin pathway) or antigen-antibody complexes (classical and alternative pathways) that ultimately provoke chemotaxis (by releasing C3a and C5a) and cell death (by terminal complex formation; C5b-9). Overall, these signals alert the immune system to recruit and activate its defense mechanisms.

During donor organ procurement and transplantation, acute ischemia p0040 and reperfusion of allograft induce tissue damage and endothelial cell activation by sparking free radicals and inducing apoptosis, which is known as ischemia/reperfusion injury (IRI). DAMPs released from damaged graft cells activate PRRs on innate immune cells, resulting in the secretion of cytokines, such as tumor necrosis factor (TNF), type I interferons, chemokines, interleukin (IL)-1, and IL-6.1 Neutrophils are the prime cells that mediate microvascular plugging and local tissue destruction in IRI. In the next phase, monocyte/macrophage infiltration contributes to the extension of early injury and to repair.2 The complement system fixation could occur through activation of classical, alternative, and/or lectin pathway during IRI. Donor-derived APCs migrate to recipient lymphoid tissue to activate lymphocytes. Ultimate parenchymal and vascular injury along with tissue edema contributes to delayed graft function. These events may also trigger adaptive, or antigen-specific, immune responses that can induce allograft rejection and negatively affect long-term graft survival.

Adaptive Immune System

s0020

B and T lymphocytes and their products, including immunoglobulins p0045 and cytokines, make up the adaptive immunity. The adaptive immune response usually follows the innate system activation. After an immune insult, APCs deliver foreign antigens to secondary lymph organs (SLOs), such as lymph nodes and spleen, to present them to naive T cells. B cells

BOX 105.1
b0010

c0105

Graft Terminology

Autograft (autologous graft): A graft from one part of the body to another. Examples include skin and vascular grafts, such as in extensive burn or coronary bypass surgery. No rejection occurs.
Isograft (isogenic or syngeneic graft): A graft from one member of a species to a genetically identical member of the same species. Examples include grafts between identical twins and between members of the same inbred rodent strain. No rejection typically occurs.
Allograft (allogeneic graft): A graft between nonidentical members of the same species. Examples include grafts between unrelated or related nonidentical humans and between members of different inbred rodent strains.
Rejection occurs primarily by lymphocytes reactive to alloantigens on the graft (i.e., alloresponse).
Xenografts (xenogeneic grafts): A graft between members of different species. Examples include pig or baboon to human and rat to mouse. Rejection occurs by lymphocytes reactive to xenoantigen on the graft (i.e., xenoresponse).

bind circulating soluble antigens through their B-cell receptor (BCR). Each one of the B and T lymphocyte clones is responsive to only a specific foreign antigen because of the selectivity of their receptors. Activation of B and T cells leads to the development of antigen-specific memory clones in the SLOs, which enables a more rapid and robust response during repetitive exposure to the same antigen. Activated effector T cells emigrate into the inflamed tissue and respond by direct cellular killing (CD8+ cells) and cytokine release (CD4+ cells). B cells respond by producing immunoglobulins against foreign antigens and releasing cytokines in the SLOs and rarely occupy the tissue parenchyma. These antigen-specific responses play a cardinal role during allograft rejection by recognition of donor’s mismatched antigens.

Resolution of Inflammation

s0025
After the source of antigen is destroyed, both innate and adaptive p0050 immune cells help abrogate the inflammation. When activated, certain TLRs concurrently silence certain genes to create a negative feedback loop. Neutrophils and eosinophils catabolize the inflammatory

Generation of Alloimmune Responses
Lymph node
MHC-I TCR
Cytotoxic T cell

MHC-II TCR

Helper T cell

MHC-II TCR
BCR
B cell

Helper T cell

APC

Cytokines

Soluble donor
antigen (i.e.,
MHC)

f0010

Allorecognition
(Recognition of antigens on graft
endothelium and parenchyma)

Allograft rejection

Fig. 105.1 Generation of Alloimmune Responses. Immunologic responses after kidney transplantation represent a series of well-defined stages that result in rejection of the allograft in the absence of exogenous immunosuppression. Injury to allograft tissue such as because of ischemia/reperfusion injury induces innate (antigen-nonspecific) immune responses, which recruit inflammatory cells and initiate adaptive (antigenspecific) immune responses. Donor major histocompatibility complex (MHC) and/or minor proteins that are revealed during tissue injury are taken up by antigen-presenting cells (APCs) of donor (direct pathway) or recipient (indirect pathway) origin. Then, APCs migrate to secondary lymphoid organs (SLO), where they present alloantigen to T cells through MHC structures on their cell surface. After T-cell receptor (TCR) signaling and appropriate costimulation, T cells become activated to produce large amounts of cytokine and undergo clonal expansion. CD4 T cells provide help to B cells, CD8 T cells, and macrophages for the production of alloantibody, cellular cytotoxicity, and delayed-type hypersensitivity responses, respectively. These effector functions result in destruction of the graft by acute rejection, which may be T-cell and/or antibody mediated. BCR, B-cell receptor; TCR, T-cell receptor.

T-Cell Receptor Complex: MHC Interaction
Antigen Presenting Cell
β2m

CD8

CD4

α3
α2

α1

MHC
Class I

α2

β2

MHC
α1
Class II

β1

Peptide
V

V

CD3

CD3

C

β α

TCR

TCR

V

V

CD3

C

ε δ α ζζ β γ ε
CD8 T Cell

CD3

C

C

γ ε α ζζ β ε δ
CD4 T Cell

f0015
Fig. 105.2 T-Cell Receptor (TCR) Complex: Major Histocompatibility Complex (MHC) Interaction. The formation of a stable immunologic synapse between T cells and antigen-presenting cells is crucial for an effective T-cell activation. Each TCR consists of an α and β chain linked by a disulfide bond. The α:β heterodimers are similar in structure to the Fab fragment of immunoglobulin molecules (see Fig. 105.4), including variable (V) and constant (C) regions. Diversity in the T-cell repertoire is encoded in the V domains of the α and β chains in three complementarity-determining regions that form the antigen-binding site at the end of the TCR (highlighted in red). CD8 binds to class I MHC molecule on antigen-presenting cells (APCs), whereas CD4 binds to class II MHC molecule on APCs. Triggering of the TCR by antigen initiates a signaling cascade started by the signaling complex made up of CD3 γ, ε, and δ chains and the ζ chain homodimer.

mediators such as eicosanoids and cytokines. DCs switch cytokine production from IL-12 to IL-10, favoring the generation of regulatory mechanisms that suppress the function of effector T cells. In the absence of continued cytokine production, T cells lack the necessary growth factors and undergo passive cell death. Activated T cells also undergo activation-induced cell death by the expression of Fas and FasL on their surface, leading to apoptosis.3 Certain regulatory T and B cells also produce antiinflammatory cytokines, such as IL-10 and TGF-β, that suppress immunity.4 These mechanisms of immune regulation are crucial for avoiding overactivation and persistence of the immune response once the threat is gone.
s0030

CELLS OF THE IMMUNE SYSTEM

s0035 T Lymphocytes

p0055 As a cellular component of adaptive immunity, T cells have a pivotal role in orchestrating the antigen-specific responses by exerting regulatory and effector functions. During T-cell ontogeny in embryogenesis, multilineage bone marrow precursors migrate to the thymus. In the thymus, T-cell receptor (TCR) genes undergo rearrangement to ensure that a diverse repertoire of T cells exists to respond to the enormous number of potential foreign antigens, including foreign HLAs, which play a crucial role in alloresponses.5 The mature T-cell repertoire is determined in the thymus by two processes, positive and negative

selection. Positive selection depends on a certain degree of antigenspecific T-cell affinity to self–major histocompatibility complex (MHC) molecules expressed on thymic cortical epithelial cells. This process ensures that mature T cells will interact effectively with selfMHC molecules. Negative selection occurs by deletion of T cells with excessively high affinity for self-peptide and MHC, thereby preventing release of high-affinity T cells with autoimmune potential.
Mature T cells expressing their clone-specific TCRs exit the thymus p0060
as either CD4 or CD8 T cells. The TCRs of CD4 T cells (also called T helper cells) are selected to interact with class II MHC molecules, whereas the TCRs of CD8 T cells interact with class I MHC molecules. Each TCR consists of two different polypeptide chains, termed the TCR α and β chains. In the functional receptor complex, TCR α:β heterodimers are associated with a complex of four other signaling chains (two ε, one δ, one γ) collectively called CD3 (Fig. 105.2). Downstream to TCR, calcineurin acts as an effector through its phosphatase activity by activating NFAT, a transcription factor, leading to IL-2 secretion. This critical molecule for the T-cell activation serves as a target for calcineurin inhibitors in transplantation.

T-Cell Stimulation

s0040

Stimulation of T cells are mediated by APCs, which require receptor- p0065 ligand interactions and cytokine signaling. In contrast to the BCRs, TCRs do not recognize antigen in its native state but instead recognize a composite ligand of a peptide bound to an MHC molecule.

Engagement of the TCR with peptide-bound MHC of an APC is called signal 1. Signal 1, the antigen-specific signal, is effective only in the presence of costimulatory signals, which is termed as signal 2. Costimulation serves as a checkpoint to prevent the activation of selfreactive T cells that escaped negative selection in the thymus. Antigen binding to the TCR in the absence of costimulation fails to activate the T cell and also leads to anergy, in which T cells become refractory to subsequent activation or even undergo apoptosis (programmed cell death). Thus, costimulation removes this inhibition and determines whether a T-cell will proceed with clonal expansion and the development of effector functions. Costimulatory molecules can provide both positive and negative signals to T cells (Fig. 105.3). It is the integration of both positive and negative costimulatory signals during and after initial T-cell activation, dictated by their temporal and spatial expression patterns, that ultimately determines the fate and functional status of the T-cell response.6 For an effective and strong T-cell stimulation, cytokine secretion is also required, serving as the signal 3. IL-2 is a cardinal cytokine for T-cell activation and proliferation, by acting in an autocrine or paracrine fashion. IL-2 activation, in turn, triggers another pathway mediated in part through the protein mammalian target of rapamycin (mTOR). New proteins are then translated, allowing the cell to progress from the G1 phase to the S phase of the cell cycle, resulting in proliferation. Table 105.1 lists selected cytokines involved in allograft rejection, their sources, and their effects.

Memory T Cell Formation

s0045

Encountering a new foreign antigen transforms part of the naive p0070 T cells into memory T cells in SLOs. The principle of immunologic memory is that the immune response to a previously encountered antigen is swifter and more effective than the initial response.

Furthermore, there is an increase in antigen-specific T-cell frequency after exposure to a given antigen. Effector memory T cells are specialized for quickly entering the inflamed tissues because they can rapidly mature into effector T cells and secrete larger amounts of cytokines independent of costimulatory signals. Central memory T cells likely remain in the SLOs and do not produce as much cytokine release.7 Memory cells are believed to persist after an initial immune

T-Cell Costimulation

APC

T Cell
CD40

ICOS-L
B7.1
B7.2

CD40L

ICOS

Positive
Costimulation

CD28
CD28

MHC

TCR - Signal 1

B7.1

CTLA-4

B7.2

CTLA-4

PD-L1

PD-1

PD-L2

PD-1

HVEM

Negative
Costimulation

BTLA

f0020

Fig. 105.3 T-Cell Costimulation. Binding of the TCR:CD3 complex to peptide:MHC on antigen-presenting cells (APCs) delivers a signal that can induce the clonal expansion of naive T cells only when the appropriate costimulatory signal is delivered (Signal 2). CD28 and its ligands, B7.1 (CD80) and B7.2 (CD86), are the best-characterized costimulatory molecules that induce clonal expansion of naive CD4 T helper cells. Once activated, T cells express increased levels of CTLA-4 (CD152). CTLA-4 has an affinity 10 to 20 times greater than that of CD28 for B7 molecules and thus binds most or all of the B7 molecules, effectively shutting down

the proliferative phase of the response. B- and T-lymphocyte attenuator (BTLA) and programmed death-1 (PD-1) are two other coinhibitory molecules on T cells. Activated T cells express proteins that contribute to sustaining or modifying the costimulatory signal to drive clonal expansion and differentiation. The inducible costimulatory molecule (ICOS) is a CD28 homologue, but unlike CD28 is not constitutively expressed on naive T cells. Rather, ICOS is induced only after T-cell activation. Engagement of ICOS by B7H enhances T-cell proliferation, cytokine production, and survival. Binding of CD40 by CD40L, which is upregulated by CD28 signaling, transmits activating signals to the T cell but also activates the APCs to secrete proinflammatory molecules and to express B7 molecules, thus stimulating further T-cell proliferation. HVEM, Member of the tumor necrosis factor receptor superfamily; MHC, Major histocompatibility complex; TCR, T-cell receptor.

response through expression of the antiapoptotic genes Bcl-2 and Bcl-xL, which are induced primarily by IL-2 and CD28 stimulation. Long-term memory cell survival is likely a function of periodic interactions with self-MHC:peptide complexes on APCs. Memory T cells constitute an important risk factor for allograft rejection in patients with history of HLA sensitization through pregnancy, blood transfusion, or prior transplant.
s0050 CD4 T Cells
p0075 CD4 T cells have both effector and regulatory functions, mostly through secreting specific cytokines. After prolonged stimulation, CD4 T cells express their signature cytokines, probably depending on the local environment, nature of the antigen, and type and activation status of the APC. These different T helper (Th) subsets, each with unique transcription factor and cytokine signatures, are referred to as Th1, Th2, Th17, and Tfh (follicular help) populations.

The Th1 clones produce IL-2, IFN-γ, and lymphotoxin, which are p0080 growth and maturation factors for cytotoxic T lymphocytes (especially IL-2) and macrophages (particularly IFN-γ). T helper 17 (Th17) cells produce proinflammatory cytokines, including IL-17, IL-21, and IL22.8 Th1, in particular, plays a dominant role in acute cellular rejection.
Th2 clones secrete TGF-β, IL-4, IL-5, and IL-10, which facilitate B cell activation and class switching. Th cells are found in lymph nodes and are also important for B cell maturation. Thus, these two cell types contribute to antibody-mediated rejection by facilitating antibody production.
In addition to T cells that promote immune responses, there are p0085 CD4 T-cell subpopulations that control immune responses termed regulatory T cells (Tregs). Tregs are responsible from peripheral tolerance by suppressing autoimmunity and contribute to the resolution of inflammation by secreting inhibitory cytokines such as TGF-B, IL-10, and IL-35. The most well-characterized Treg is known for its

t0010

TABLE 105.1

Cytokines Involved in Allograft Rejection

Cytokine	Source	Biologic Activity
IL-1	Macrophages, DCs, ECs, NK cells	Proinflammatory, adhesion molecule expression on ECs, NK cell function
IL-2	Activated T cells	T-cell proliferation, CTL and NK cell function, Treg maintenance, immunoglobulin production by B cells, AICD of activated T cells
IL-4	Activated T cells	Activated T and B cell proliferation, Th2 differentiation, allergic responses, MHC II upregulation on B cells
IL-6	T cells, macrophages, ECs	Proinflammatory and anti-inflammatory, acute-phase responses
IL-10	T cells, Tregs, Bregs, macrophages, DCs	Anti-inflammatory, suppression of APC function, NK cell inhibition
IL-12	Macrophages, DCs	Proinflammatory, Th1 differentiation, NK cell and CTL activity, IFN-γ and TNF-α production by NK and T cells
IL-15	Epithelial cells, stromal cells, macrophages	NK cell proliferation, T-cell proliferation, memory T-cell survival
IL-17	T cells	Proinflammatory and allergic responses, Th17 function, cytokine production from many cell types
IFN-γ	Activated Th1 cells, CTLs, DCs, NK cells	MHC expression by EC, macrophage function, Th1 differentiation, Th2 suppression, adhesion and binding of T cells to ECs, NK cell activity
TGF-β	T and B cells, Tregs, Bregs, macrophages, platelets	
TNF-α	Macrophages, T and B cells, ECs, NK cells	

Anti-inflammatory, wound healing, fibrosis
Proinflammatory, acute phase responses, cytotoxicity

AICD, Activation-induced cell death; Breg, regulatory B cells; CTL, cytotoxic T lymphocytes; DC, dendritic cells; EC, endothelial cells; IFN-γ interferon-γ; IL, interleukin; NK, natural killer; TGF-β transforming growth factor-β; Th, T helper (cell); TNF-α tumor necrosis factor-α; Treg, regulatory T cells.

high expression of Foxp3 and IL-2 receptor alpha chain, CD25. Tregexpanding strategies, such as low-dose IL-2 or infusion of ex vivo expanded Tregs, have shown promising results in patients with autoimmune disorders and in transplantation.9–11

s0055 CD8 T Cells

p0090 CD8 T cells are effector cells with functions of direct cellular killing and they are called cytotoxic T lymphocytes (CTLs) in their activated form. CTLs possess two mechanisms to kill target cells that require cell-tocell contact.12 First, they release perforin and granzyme B from specialized lytic granules. The granzyme B–perforin complex enters the cell through the mannose 6-phosphate receptor, and, after internalization, perforin allows granzyme B to enter the cell by pore formation on the vesicle surface to induce programmed cell death through apoptosis.13 The second mechanism is mediated by Fas/Fas ligand (FasL) interactions. Fas (CD95) on the target cell surface is activated by FasL on CTLs to induce apoptosis. Both pathways induce apoptosis through activation of the caspase cascade in target cells.14 CD8 CTLs also release several cytokines that exert direct cytotoxic effects, including IFN-γ, TNF-α, and TNF-β 15 Current studies delineated the presence of CD4 CTLs that own similar cytolytic features to CD8 CTLs.16

s0060 B Lymphocytes

p0095 B cells protect extracellular spaces of the body by producing antibodies and contribute to antibody-mediated allograft rejection. B-cell development starts in the primary lymphoid organs including fetal liver (until birth) and bone marrow from common lymphoid progenitor cells. From the very early stages of development, B cells constitute a BCR, which contains an antigen specific immunoglobulin (Ig)M and/ or IgD component and associated antigen nonspecific Ig-α and -β proteins (Fig. 105.4). In primary lymphoid organs, autoreactive B cells undergo either receptor editing to eliminate self-reactivity or negative selection by apoptosis.

p0100
Survivor naive B cells emigrate into SLOs where the majority die and the rest will switch into mature B cells to become either memory cells or plasma cells. In the SLOs, B cells continue to mature by class switching to produce IgA, IgE, or IgG apart from IgM and IgD and somatic hypermutation of variable domains of BCR to further increase their affinity to a given antigen. The first could occur either in a T-cell–dependent or independent manner that leads to differentiation into the

B-Cell Receptor and IgG Structure
B-cell receptor complex
Igα
Igβ

B cell
Membrane-bound IgM
Antigen binding
site
VL V H
IgG molecule

Fab
CL C H

Heavy

chain

Fc
hain

Light c

f0025
Fig. 105.4 B-Cell Receptor and Immunoglobulin G (IgG) Structure. B-cell surface membrane–bound immunoglobulin M (IgM) associated with antigen-nonspecific signaling molecules, Igα and Igβ, forms the B-cell receptor complex. The IgG molecule is made up of four polypeptide chains, involving two identical light (L) chains (yellow) and two identical heavy (H) chains (green). Each of the four chains has a variable (V) region at its amino terminus (Fab portion), which contributes to the antigen-binding site, and a constant (C) region (Fc portion), which determines the isotype. The V domains contain hypervariable regions that determine antigen specificity called complementarity-determining regions (highlighted in red).

short-lived plasma cells that remain in the SLOs. The latter only ensue in the presence of T helper cells in the germinal centers, which evolve higher affinity B cells into memory cells and plasma cells generating a long-lived humoral immunity. BAFF and APRIL, which are survival

T-Cell– and Antibody-Mediated Rejection
Antibody-Mediated Rejection

T-Cell–Mediated Rejection

Th

BAFF
IL-2
APRIL

BAFF-R
TACI
BCMA
TACI
BCMA

CD40-CD40L

B cell

Th
MHCII-CD4

Cytokines

CTL
IFN-γ
TNF-α
TNF-β

IFN-γ
TNF-α
TNF-β
+
C40L

Perforin
Granzyme
Fas-Fas ligand

Endothelium

Mq

Classical
Complement
Activation

TNF-α
Reactive O2 species
Nitrite oxide

Glomerulitis

Apoptosis and/or
Cell damage
Renal tubular cells

Interstitial inflammation

Tubulitis
Arteritis

f0030

Antibody-mediated
cellular killing

Microvascular inflammation
- Peritubular capillaritis
- Glomerulitis
-Thrombotic microangiopathy
Arteritis

Fig. 105.5 T-Cell–Mediated and Antibody-Mediated Rejection. CD4 T cells induce epithelial and endothelial cell damage directly by secretion of cytokines but also indirectly by activation of cytotoxic T lymphocytes (CTLs) and macrophages. CTLs may cause apoptosis by releasing cytolytic granules containing granzymes and perforin or by exposure of Fas ligand (FasL) on the T-cell surface. Macrophages induce local tissue damage through secretion of cytokines, oxygen species, and nitric oxide (delayed-type hypersensitivity response). CD4 T cells secrete cytokines, which induce upregulation of major histocompatibility complex (MHC) molecules on epithelial and endothelial cells. CD4 T cells also provide help to B cells for production of alloantibody by engagement of CD40L and production of cytokines. BAFF and APRIL induce B-cell development and survival. Antigraft antibody is usually directed at MHC molecules, and it leads to injury either through the activation of the complement pathway or by recruiting innate cytotoxic cells through the Fc receptor binding to the antibody. Damaged endothelial cells secrete factors that activate coagulation systems and result in formation of microthrombi. Exposure of tubular cells and glomerular capillary loops to alloimmunity over time results in interstitial fibrosis, tubular atrophy, and glomerulosclerosis. BAFF-R, BAFF receptor; BCMA, B-cell maturating antigen; CTL, cytotoxic T lymphocytes; IFN, interferon; Mq, macrophages; TACI, T cell activator and calcium modulating ligand interactor; TNF, tumor necrosis factor; Th, T helper cell.

stimulating proteins for B cells, contribute to optimal development of B cells (Fig. 105.5). After their generation, plasma cells locate into bone marrow where a niche for longevity exists.

p0105

B cells express CD-19 and CD-20 starting from pro-B cell and pre-B cell phase, respectively, up to memory B cells. These markers are lost during differentiation into plasma cells and replaced by high expression of CD-38. Given differential expression of these surface markers, rituximab (a monoclonal antibody against CD-20 used to treat antibody-mediated rejection) targets a broad range of B cell stages but excludes primitive B cells and plasma cells.

p0110

There are three effector functions of B-lymphocytes: (1) antibody production, (2) antigen presentation to T cells, and (3) cytokine production. Immunoglobulins function in several different ways once bound to their target antigen: fixation of complement, opsonization for phagocytosis by Fc receptor (FcR)-positive cells (including B cells, NK cells, macrophages, and neutrophils), opsonization for cell lysis by the cells capable of antibody-dependent cellular cytotoxicity (NK cells, macrophages, neutrophils, and eosinophils), and induction of eosinophil degranulation. The five major classes of antibodies are IgM, IgD, IgG, IgA, and IgE. IgG is by far the most abundant immunoglobulin. The IgG molecule is made up of two identical light (L) and two identical heavy (H) chains that form a flexible Y-shaped structure (see Fig. 105.4). Variable (V) regions of each of the four chains contain the antigen specific part (Fab portion), and constant (C) regions determine

HLA Inheritance
Father
A

f0035

B

Mother
DR

B

DR

a

2

44

4

c

3

33

5

b

1

8

3

d

29

44

7

Sibling 2
Sibling 1
Sibling 3
Sibling 4
A B DR
A B DR
A B DR
A B DR
b 1 8
3
b 1 8 3
a 2 44 4 a 2 44 4
c 3 33 5 d 29 44 7

c 3 33
5 d 29 44 7

Fig. 105.6 Example of Human Leukocyte Antigen (HLA) Inheritance. HLA antigens are inherited and expressed in a mendelian codominant fashion, whereby one copy of each HLA gene called a haplotype (e.g., a, b, c, d) is inherited from each parent. Efforts are made to match both class I (HLA-A and -B) and class II (HLA-DR) antigens.

the isotype (Fc portion). The V regions of a given antibody contain hypervariable segments that determine antigen specificity by forming a surface complementary to the antigen referred to as complementaritydetermining regions (CDRs)

s0065

A

ANTIGEN-PRESENTING CELLS

p0115 APCs are specialized cells with capability of activating T cells. DCs, macrophages, and B lymphocytes are considered “professional APCs,” although DCs are the most potent. Professional APCs engulf target antigens by phagocytosis, migrate into T cell areas of lymphoid organs, and present processed antigen on MHC I molecule to CD8 T cells or on MHC II molecule to CD4 T cells (signal 1). As previously explained, costimulation and cytokine signals (signal 2 and 3) are also essential for a successful T-cell stimulation. In the allograft after transplantation, APCs (mostly DCs) of either donor or host origin take up the donor MHC proteins and present to recipient T cells.

p0120

Two most important APCs during transplant rejection are macrophages and DCs. Macrophages are recruited to the graft in response to proinflammatory cytokines, such as IL-1 and IL-6. Th1 and CD8 T cells activate macrophages by producing IFN-γ or binding of CD40L-CD40. As an effector function, macrophages mediate cytolysis by producing TNF-α, oxygen radicals, and nitric oxide. Activated macrophages also can produce IL-12, which directs the differentiation of activated naive CD4 T cells into Th1 effector cells. On the other hand, macrophage activation is inhibited by cytokines such as transforming growth factor-β (TGF-β) and IL-10, many of which are produced by Th2 and regulatory T and B cells. DCs are also part of the mononuclear phagocyte system. As an effector function, DCs release IL-12 and type I and III interferons to induce Th1 differentiation and CD8 T-cell activation.17 18 Lastly, local endothelium and parenchyma could also serve as in situ APCs when they are activated.19

s0070 Natural Killer Cells

p0125 NK cells are a subset of peripheral lymphocytes that share developmental and functional features with CD8 T lymphocytes.20 Unlike T or B cells, NK cells do not possess an antigen-specific cell surface receptor that is generated by gene recombination. Instead, NK cells use receptors that recognize the loss of HLA class I molecules on susceptible targets. Thus, NK cells can recognize when self-MHC class I is absent, the so-called “missing self,” which triggers their activation.

Peripheral NK cells are mature, do not require costimulation or differentiation as with T cells, and immediately release cytotoxic granules and inflammatory cytokines such as TNF-α and IFN-γ on detection of relevant targets. Given the strong cytolytic function and potential for autoreactivity, NK cell activity is tightly regulated. Mechanisms of activation include cytokines, binding of antibody to FcRs, and binding of ligands to activating receptors. In kidney transplantation, NK cells contribute to allograft rejection through antibody-mediated cytotoxicity in the presence of donor-specific antibodies (DSAs) and missing self-mechanism on the allograft cells with HLA class I mismatch.[21]

MAJOR HISTOCOMPATIBILITY COMPLEX AND ALLORECOGNITION

s0075

p0130 The MHC, which encodes HLAs, are the most polymorphic molecules in humans and are made up of closely linked series of genes at the short arm of chromosome 6. MHC genes are inherited in a mendelian codominant fashion (Fig. 105.6) and divided into three regions: class I, II, and III. Class I and II HLAs play a key role in antigen presentation and self-recognition. The key antigens encoded by class I MHC genes include HLA-A, -B, and -C, and the class II gene products include HLA-DP, -DQ, and -DR.

p0135 The class I and II proteins share structural homology but are functionally different[22] (Fig. 105.7). MHC I is designed to sample intracellular proteins to detect tumors or intracellular pathogens, such as virus and intracellular bacteria. It is expressed on all nucleated cells. MHC I–peptide complex is recognized by CD8 T cells, which leads to destruction of target cells. The class II MHC system is designed to sample extracellular proteins that have been taken up by APCs to present to CD4 T helper cells. Class II proteins are expressed by only limited cell types including “professional” APCs (DCs, B cells, macrophages, and Langerhans cells) and by activated parenchymal and endothelial cells. Importantly, both class I and II MHC expression are prompted on allograft cells by IFN-γ in synergy with other cytokines during transplant rejection, which leads to a sustained inflammation. Lastly, certain APCs employ cross-presentation by taking up, processing, and presenting extracellular antigen on their class I MHC molecules to CD8 T cells.[23] This mechanism is used for generation of immunity against tumors and viruses that do not infect APCs.

p0140 In transplantation, recipient T cells encounter alloantigen by either direct, semidirect, or indirect pathways of allorecognition depending on

Structures of MHC Class I and II

α2

α1

β1

α1

α3

β2m

MHC Class I

α1

β2

α2

MHC Class II

α2

α1

β1

α3

α2

β2

β2m

f0040

Fig. 105.7 Structures of Major Histocompatibility Complex (MHC) Classes I and II. MHC class I is composed of a heavy chain divided into α1, α2, and α3 domains noncovalently associated with β2-microglobulin (β2m). The α1 and α2 domains each form a long α helix and β sheet to make up the floor and walls of the peptide-binding groove (peptide indicated by red ribbon). MHC class II is a dimer composed of α and β chains. Each chain is divided into two domains, with α1 and β1 domains forming the two α helices and β-pleated sheet that surround the peptide-binding groove.

recipient’s or donor’s APC involvement (Fig. 105.8). In the direct pathway, donor APCs present their own peptides, most importantly MHC proteins, on their intact MHCs to recipient T cells. The direct pathway may be more active early after transplantation, when a large number of donor APCs are present in the allograft. The direct pathway also occurs later when recipient T cells directly interact with intact donor MHC molecules on the surface of endothelium or parenchymal cells. The indirect pathway is the physiologic mechanism of foreign antigen recognition in which recipient APCs present donor antigens to recipient T cells.24 Lastly, the semidirect pathway involves the transfer of intact donor MHC:peptide complexes from donor APCs or from the graft cells to the surface of recipient APCs to be delivered to recipient T cells, a process called cross-dressing or cell nibbling 25

s0080 Human Leukocyte Antigen Typing and Transplantation

p0145 MHC class I and II genes are highly polymorphic in the regions that encode the peptide-binding groove, leading to thousands of different HLA types (see www.ebi.ac.uk/imgt/hla).26 Mismatched donor HLAs are regarded as foreign antigens by the recipient’s immune system, which predisposes to allograft rejection. Originally, HLA typing was performed by mixing donor or recipient’s lymphocytes with sera from multiparous women or persons who had received blood transfusions. Currently, HLA typing is performed by molecular biology techniques including polymerase chain reaction (PCR) sequencing or nextgeneration sequencing, which allows more precise analysis. Although complete allele matching between donor and recipient would minimize the risk of sensitization against donor kidney, this also reduces likelihood of receiving a transplant offer. Hence, studies compared impact of matching different HLA types on graft survival. Currently, HLA-A, -B, and -DR alleles are used in HLA-matching algorithms, but this could show variation between centers.27 28

In addition to HLA matching, the patient should be screened for p0150 preexisting anti-HLA antibodies (DSA), which are associated with antibody-mediated rejection and poor graft survival. Currently, single antigen bead assay is the preferred method for DSA testing. In this method, patient serum is added to multiple different HLA-coated beads. Binding of antibodies from patient’s serum is detected with a secondary antibody. Potential recipient’s antibody profile is used to

Direct, Semidirect, and Indirect Antigen Presentation
Direct pathway

Semidirect pathway

Lymph node

Lymph node

Lymph node
Donor
MHC TCR

MHC TCR

MHC

Donor
MHC
Kidney Allograft

MHC

Recipient
T cell

Do

Host APC

Donor APC

TCR

Recipient
T cell

no
r
C

Recipient
T cell

f0045

Indirect pathway

Donor APC

Donor
MHC

Host APC

Donor
MHC

Kidney Allograft

Fig. 105.8 Direct, Semidirect, and Indirect Antigen Presentation. In direct allorecognition, donor antigen (shown in red) is presented to recipient T cells as a peptide in the context of intact donor major histocompatibility complex (MHC) molecules on the surface of donor antigen-presenting cells (APCs). In semidirect allorecognition, donor APCs transfer their own peptide-MHC complexes to the surface of recipient APCs (without intracellular processing) that deliver them to recipient T cells. In indirect allorecognition, the donor antigen is processed by recipient APCs and presented as a peptide in the context of recipient MHC molecules.

determine calculated panel-reactive antibody, which gives the percentage of potentially positive-cross matches among the HLA types in a donor pool.29 Defining the presence of specific anti-HLA antibodies may also allow us to perform a virtual crossmatch, which entails verifying the presence of any anti-HLA antibodies that may react against a specific donor HLA antigen. This approach could help exclude potential recipients who may have a positive cross-match test against a specific donor without actually performing the cross-match assay.

s0085 Non–Major Histocompatibility Antigens

p0155 Minor histocompatibility antigens are normal proteins that are polymorphic within a given species. Even when a transplant donor and recipient are identical with regard to MHC genes, amino acid differences in these minor proteins can lead to rejection. Minor antigens are encoded by a large number of chromosomes and are presented only as peptides in the context of recipient MHC (indirect allorecognition). Minor antigens are responsible for the need for immunosuppression after donation between HLA matched but nonidentical twin siblings. The prototypic minor histocompatibility antigen, the male or H-Y antigen, is derived from a group of proteins encoded on the Y chromosome. Alloresponses to this antigen are responsible for the rejection of male mouse skin grafts by otherwise identical female recipients and may explain observations of reduced long-term graft survival in human male-to-female donations. MHC I–related chain A (MICA) antigens are endothelial surface glycoproteins with functions related to innate immunity. Exposure to allogeneic MICA during transplantation was shown to elicit antibody formation.30 ABO blood group glycolipids expressed on endothelial and red blood cells and angiotension-1 receptors are other notable non-MHC antigens.31

Allograft Rejection

s0090

Allograft rejection is defined as tissue injury produced by the effector p0160 mechanisms of the alloimmune response, leading to deterioration of graft function.32 There are two main types of rejection: T-cell–mediated or cellular rejection (TCMR) and antibody-mediated rejection (AMR). Both types of rejection can be early or late, fulminant or indolent, and isolated or concomitant and can share pathologic features on biopsy.1 Kidney allograft biopsies have been evaluated according to the Banff classification, which guides clinicians in treating the different allograft pathologies.33

Allograft rejection is caused by several cellular elements of the p0165 immune system, including T cells, B cells, plasma cells, macrophages, NK cells, and neutrophils. Although there are a variety of target cells in the graft, endothelial and tubular cells are particularly affected by these mediators. T cells serve as the main effectors and regulators of the alloimmune response, and macrophages serve as effectors but also aid in the removal of apoptotic cells. B cells and plasma cells serve in the production of alloantibodies, and neutrophils and NK cells may cause significant damage, particularly during AMR through antibodymediated cell toxicity.21 34

Acute T-Cell–Mediated Rejection

s0095

Acute TCMR starts with the phagocytosis of donor antigens by p0170
either the donor or recipient’s APCs, such as macrophages and DCs
(see Fig. 105.8). Afterwards, APCs migrate into SLOs and activate
naive or memory T cell clones, which then migrate into the allograft.
Inflammation in the allograft microenvironment grow in time by chemotaxis of further macrophages and T cells. Although a small number of B cells may also be present in the TCMR infiltrate, these are
likely recruited nonspecifically.35 The first pathologic event in TCMR

is interstitial inflammation, and this is followed by T cell infiltration of the tubules, causing tubulitis. Thus, interstitial nephritis and tubulitis constitute two core features of TCMR (see Fig. 105.5). Similar inflammation can take place in the arteries causing endarteritis in a minority of cases.

p0175

Deterioration of kidney function during TCMR correlates with tubulitis and arterial inflammation (endothelialitis), which is less common. CTLs can kill target cells by release of cytotoxic molecules (perforin, granzyme B, and granulysin) or engagement of Fas on target cells by FasL. CD4 T-helper cells, especially Th1, release numerous cytokines that affect the alloimmune response. They stimulate macrophages to produce nitric oxide, reactive oxygen species, and TNF-α 36 T-cell cytokines also act directly on parenchymal cells or endothelium. TNFα and TNF-β exert local cytotoxic effects on graft endothelial cells and tubular cells through TNF receptors. IFN-γ, the prototypical Th1 cytokine, induces MHC class II expression on endothelium and MHC class I expression on vascular endothelial cells, epithelial cells, and parenchymal cells in the graft promoting the allorecognition. Production of cytokines such as IL-2 by CD4 T cells provides help for the generation of CTLs from their CD8 T-cell precursors. CD4 T cells may themselves become cytolytic T cells, by mechanisms similar to those used by CD8 CTLs. CD4 T cells also provide help to B cells to enhance their production of alloantibodies. Finally, Foxp3 + CD4 Tregs that are responsible for peripheral immune regulation are concentrated in the tubules during TCMR as a counterregulatory mechanism.

s0100 Acute Antibody-Mediated Rejection

p0180 Acute AMR may develop because of either preexisting antibodies in presensitized patients or de novo antibody formation against donor HLA antigens, which together are called DSAs In de novo antibody formation, donor antigens are shed into the bloodstream and interact with B cells in SLOs, which induce differentiation of naive B cells into memory B cells and plasma cells (see Fig. 105.5). Although AMR typically occurs with antibody response against the donor HLA antigens, it can also occur to non-HLA antigens (minor antigens). Hyperacute rejection, which is most commonly because of the presence of preformed antidonor HLA antibody in sensitized recipients, is a form of AMR that can result in immediate graft failure. This type of AMR is rare now given current anti-HLA testing and crossmatching practices employed by transplant centers.

p0185

Alloantibody-antigen binding mediates graft damage through different mechanisms including opsonization for phagocytosis, opsonization for antibody-dependent cellular cytotoxicity, and fixation of complement.37 The kidney typically shows an accumulation of NK cells, neutrophils, and monocytes in peritubular capillaries (PTCs) and glomeruli (microvascular inflammation), although the infiltrate can be quite sparse.38 As a result of antibody-mediated damage, endothelium release von Willebrand factor and proinflammatory cytokines, leading to platelet aggregation and microthrombi and the aggravation of inflammation.39 40 Endarteritis is another pathologic finding observed in AMR, which could also be seen in TCMR in a lesser degree.41 Tubulitis is generally minimal, unless a component of TCMR is present.

p0190

Only the classical pathway has been shown to participate in acute or chronic AMR. Binding of C1 to alloantibody-antigen complex initiates classical complement cascade. C4b and its inactive fragment C4d are products of the classical pathway. Both contain an occult sulfhydryl group that forms a covalent thioester bond with nearby proteins in the tissue. No functional role for C4d is known, but it remains in the tissue for several days after immunoglobulin and C1 have been released. C4d deposition is strongly associated with circulating antibody to donor

HLA class I or II antigens and is currently the best single marker of

complement-fixing circulating antibodies to the endothelium. C3a and C5a drive chemoattraction of neutrophils and macrophages.42 The membrane attack complex, C5b-9, causes lysis of endothelial cells.

p0195 The current diagnostic criteria for acute AMR include the histologic evidence of acute tissue injury (in the absence of other possible causes), immunopathologic evidence of current/recent antibody interaction with vascular endothelium (e.g., C4d staining or microvascular inflammation), and the evidence of circulating antibody reactive to the donor HLA or minor antigens.

Chronic Rejection

s0105

p0200 Late allograft dysfunction is because of both alloimmune mechanisms (i.e., chronic rejection) and alloimmune-independent mechanisms, including hypertension, calcineurin inhibitor toxicity, and recurrent disease.43 Chronic rejection may occur by either cellular or humoral mechanisms, or both.

p0205 Chronic active AMR is diagnosed in the presence of histologic evidence for chronic injury including transplant glomerulopathy, peritubular capillaropathy, or arteriopathy; immunopathologic evidence of antibody action (e.g., C4d staining), and evidence of circulating antibody reactive to the donor (HLA or minor antigens).38 Transplant glomerulopathy is defined by the widespread duplication or multilamination of the glomerular basement membrane (GBM), sometimes accompanied by mesangial expansion and accumulation of mononuclear cells in glomerular capillaries. Majority of cases of transplant glomerulopathy are associated with circulating DSAs, and approximately 30% of these cases have C4d deposition in the PTCs.44 Absence of C4d deposition in the remainder of cases may represent intermittent antibody involvement or complement-independent antibody-mediated injury. In peritubular capillaropathy, PTCs display multilamination under electron microscopy. Repeated episodes of antibody-mediated injury to the endothelium may result in repair mechanisms characterized by duplication of the basement membrane. What leads to episodic antibody injury is unknown, but fluctuating DSA levels are observed in some patients. Lastly, transplant arteriopathy is characterized by arterial intimal fibrosis without cellular elements, which ultimately narrows vascular lumen, reducing blood flow to the glomeruli and tubules.

p0210 Chronic active TCMR is diagnosed when the histology shows interstitial fibrosis along with at least moderate interstitial inflammation, concurrent tubulitis, and the presence of inflammation in at least 25% of the cortex. An alternative diagnostic criterion is the presence of allograft arteriopathy with arterial intimal fibrosis, mononuclear cell infiltration in the fibrosis, and formation of neointima.45

TRANSPLANTATION TOLERANCE

s0110

p0215 Transplantation tolerance is a state characterized by the absence of a destructive immune response in the recipient toward a wellfunctioning donor allograft, with a fully intact immune system and no exogenous immunosuppression.46,47 As with self-tolerance, transplantation tolerance is achieved through control of T-cell reactivity by both central and peripheral mechanisms. Central tolerance involves thymic deletional mechanisms that eliminate T cells with reactivity against self-antigens (or donor antigens in the case of transplantation tolerance). In experimental transplant models, central tolerance is achieved by elimination of the preexisting mature T-cell population by irradiation and/or cytotoxic agents, followed by infusion of donor hematopoietic progenitor cells. Reconstituted donor antigen “reeducates” the thymus to delete developing T cells with antidonor reactivity, leading to a state of chimerism, in which both donor and recipient cells coexist. Although adult humans lack a thymus, this was translated into the clinical setting with concurrent bone marrow and kidney transplantation

along with transient immunosuppression, which led to promising outcomes in case series.48
p0220
Peripheral tolerance mechanisms include deletion, anergy, and regulation. With self-tolerance, these mechanisms prevent deleterious autoimmune responses from T cells that escape central deletion.
Tregs play a pivotal role in peripheral tolerance. Various approaches to induce peripheral transplant tolerance with the goal of inhibiting deleterious alloimmune responses are currently under investigation, including costimulatory blockade, pharmacologic manipulation of DCs, and the induction of Tregs. Clinical studies indicated that the

selective stimulation of Tregs through IL-2 receptors could induce peripheral tolerance and allow the reduction of the immunosuppression in autoimmunity and potentially transplant recipients.9 11 Most recently, the infusion of ex vivo expanded Tregs in the kidney transplant patients enabled reduction of immunosuppression safely and effectively.10 A hurdle to the development of clinical tolerance strategies is the lack of reproducible immune monitoring assays for tolerance, which would determine when immunosuppressive medications could be safely withdrawn. Although transplantation tolerance is not yet a clinical reality, progress is being made.49 50

SELF-ASSESSMENT QUESTIONS

o0010 1. Which one of the following costimulation molecules on APCs has an inhibitory function on T cells?
o0015
A. B7.1
o0020
B. B7.2
o0025
C. CD40
o0030
D. ICOS-L
o0035
E. PD-L1
o0040 2. Which B-cell development stages are not targeted by rituximab (anti-CD20 antibody)?
o0045
A. Pro-B cell
o0050
B. Pre-B cell
o0055
C. Memory B cell
o0060
D. Plasma cells
o0065
E. A and D
o0070 3. Which of the below options includes the pathologic findings of acute T-cell–mediated rejection?
o0075
A. Peritubular capillaritis, tubulitis, interstitial inflammation
o0080
B. Glomerulitis, peritubular capillaritis, arteritis
o0085
C. Tubulitis, interstitial inflammation, arteritis
o0090
D. Glomerulitis, tubulitis, interstitial inflammation

E. Interstitial inflammation, tubulitis, thrombotic microangiopathy

4. Which one of the following statements is not true regarding HLA genes?

A. HLA genes are inherited in a mendelian codominant fashion.

B. Siblings from the same parents are predicted to have a 50% chance of having zero HLA mismatches.

C. In kidney transplantation, efforts are made to avoid the presence of preformed antibodies against donor HLA antigens.

D. One haplotype of HLA genes is inherited from each parent.

5. Which one of the following statements is not true regarding alloantigen presentation to T cells?

A. T cells recognize alloantigen via direct, indirect, and semidirect pathways.

B. Class II MHC molecules are recognized by CD4 T cells.

C. The MHC class I system is designed to present extracellular proteins taken up and processed by antigen-presenting cells.

D. T cells recognize alloantigen as peptides presented by MHC molecules.

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REFERENCES

1. Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012;93:1–10.
2. Swaminathan S, Griffin MD. First responders: understanding monocytelineage traffic in the acutely injured kidney. Kidney Int. 2008;74:1509–1511.
3. Wood KJ, Bushell A, Hester J. Regulatory immune cells in transplantation. Nat Rev Immunol. 2012;12:417–430.
4. Serhan CN, Brain SD, Buckley CD, et al. Resolution of inflammation: state of the art, definitions and terms. FASEB J. 2007;21(2):325–332.
5. Schwartz RS. Shattuck lecture: diversity of the immune repertoire and immunoregulation. N Engl J Med. 2003;348:1017–1026.
6. Li XC, Rothstein DM, Sayegh MH. Costimulatory pathways in transplantation: challenges and new developments. Immunol Rev. 2009;229:271–293.
7. Willinger T, Freeman T, Hasegawa H, et al. Molecular signatures distinguish human central memory from effector memory CD8 T cell subsets. J Immunol. 2005;175:5895–5903.
8. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008;28:454–467.
9. Saadoun D, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl J Med. 2011;365(22):2067–2077.
10. Sawitzki B, et al. Regulatory cell therapy in kidney transplantation (The ONE Study): a harmonised design and analysis of seven non-randomised, single-arm, phase 1/2A trials. Lancet. 2020;395(10237):1627–1639.
11. Koreth J, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. N Engl J Med. 2011;365(22):2055–2066.
12. Barry M, Bleackley RC. Cytotoxic T lymphocytes: all roads lead to death. Nat Rev Immunol. 2002;2:401–409.
13. Buzza MS, Bird PI. Extracellular granzymes: current perspectives. Biol Chem. 2006;387:827–837.
14. Barry M, Chris Bleackley R. Cytotoxic T lymphocytes: all roads lead to death. Nat Rev Immunol. 2002;2(6):401–409.
15. Al-Lamki RS, Wang J, Skepper JN, et al. Expression of tumor necrosis factor receptors in normal kidney and rejecting renal transplants. Lab Invest. 2001;81:1503–1515.
16. Takeuchi A, Saito T. CD4 CTL, a cytotoxic subset of CD4+ T cells, their differentiation and function. Front Immunol. 2017;8:194.
17. Collin M, McGovern N, Haniffa M. Human dendritic cell subsets. Immunology. 2013;140(1):22–30.
18. Macatonia SE, et al. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. J Immunol. 1995;154(10):5071–5079.
19. Valujskikh A, Lakkis FG. Remembrance of things past: memory T cells and transplant rejection. Immunol Rev. 2003;196:65–74.
20. Young NT. Immunobiology of natural killer lymphocytes in transplantation. Transplantation. 2004;78:1–6.
21. Koenig A, et al. Missing self-induced activation of NK cells combines with non-complement-fixing donor-specific antibodies to accelerate kidney transplant loss in chronic antibody-mediated rejection. J Am Soc Nephrol. 2020.
22. Jones EY. MHC class I and class II structures. Curr Opin Immunol. 1997;9:75–79.
23. Bevan MJ. Cross-priming. Nat Immunol. 2006;7:363–365.
24. Gokmen MR, Lombardi G, Lechler RI. The importance of the indirect pathway of allorecognition in clinical transplantation. Curr Opin Immunol. 2008;20:568–574.
25. Alegre ML, Lakkis FG, Morelli AE. Antigen presentation in transplantation. Trends Immunol. 2016;37:831–843.
26. Gao X, Nelson GW, Karacki P, et al. Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. N Engl J Med. 2001;344:1668–1675.

27. Opelz G. Correlation of HLA matching with kidney graft survival in patients with or without cyclosporine treatment. Transplantation. 1985;40:240–243.
28. Doxiadis II, et al. Simpler and equitable allocation of kidneys from postmortem donors primarily based on full HLA- DR compatibility. Transplantation. 2007;83:1207–1213.
29. Sypek M, et al. HLA epitope matching in kidney transplantation: an overview for the general nephrologist. Am J Kidney Dis. 2018;71(5):720–731.
30. Zou Y, Stastny P, Susal C, et al. Antibodies against MICA antigens and kidney-transplant rejection. N Engl J Med. 2007;357:1293–1300.
31. Farouk S, Zhang Z, Madhav C, Menon. Non-HLA donor–recipient mismatches in kidney transplantation—a stone left unturned. Am J Transplant. 2020;20(1):19–24.
32. Ponticelli C. The mechanisms of acute transplant rejection revisited. J Nephrol. 2012;25:150–158.
33. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. 2018 reference guide to the Banff classification of renal allograft Pathology. Transplantation. 2018;102(11):1795–1814.
34. Scozzi D, et al. The role of neutrophils in transplanted organs. Am J Transplant. 2017;17(2):328–335.
35. Halloran PF. T cell-mediated rejection of kidney transplants: a personal viewpoint. Am J Transplant. 2010;10(5):1126–1134.
36. Halloran PF. T cell-mediated rejection of kidney transplants: a personal viewpoint. Am J Transplant. 2010;10:1126–1134.
37. Rahimi S, Qian Z, Layton J, et al. Non-complement- and complementactivating antibodies synergize to cause rejection of cardiac allografts. Am J Transplant. 2004;4:326–334.
38. Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol. 2007;18:1046–1056.
39. Ota H, Fox-Talbot K, Hu W, et al. Terminal complement components mediate release of von Willebrand factor and adhesion of platelets in arteries of allografts. Transplantation. 2005;79:276–281.
40. Camerer E, Huang W, Coughlin SR. Tissue factor- and factor Xdependent activation of protease-activated receptor 2 by factor VIIa. Proc Natl Acad Sci USA. 2000;97:5255–5260.
41. Lefaucheur C, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. Lancet. 2013;381(9863):313–319.
42. Colvin RB, Smith RN. Antibody-mediated organ-allograft rejection. Nat Rev Immunol. 2005;5:807–817.
43. Womer KL, Vella JP, Sayegh MH. Chronic allograft dysfunction: mechanisms and new approaches to therapy. Semin Nephrol. 2000;20:126–147.
44. Sis B, Campbell PM, Mueller T, et al. Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. Am J Transplant. 2007;7:1743–1752.
45. Haas M, et al. The Banff 2017 Kidney Meeting Report: revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant. 2018;18(2):293–307.
46. Salama AD, Womer KL, Sayegh MH. Clinical transplantation tolerance: many rivers to cross. J Immunol. 2007;178:5419–5423.
47. Newell KA. Clinical transplantation tolerance. Semin Immunopathol. 2011;33:91–104.
48. Kawai T, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. N Engl J Med. 2008;358(4):353–361.
49. Fudaba Y, Spitzer TR, Shaffer J, et al. Myeloma responses and tolerance following combined kidney and nonmyeloablative marrow transplantation: in vivo and in vitro analyses. Am J Transplant. 2006;6:2121–2133.
50. Kawai T, Cosimi AB, Spitzer TR, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. N Engl J Med. 2008;358:353–361.

106
Immunosuppressive Medications in Kidney Transplantation

c0106

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s0010

INTRODUCTION

p0010 Much of the success of kidney transplantation is due to advances in immunosuppressive medications used during the induction and maintenance phases and for treatment of acute rejection.1 The term maintenance immunosuppression is usually used to describe drug regimens consisting of small-molecule agents administered to stable kidney transplant recipients to prevent transplant rejection. Increasingly, physicians outside specialist transplant centers are involved in the care of kidney transplant recipients. In contrast, biologic agents that are used as induction immunosuppression before the maintenance stage or for the treatment of acute rejection episodes are usually managed by specialist transplant physicians.

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SMALL-MOLECULE DRUGS

s0020 Corticosteroids

p0015 Corticosteroids have been a cornerstone of transplant immunosuppression for the past 50 years, both as maintenance immunosuppression and for treatment of acute rejection.

s0025 Mechanism of Action

p0020 Corticosteroids suppress the production of numerous cytokines and vasoactive substances, including interleukin (IL)-1, IL-2, tumor necrosis factor (TNF)-α, major histocompatibility complex class II, chemokines, and proteases. Corticosteroids also cause neutrophilia (often with a left shift), but neutrophil chemotaxis and adhesion are inhibited. Corticosteroids act as agonists of glucocorticoid receptors but at higher doses have receptor-independent effects. Corticosteroid receptors (CRs) belong to a family of ligand-regulated transcription factors called nuclear receptors and are generally present in the cytoplasm in an inactive complex with heat shock proteins. The binding of corticosteroids to the CRs dissociates heat shock protein and forms the active corticosteroid-CR complex, which migrates to the nucleus and dimerizes on palindromic DNA sequences in many genes; this action is called the corticosteroid response element. The binding of CR in the target genes' promoter region can lead to either induction or suppression of gene transcripts (e.g., of cytokines). CRs also exert effects by interacting directly with other transcription factors independent of DNA binding. Corticosteroids influence immune responses by regulating the transcription factors activator protein 1 (AP-1) and nuclear factor-κB (NF-κB). Typically, NF-κB is present as an inactive complex with an inhibitor of NF-κB (IκB), but it can be released by IκB kinase. Corticosteroids limit inflammation by stimulating IκB, which then competes with the IκB–NF-κB complex for degradation by IκB kinase. Corticosteroids also stimulate lipocortin, which inhibits phospholipase A2, thereby inhibiting the production of leukotrienes and prostaglandins. Also, animal data suggest that there may be direct corticosteroid effects on kidney glomerular cells separate from its immunosuppressive effects.2 The net effect of corticosteroids involves immunosuppressive effects on cytokines, adhesion molecules, apoptosis, and inflammatory cells, as well as possible direct effects on glomerular cells.

Pharmacokinetics

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The major corticosteroids used are oral prednisone (or prednisolone) p0025 and oral or intravenous (IV) methylprednisolone. The oral agents have good bioavailability and short pharmacokinetic half-lives (60–180 minutes) but long biologic half-lives (18–36 hours). Corticosteroids are eliminated by hepatic conjugation and are excreted by the kidneys as inactive metabolites. Coadministration of inducers of cytochrome P-450 enzymes that metabolize corticosteroids (e.g., phenytoin, rifampin) decreases corticosteroid half-life, whereas concomitant use of P-450 3A4 inhibitors (e.g., ketoconazole) has the opposite effect. Because corticosteroid levels are not routinely monitored, dosage adjustment during concurrent therapy with these medications is problematic. For treatment of acute rejection, pulse doses of 250 to 500 mg of methylprednisolone are typically used.

Side Effects

s0035

Side effects of corticosteroid therapy are common and associated with p0030 significant morbidity, particularly cataracts, osteoporosis, and avascular necrosis, especially of the femoral head (Table 106.1). Other side effects include hypertension, increased appetite with weight gain, hyperglycemia, hyperlipidemia, cushingoid features, acne, skin striae, psychiatric disturbances, sleep disorders, peptic ulcer disease, pancreatitis, colonic perforation, growth retardation, and myopathy. Infection risk is also increased and is excessive if high-dose therapy is prolonged. Interestingly, corticosteroids are not associated with an increased incidence of malignancy. Although corticosteroids are generally considered safe in pregnancy, fetal adrenal suppression has been reported. Rapid corticosteroid reduction protocols with low maintenance doses (5–10 mg/day of prednisone) can improve corticosteroid tolerability by ameliorating many of these side effects. Withdrawing corticosteroids altogether is another strategy that has been implemented to minimize these side effects, especially in selected low-immunologic risk patients.3 This was demonstrated by a recent trial comparing rabbit antithymocyte globulin (ATG) to basiliximab induction therapy with rapid steroid withdrawal. Not only was rabbit ATG nonsuperior to basiliximab for the prevention of biopsy-proven acute rejection after steroid withdrawal within 1 year after kidney transplantation, for patients with low immunologic risk, rapid steroid withdrawal was achieved without loss of efficacy and with lower risk of post-transplant diabetes.4 However, most transplant centers advocate for low-dose maintenance steroids, especially in those at high risk for adverse outcomes, such as those highly sensitized and those who may experience delayed graft function, in

t0010

Hyperlipidemia,
hyperuricemia, gout,
glucose intolerance

Gingival hyperplasia,
coarsened facial
features
Encephalopathy,
insomnia, myopathy,
tremors
Edema

Metabolic

Dermatologic

Tacrolimus

Encephalopathy,
insomnia, myopathy,
tremors
Myocardial
hypertrophy

Alopecia

New-onset diabetes

Thrombotic
microangiopathy

Nephrotoxicity,
type 4 RTA, HTN,
diuretic resistance,
hyperkalemia,
hypomagnesemia,
hypophosphatemia
Diarrhea, abdominal
pain

Viral infections,
pulmonary edema in
elderly

Progressive multifocal
leukoencephalopathy

Diarrhea, nausea and
vomiting, gastritis,
esophagitis, oral
and colonic ulcers
Anemia, leukopenia,
thrombocytopenia

Mycophenolate

Nausea and
vomiting,
hepatotoxicity,
pancreatitis
Anemia, leukopenia,
thrombocytopenia

Azathioprine

Cataracts

Hyperlipidemia, hyperuricemia, hyperglycemia, osteoporosis, avascular necrosis, increased appetite and weight gain
Hirsutism, acne, cushingoid facies, buffalo hump
Psychosis, insomnia, myopathy

Leukocytosis, polycythemia

Peptic ulcers, gastritis, esophagitis, diarrhea, colonic perforation

HTN, hypokalemia, diuretic resistance

Corticosteroids

mTOR Inhibitors

Lymphocele, interstitial pneumonitis, rash, edema

Reflex sympathetic dystrophy

Impaired wound healing, oral ulcers

Thrombotic microangiopathy, anemia, thrombocytopenia
Hyperlipidemia

Diarrhea

Synergistic nephrotoxicity with CNIs, delayed recovery from ATN, proteinuria, hypokalemia, HTN

ATN, Acute tubular necrosis; CNIs, calcineurin inhibitors; HTN, hypertension; mTOR, mammalian target of rapamycin; RTA, renal tubular acidosis.

Other

Neurologic

Thrombotic microangiopathy

Nephrotoxicity,
type 4 RTA, HTN,
diuretic resistance,
hyperkalemia,
hypomagnesemia,
hypophosphatemia

Cyclosporine

Side Effects of Small-Molecule Immunosuppressive Medications

Hematologic

Gastrointestinal

Kidney

TABLE 106.1

Alopecia, rash

Anemia,
leukopenia

Nausea,
diarrhea,
hepatitis

Leflunomide

Tacrolimus Drug Levels

Calcineurin Inhibition

Peak (Cmax)

Immediate release
Extended release

Dose

Calcium

Calcineurin

P

Unbound
Immunophilin

Inhibition
Calcineurin

NF-AT

P
Dephosphorylation

Concentration (ng/mL)

Normal

Translocation

P

Trough (C0)

AUC

Cyclosporine
Tacrolimus

0

f0010

Nucleus

Fig. 106.1 Calcineurin Inhibition. During normal T-cell activation, calcium release activates calcineurin’s phosphatase activity, causing dephosphorylation of the transcription factor, nuclear factor of activated T cells (NF-AT), and subsequent translocation to the nucleus. Cyclosporine and tacrolimus form a complex with immunophilins (cyclophilin or FK-binding protein 12, respectively), which bind calcineurin and sterically inhibit the phosphatase activity, preventing dephosphorylation and nuclear translocation of NF-AT.

which early glucocorticoid withdrawal has been associated with an increased risk of allograft loss.5

s0040 Calcineurin Inhibitors

p0035 Calcineurin inhibitors (CNIs), including cyclosporine and tacrolimus, are fungus-derived lipid-soluble small molecules that are the mainstay of current maintenance immunosuppression. Considerable variability exists in their pharmacokinetics, interactions, and side effect profiles, which raises the question of which agent to use in the individual patient. Cyclosporine is a cyclic, lipophilic undecapeptide with several N-methylated amino acids, which may explain its resistance to inactivation in the gastrointestinal (GI) tract. Tacrolimus is a macrolide lactone antibiotic.

s0045 Mechanism of Action

p0040 CNIs exert their effect by binding to cytoplasmic proteins called immunophilins (Fig. 106.1). Cyclosporine binds to cyclophilin, and tacrolimus binds to FK-binding protein 12 (FKBP12).6 Such binding enhances immunophilin affinity for and subsequent inhibition of calcineurin, which is a calmodulin-activated serine phosphatase important for dephosphorylation of inactive nuclear factor of activated T cells (NFAT). Nuclear translocation of dephosphorylated (active) NF-AT, in association with other transcription factors, initiates downstream events, leading to T-cell activation. The tacrolimus-FKBP12 complex inhibits calcineurin with greater molar potency than the corresponding cyclosporine complex. Cyclosporine and tacrolimus can interfere with calcineurin's activation on substrates other than NF-AT, which likely explains many of their side effects. Treatment with CNIs also causes upregulation of the cytokine transforming growth factor-β (TGF-β), which has significant immunosuppressive properties but also promotes the production of matrix proteins and tissue fibrosis. CNIs can suppress the immune response by calcineurin-independent pathways, likely by blocking intracellular signaling pathways specific to T cells. These agents' ability to interfere with two distinct mechanisms of T-cell activation contributes to their highly specific immunosuppressive properties.

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12

Time (h)

f0015

Fig. 106.2 Drug Levels During a Dosing Interval Using Either Immediate- or Extended-Release Tacrolimus. The drug concentration is lowest just before the dose is taken (C 0), then rises to a peak concentration at a certain time after the dose (C max). The area under the

concentration-time curve (AUC) describes total drug exposure during the entire administration interval.

Pharmacokinetics, Monitoring, and Drug Interactions

s0050

After a dose of CNI, there is an initial absorptive phase, during which p0045
blood concentrations reach a peak level (Cmax).[7] Typically, Cmax occurs during the first 2 to 3 hours after the dose and corresponds to the time of maximum calcineurin inhibition. Drug levels then fall because of metabolism (also known as the elimination phase) until they are at the trough level (C0) immediately before the next dose. The total drug exposure throughout the period from one dose until the next is the area under the concentration-time curve (AUC; Fig. 106.2).

For both CNIs, most of the interpatient and intrapatient vari- p0050
ability occurs in the absorption rather than in the elimination phase. The oil-based formulation of cyclosporine requires solubilization in bile and is plagued by highly variable and unpredictable bioavailability. The microemulsion preparation of cyclosporine (modified) has enhanced bioavailability and less dependence on bile secretion. In blood, cyclosporine resides primarily in erythrocytes (60%–70%) and leukocytes, with some binding to lipoproteins and, to a lesser extent, other plasma proteins. Cyclosporine is metabolized primarily by CYP3A4, a member of the cytochrome P450 superfamily.
Metabolism occurs mostly in the liver. Interindividual differences in CYP3A4 activity and the large number of exogenous and endogenous substances capable of altering its function and expression explain the wide variation in clearance rates. One factor is the multidrug resistance 1 gene product, P-glycoprotein, which is variably expressed in the intestine and reduces the absorption of several xenobiotics, including CNIs, by transport out of intestinal epithelial cells. The average half-life of cyclosporine is about 19 hours, with excretion primarily in bile. Generic formulations of modified cyclosporine exist, although they may not have identical pharmacokinetics and therefore may not be readily interchangeable.

The absorption of tacrolimus, like that of cyclosporine, is highly vari- p0055
able, with bioavailability ranging from 5% to 67%. Absorption is not bile dependent but does depend on GI transit time and is affected by the presence or absence of food and the lipid content of food. Clearance appears to be faster in children, necessitating higher or more frequent dosing. In the United States, Black and Hispanic patients also require higher doses than White patients to achieve equivalent therapeutic

levels, likely because of genetic differences in subtypes of CYP3A, such as CYP3A5 (faster metabolism of CNIs).8 Similarly, higher tacrolimus dose requirements were reported for non-White Brazilian transplant recipients and for Black transplant recipients in the United Kingdom.9 10

p0060

In blood, tacrolimus distributes primarily to erythrocytes, with whole-blood concentrations 10 to 30 times higher than in plasma. In contrast to cyclosporine, no lipoprotein binding occurs. Tacrolimus has 20- to 30-fold higher potency than cyclosporine on a molecular weight basis. Like cyclosporine, metabolism occurs through the CYP3A4 system, with pharmacokinetics also affected by intestinal P-glycoprotein. Both CNIs are generally administered twice daily, but newer slow-release formulations for tacrolimus are now available with once-a-day dosing and reduced peak levels, with potential benefits in lowering side effects such as tremor (reduced peak) and improvement in compliance (see Fig. 106.2). Because of the narrow therapeutic index for CNIs, the variability of concentrations among patients after a dose, and the potential for drug interactions, monitoring of drug levels is required to ensure both safety and adequacy.

p0065

Given the complementary influence of both CYP3A4 and P-glycoprotein on the pharmacokinetic profiles of CNIs, it is assumed that CNI-drug interactions on both CYP3A4 and P-glycoprotein have similar complementary effects on CNI pharmacokinetics. Drugs that competitively inhibit CYP3A4 activity, such as ketoconazole, usually also inhibit P-glycoprotein, thereby increasing the bioavailability of CNIs, with potential for toxicity. Likewise, drugs such as phenytoin that increase CYP3A4 levels tend to upregulate P-glycoprotein, decreasing overall bioavailability. In this case the likelihood of rejection increases. Diarrhea may increase the absorption of CNIs by affecting P-glycoprotein transport in the gut, and monitoring of CNI levels is recommended in the setting of persistent diarrhea for more than 3 days. Despite similar drug interactions, the age-related and ethnic differences in pharmacokinetics between the two CNIs are likely to influence the degree and importance of such interactions. Common interactions are presented in Box 106.1

s0055 Side Effects

p0070 Cyclosporine and tacrolimus have similarities and differences in their toxicity profiles (see Table 106.1). Both can cause nephrotoxicity, hyperkalemia, hyperuricemia, hypomagnesemia and hypophosphatemia (secondary to urinary loss), type 4 renal tubular acidosis, hypertension, diabetes, and neurotoxicity. Gingival hyperplasia, hirsutism, hypertension, hyperuricemia, and hyperlipidemia are more common with cyclosporine, whereas tremor and glucose intolerance are more common with tacrolimus. The most common and vexing problem with CNIs is nephrotoxicity, with its importance evident from heart and liver transplant recipients, in whom CNIs were associated with progression to end-stage kidney disease. Both reversible hemodynamic and irreversible structural components underlie the nephrotoxicity of CNIs. Reversible vasoconstriction is caused by direct vascular effects but is also because of activation of the renin-angiotensin system (RAS), endothelin, thromboxane, and the sympathetic nervous system. Over time, chronic kidney injury occurs, characterized by afferent arterial hyalinosis and tubulointerstitial fibrosis, presumably as the result of prolonged kidney vasoconstriction with ischemia and direct tubular toxicity. Finally, CNIs can cause thrombotic microangiopathy (TMA) in a minority of cases, probably by direct endothelial cell injury and dysfunction.

s0060 Mycophenolate

p0075 Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) are important components of immunosuppressive regimens that are associated with some of the most successful outcomes in kidney transplantation.11 Because of its well-documented

BOX 106.1 Drugs and Other Substances That Interact With Calcineurin Inhibitors

Increase Blood Levels (P450-3A4 and/or P-Glycoprotein Inhibitors)

- Ketoconazole
- Fluconazole
- Itraconazole
- Voriconazole
- Erythromycin
- Clarithromycin
- Diltiazem
- Verapamil
- Nicardipine
- Cimetidine
- Methylprednisolone
- Metronidazole
- Ezetimibe
- Metoclopramide
- Fluvoxamine
- Human immunodeficiency virus (HIV) protease inhibitors
- Lovastatin
- Atorvastatin
- Simvastatin
- Grapefruit juice
- Chamomile
- Wild cherry

b0010

Decrease Blood Levels (P450-3A4 and/or P-Glycoprotein Inducers)

- Rifampin
- Rifabutin
- Phenytoin
- Carbamazepine
- Phenobarbital
- Caspofungin
- St. John’s wort

efficacy and acceptable side effect profile, MMF is by far the most frequently used antiproliferative agent and is commonly used in combination with CNIs.

Mechanism of Action

s0065

The immunosuppressive effects of mycophenolate are likely mediated p0080 through the active metabolite mycophenolic acid (MPA). MMF is a morpholinoethyl ester of MPA, a potent reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), isoform 2. EC-MPS is a salt that combines an acid (MPA) with a base (sodium). The enteric coating delays MPS release so that the MPA is absorbed in the small intestine rather than in the stomach. MPA noncompetitively inhibits IMPDH, which is the rate-limiting enzyme in the de novo synthesis of guanosine monophosphate (GMP). Inhibition of IMPDH creates a relative deficiency of GMP and a relative excess of adenosine monophosphate (AMP). GMP and AMP levels act as a control on de novo purine biosynthesis; therefore MPA, by inhibiting IMPDH, blocks de novo purine synthesis, which selectively interferes with proliferative responses of T and B cells. Some other cell types, such as GI epithelial cells, use the de novo pathway. Thus, MPA may inhibit replication of GI epithelial cells, leading to the disruption of fluid absorption and diarrhea. However, most other cell types depend primarily on the alternative pathway for DNA synthesis and cell division and thus are relatively spared from toxicity.

s0070 Pharmacokinetics

p0085 MMF is absorbed rapidly and completely from the GI tract and undergoes extensive presystemic deesterification to become MPA, the active form. Food intake can delay the rate of MMF absorption but does not affect the extent. However, coadministration of antacids (proton pump inhibitors), calcium, or cholestyramine decreases absorption by 20% to 40%. EC-MPS has shown bioavailability equivalence and similar efficacy to that of MMF. MPA undergoes enterohepatic circulation, and its plasma concentration shows a secondary peak at 6 to 12 hours after oral administration. The mean contribution of enterohepatic circulation to the overall AUC of MPA is 37% (range, 10%–61%). Most MPA is metabolized in the liver through a phase II glucuronidation process.

p0090

The major metabolite of MPA is the pharmacologically inactive 7-O-glucuronide metabolite (MPAG), although two other metabolites, MPA-acylglucuronide (AcMPAG) and MPA-phenyl-glucoside (glucoside-MPA), are isolated from the plasma of kidney transplant patients. AcMPAG has shown in vitro pharmacologic activity (inhibition of IMPDH) and proinflammatory effects and potentially is responsible for the GI toxicity of MPA. The glucuronide metabolites are excreted into the bile, a process mediated by the multidrug resistance–related protein 2 (MRPR2), then undergo deglucuronidation back to MPA by enzymes that are produced by colonic bacteria. Blockade of MRPR2 by an inhibitor, such as cyclosporine but not tacrolimus, decreases the biliary excretion of MPAG and increases plasma MPAG levels. This eventually leads to lower plasma levels of MPA because the glucuronide metabolites no longer can be reabsorbed as MPA by enterohepatic cycling. Thus, tacrolimus-treated patients have higher exposure to MPA than cyclosporine-treated patients. The ultimate elimination pathway for the glucuronide metabolites is through the kidney, and more than 95% of an administered dose eventually is found in the urine as glucuronide metabolites. For the most part, MMF and EC-MPS are used in fixed-dose regimens. No studies in transplantation have shown that monitoring MPA drug AUC or trough levels reduces the rejection rate or minimizes toxicity.

s0075 Side Effects

p0095 MMF and EC-MPS have similar side effect profiles, including GI toxicity, bone marrow suppression, and increased infections, especially those of viral cause (see Table 106.1). GI disturbances include oral ulcerations, esophagitis, gastritis, nausea, vomiting, diarrhea, and colonic ulcers. Diarrhea and leukopenia frequently necessitate a dose reduction that could precipitate allograft rejection. Because the metabolites of MPA appear to play a major role in the GI disturbances associated with MMF, there is little rationale for enteric coating of the prodrug to reduce these symptoms. In fact, randomized controlled trials (RCTs) have found no significant difference in GI adverse events between MMF and EC-MPS.12–14 MMF is generally avoided during pregnancy because of its teratogenicity in experimental animal models and clinical reports of major fetal malformations.

s0080 Azathioprine

p0100 The use of azathioprine has decreased dramatically in kidney transplantation since the introduction of MMF. Azathioprine is metabolized in the liver to 6-mercaptopurine and further converted to the active metabolite thioinosinic acid by hypoxanthine-guanine phosphoribosyltransferase. Because allopurinol (a xanthine oxidase inhibitor) increases levels of thioinosinic acid and can lead to life-threatening bone marrow suppression, the dose of azathioprine must be substantially reduced or azathioprine substituted with another agent—commonly MMF—in patients taking allopurinol. Azathioprine suppresses the proliferation of activated T and B cells and reduces the number of circulating monocytes by arresting the cell cycle of promyelocytes in the bone marrow. The antiproliferative effect is mediated by the metabolites of azathioprine, including 6-mercaptopurine, 6-thiouric acid, 6-methylmercaptopurine, and 6-thioguanine. These compounds are incorporated into replicating DNA and halt replication. They also block the de novo pathway of purine synthesis by formation of thioinosinic acid; this effect confers specificity of action on lymphocytes that lack a salvage pathway for purine synthesis. The major side effect of azathioprine is bone marrow suppression, leading to leukopenia, thrombocytopenia, and anemia (see Table 106.1), with potentially lifethreatening complications arising from the concurrent use of azathioprine and xanthine oxidase inhibitors such as allopurinol. The mean cell volume is commonly increased in patients taking azathioprine, and red cell aplasia occasionally can occur. The hematologic side effects are dose-related and usually reversible on dose reduction or temporary discontinuation of the drug. Other common side effects are increased risk for malignancy (especially skin cancers), hepatotoxicity, pancreatitis, and hair loss.

Mammalian Target of Rapamycin Inhibitors

s0085

Mammalian target of rapamycin (mTOR) inhibitors are proliferation p0105 signal inhibitors with immunosuppressive activity. Sirolimus, also known as rapamycin, was the first mTOR inhibitor used in transplantation and is a macrolide product of a soil fungus discovered on Easter Island.15 Everolimus is a rapamycin analog with a similar mechanism of action, immunosuppressive properties, and side effect profile. Although initially used in drug regimens with the intent of minimizing exposure to CNIs with its known side effects, the mTOR inhibitors have been associated with their own set of toxicities that have prevented their widespread use. A recent study failed to demonstrate noninferiority of everolimus compared with MPA in groups with similar tacrolimus or cyclosporine exposure in terms of mean estimated glomerular filtration rate (eGFR) 12 months after transplant.16 Many trials using mTOR inhibitors in place of CNIs revealed a higher risk of kidney transplant rejection and variable improvement in kidney function.17–21 Lastly, trials using mTOR inhibitor in place of MMF have suggested a lower risk of opportunistic viral infections, such as cytomegalovirus.22

Mechanism of Action

s0090

Sirolimus has a structural similarity to tacrolimus and binds to FKBP12. p0110 The affinity of sirolimus for FKBP12 is higher than that of everolimus. mTOR inhibitors do not inhibit calcineurin or the calcium-dependent activation of cytokine genes but instead inhibit cytokine receptor–mediated signal transduction and cell proliferation that block lymphocyte responses to cytokines and growth factors. The sirolimus-FKBP12 or everolimus-FKBP12 complex binds with high affinity to the kinase enzyme mTOR, which is a serine-threonine kinase of the phosphatidylinositol 3–kinase pathway that acts during costimulatory and cytokine-driven pathways. mTOR inhibits a translation repressor protein (4E-BP1) and activates a ribosomal enzyme (p70-S6 kinase), both of which are important for translation of the mRNAs for certain proteins needed for progression from the G1 phase to the S phase of DNA synthesis. mTOR has been identified as the principal controller of cell growth and proliferation. The sirolimus-FKBP12 complex inhibits mTOR-mediated signal transduction pathways by blocking postreceptor immune responses to costimulatory signal 2 during G0 to G1 transition and to cytokine signaling during G1 progression. It also inhibits IL-2– and IL-4–dependent proliferation of T and B cells, leading to suppression of new ribosomal protein synthesis and arrest of the G1-S phase of the cell cycle. Proliferation of nonimmune cells, such as fibroblasts, endothelial cells, hepatocytes, and smooth muscle cells, is also impaired by inhibition of the growth factor–mediated responses (e.g., basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial cell growth factor, and TGF-β). In addition, mTOR contributes to several protein synthesis pathways that could be involved in oncogenesis.

Mouse Antibody

V
V

C

C

C

C

V
V

V
C

C

V

V

C C

C C

C C

C C

Chimeric Antibody

Humanized Antibody

V
V
C

V
C

C

V

V

V
C

C

C

C

V

V

BIOLOGIC AGENTS

p0130 Biologic agents in the form of polyclonal antibodies and monoclonal antibodies (mAbs) are frequently used in kidney transplantation either as induction therapy or for the treatment of rejection. Polyclonal antibodies are derived from horses or rabbits; historically, mAbs have been murine in origin. However, because foreign proteins can elicit an immune response, there has been an attempt to replace murine monoclonal products with humanized or chimeric mAbs (Fig. 106.3). Humanized antibodies are produced by merging the DNA that encodes the antigen-binding portion of a monoclonal mouse antibody with human antibody–producing DNA. Mouse hybridomas are then used to express this DNA to produce hybrid antibodies that are not as immunogenic as the murine variety. Chimeric antibodies use the same

Variable
Region

C

s0105

Antigen Binding
Site

CDR
C

s0100 Side Effects

p0125 The mTOR inhibitors have a wide variety of toxicities (see Table 106.1). The most common adverse effects associated with sirolimus are dose-dependent hypertriglyceridemia, anemia, thrombocytopenia, and leukopenia. Other adverse effects include impaired wound healing and dehiscence, formation of lymphoceles, oral ulcers, reduced testosterone levels, proteinuria, diarrhea, and pneumonitis. Although not inherently nephrotoxic, the mTOR inhibitors result in kidney graft damage through several mechanisms. When used in combination with full-dose cyclosporine (and probably tacrolimus), sirolimus potentiates CNI-induced nephrotoxicity. In patients with kidney impairment, sirolimus is associated with marked yet potentially reversible proteinuria and worsening of established proteinuria. Sirolimus also can cause delayed recovery from acute tubular necrosis and may be linked to podocyte injury and focal segmental glomerulosclerosis. Finally, cases of TMA have been reported, and there is concern that higher doses of sirolimus may inhibit endothelial cell growth. Interestingly, sirolimusbased regimens have been associated with a reduced incidence of post-transplantation malignancy. Some physicians regard sirolimus as the preferred immunosuppressive agent in transplant patients who develop malignancy because of data suggesting that mTOR inhibitors may reduce the risk of malignancies23 24; however, most data are limited to kidney transplant recipients with squamous cell skin cancer.25 26 Sirolimus is not routinely used during pregnancy because of its teratogenicity in animal models, although successful pregnancies have been reported.

Human Antibody

V

s0095 Pharmacokinetics

p0115 The oral bioavailability of sirolimus is poor (10%–16%), with significant interindividual and intraindividual variability. Peak concentrations occur approximately 1 to 2 hours after an oral dose, and sirolimus distributes extensively into tissues, including blood cells. The oral bioavailability of everolimus is higher than that of sirolimus. High-fat meals increase sirolimus levels while decreasing everolimus levels. Because sirolimus has a relatively long half-life (~62 hours), it is reasonable to wait 1 week (approximately three half-lives to achieve steady state) before monitoring sirolimus blood levels after initiation or dose adjustment. Sirolimus is metabolized by the P-450 3A4 isoenzyme and P-glycoprotein system and thus has interactions similar to those described for CNIs (see Box 106.1).

p0120

When an mTOR inhibitor is administered simultaneously with cyclosporine, the Cmax and AUC for both compounds are increased. Also, cyclosporine clearance may be reduced during concurrent therapy.

Chimeric and Humanized
Monoclonal Antibodies

C

1174

C C

C C

C C

C C

f0020

Fig. 106.3 Chimeric and Humanized Antibodies. Chimeric antibodies consist of human constant (C) regions and mouse variable (V) regions. A chimeric antibody therefore retains the antigen binding site of the mouse antibody but with fewer amino acid sequences foreign to the human immune system than a standard mouse antibody. Humanized monoclonal antibodies retain only the minimum necessary parts of the mouse antibody for antigen binding, the complementarity-determining region (CDR, highlighted in red), and therefore are even less immunogenic in the human host.

strategy but for the entire variable region and thus are more immunogenic than humanized antibodies. Polyclonal antibodies and mAbs can be depleting agents or immune modulators.

Polyclonal Antilymphocyte Sera

s0110

Polyclonal antilymphocyte agents are produced by immunizing animals with human thymus–derived lymphoid cells. Although rabbit ATG is currently the preferred preparation, equine preparations historically have been used. Most regimens involve daily IV administration of ATG for 3 to 4 days either as induction therapy or for treatment of corticosteroid-resistant rejection. ATG contains antibodies that react against a variety of targets, including red blood cells, neutrophils, dendritic cells, and platelets. ATG binds to multiple epitopes on the surface of T cells and induces a rapid lymphocytopenia by several mechanisms, including complement-dependent cytolysis, cell-dependent phagocytosis, and apoptosis. ATG is a potent immunosuppressive, and T- and B-lymphocyte counts can remain depressed p0135 up to 24 hours after administration. The lack of specificity coupled with marked immunosuppression increases the risk for infection and cancer. Because polyclonal agents are xenogeneic proteins, they may elicit a number of side effects, including fever and chills. The initial lysis and activation of T cells that follow ATG administration may generate significant side effects after the first dose with the release of TNF-α, interferon-γ (IFN-γ), and other cytokines. Therefore, steroids are frequently used before ATG infusion. Less commonly, ATG can induce a serum sickness–like syndrome and, rarely, acute respiratory distress syndrome.

s0115 Humanized Monoclonal Anti-CD52 Antibody

p0140 Alemtuzumab is a humanized IgG1 mAb directed against CD52, a glycoprotein found on circulating T and B cells, monocytes, macrophages, natural killer cells, and granulocytes. Alemtuzumab was originally approved for the treatment of B-cell chronic lymphocytic leukemia, but it has been used off label as an induction agent in kidney transplantation. Treatment results in a rapid and effective depletion of peripheral and central lymphoid cells, which may take months to return to pretransplantation levels. Side effects of alemtuzumab include first-dose reactions, neutropenia, anemia, and rarely, pancytopenia and autoimmunity (e.g., hemolytic anemia, thrombocytopenia, and hyperthyroidism). The risks for immunodeficiency complications such as infection and malignant neoplasia with alemtuzumab appear to be similar to ATG.

s0120 Monoclonal Anti-CD25 Antibody

p0145 The alpha subunit of the IL-2 receptor (CD25) is upregulated on activated T cells and leads to the expression of high-affinity IL-2 receptors. The engagement of IL-2 receptors by IL-2 triggers the activated T cell to undergo proliferation. Basiliximab is a chimeric mAb with a specificity for CD25; it induces relatively mild immunosuppression and is used as an induction agent to prevent rejection but not to treat established rejection.27,28 Although the exact mechanism of action is not fully understood, it is clear that significant depletion of T cells does not play a major role. Saturation of the IL-2 receptor alpha subunit persists for up to 25 to 35 days after treatment with basiliximab. Although saturation is important as a determinant of minimal blood concentrations, it is not predictive of rejection. No major side effects have been associated with anti-CD25 induction compared with transplant recipients receiving no anti-CD25 induction.

s0125 B-Cell–Depleting Monoclonal Anti-CD20 Antibody

p0150 Rituximab is an engineered chimeric mAb that contains murine heavyand light-chain variable regions directed against CD20 plus a human IgG1 constant region.29 The CD20 antigen, a transmembrane protein, is found on immature and mature B cells and on malignant B cells. CD20 mediates proliferation and differentiation of B cells. Rituximab directly inhibits B-cell proliferation and induces apoptosis and lysis by complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and activation of tyrosine kinases as a direct effect of the antibody binding to its CD20 ligand. Rapid and sustained depletion of circulating and tissue-based B cells occurs after IV administration, and recovery does not begin until approximately 6 months after treatment. Although plasma cells are usually CD20 negative, many are short lived and require replacement from CD20-positive precursor cells. In addition, CD20-positive B cells can act as secondary antigen-presenting cells (APCs), thereby enhancing T-cell responses. Thus, by targeting CD20 on precursor B cells, rituximab decreases the production of activated B cells and limits their antibody production and antigen presentation capability. Most adverse events are first-infusion effects, such as fevers and chills, and are generally of mild severity, becoming less frequent with subsequent infusions. Viral infections, including reactivation of hepatitis B virus and JC virus, have been reported, although it is not known whether these events are specific to the agent or instead reflect the overall state of immunosuppression. Antichimeric antibodies develop in some patients, but their true incidence and therapeutic significance are uncertain. Rituximab has been used in kidney transplantation to treat antibody-mediated rejection and in combination with IV immunoglobulin (IVIG) to reduce high-titer anti–human leukocyte antigen (anti-HLA) antibodies in highly sensitized patients awaiting kidney transplantation.30 Rituximab is also used as induction therapy after desensitization therapy for ABO blood group–incompatible and high-risk positive crossmatch kidney transplantation. Finally, rituximab is often used to treat post-transplantation lymphoproliferative disease. A phase 1b study assessing the safety, pharmokinetics, and pharmacodynamics of obinutuzumab, a novel type 2 anti-CD20 monoclonal antibody in highly sensitized patients with kidney failure, demonstrated good tolerability and effective depletion of B lymphocytes. However, its effect on reductions in anti-HLA alloantibodies were inconsistent and not clinically meaningful.31

Intravenous Immunoglobulin

s0130

IVIG products are known to have powerful immunomodulatory p0155 effects in inflammatory and autoimmune conditions. The mode of action of IVIG is not well understood. In kidney transplantation, the most important effect appears to be a reduction of alloantibodies through inhibition of antibody production and increased catabolism of circulating antibodies. Additional potential mechanisms include inhibition of complement-mediated injury, inhibition of inflammatory cytokine generation, and neutralization of circulating antibodies by anti-idiotypes. Side effects related to IVIG administration include minor self-limited reactions, such as flushing, chills, headache, myalgia, and arthralgia. Rarely, anaphylactic reactions may occur. Delayed reactions include severe headache and aseptic meningitis, which respond to analgesics. More recently, severe thrombotic events have been linked to the administration of IVIG products. Osmotic injury of the proximal tubular epithelium can occur after administration of sucrose-containing IVIG preparations. This tubular injury is self-limited and can be minimized or avoided by use of sucrosefree preparations and by slowing rate of infusion. In combination with plasma exchange, IVIG appears to offer significant benefits in the desensitization of positive-crossmatch and ABO-incompatible patients to allow successful transplantation as well as in the treatment of antibody-mediated rejection. Alone or in combination with rituximab, IVIG has been successful in the desensitization of highly sensitized waitlisted patients to increase the chances of finding a compatible donor.

Belatacept

s0135

Costimulation blockade is an immunosuppression alternative for p0160 kidney transplant recipients. Belatacept, a first-in-class costimulation blocker, is a fusion protein that binds to CD80 and CD86 on APCs to prevent T cell activation and proliferation (Fig. 106.4). The drug primarily affects the costimulatory CD28 pathway, preventing full T-cell activation. Belatacept was initially approved by the U.S. Food and Drug Administration (FDA) for de novo kidney transplantation only in Epstein-Barr virus (EBV)-seropositive adult patients because of concerns that administering belatacept might increase the risk for early post-transplant lymphoproliferative disorder (PTLD) in EBVseronegative patients. Also, it has been used off label for conversion from CNIs after kidney transplantation, in particular in patients intolerant to CNIs. Converting from CNIs to belatacept has been associated with a higher risk of rejection when done in the first year after transplant in sensitized patients; however, there was no difference in rejection-free, patient, or graft survival over 5 years.32 Other potential benefits of conversion include improved glycemic parameters in those with diabetes33 and improved kidney function in those with chronic vascular lesions34 on kidney biopsy. Side effects of belatacept include anemia and leukopenia. Rare but serious side effects include progressive multifocal leukodystrophy and PTLD.

In the phase III BENEFIT trial, belatacept showed a significantly p0165 better GFR despite higher rates of early acute rejection compared with cyclosporine.35 Belatacept-treated patients also had better blood pressure and lipid control compared with cyclosporine controls. The

Costimulation Blockade
T Cell
Fc

CTL

A-4

Belatacept

Antigen Presenting Cell

CD80

CD28

CD86

CD28

MHC

Positive
costimulation

T-cell receptor
Alloantigen
CD80

CTLA-4

CD86

CTLA-4

Negative
costimulation

f0025
Fig. 106.4 Costimulation Blockade. Lymphocyte T-cell activation requires two signals with the first signal mediated by the major histocompatibility complex (MHC) and the T-cell receptor, and the second signal (positive costimulation) mediated by CD80/CD86 on the antigen-presenting cell (APC) and CD28 on the T cell. Negative costimulation is mediated by the cytotoxic T lymphocyte–associated protein 4 (CTLA-4) on activated T cells that binds to CD80/CD86 on the APC and suppresses T-cell responses (negative costimulation). Belatacept is a CTLA-4 fusion protein that binds CD80/CD86 and blocks positive costimulation via the CD28 pathway, thus preventing T-cell activation.

s0140 7-year follow-up data showed that the composite endpoint of graft
s0145 and patient survival was better with belatacept, but the individual graft
p0175 survival and patient survival were separately not statistically different compared with cyclosporine.36 Belatacept continued to show better 7-year kidney function with no increased risk for late PTLD in EBV seropositive patients.

p0170
Other studies looked at patients who were not included in the

BENEFIT trial. The BENEFIT-EXT trial included patients who received a kidney transplant from an expanded criteria donor, donation after cardiac death donor, or a donor with long cold ischemia time.37 This trial also found that patient and graft survival with belatacept were not inferior, but unlike in the BENEFIT trial, the acute rejection rate and GFR were similar between belatacept and cyclosporine. More recently a retrospective study of the Scientific Registry of Transplant Recipients database compared the 1-year outcomes between belatacept and tacrolimus.38 Similar to the BENEFIT trial, this study showed no difference in graft survival, but better kidney function despite a greater risk for acute rejection was seen with belatacept compared with tacrolimus. Also, a lower risk for new-onset diabetes after transplantation was observed with belatacept. In summary, belatacept seems to better preserve GFR and have a better metabolic profile compared with CNIs, but the high acute rejection rate has affected its broader use because of concerns of long-term impact on graft survival.

Other Agents Used in Transplantation

Bortezomib

Bortezomib is an antineoplastic agent originally approved for the treatment of plasma cell dyscrasias such as multiple myeloma and several types of lymphomas. It inhibits proteasomes, which are enzyme complexes that regulate protein homeostasis. Specifically, bortezomib reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis. It targets mature rapidly proliferating antibody-producing plasma cells but also interferes with T-cell function and IL and TNF production. Bortezomib has been used off label for both primary and refractory antibody-mediated rejection, experimental desensitization protocols, and induction immunosuppression in patients who are highly sensitized with HLA antibodies.39–41 Also, the BORTEJECT study is an ongoing phase 2 RCT investigating the impact bortezomib might have on treating late antibody-mediated rejection.42 Bortezomib is administered via IV and is metabolized by the liver. GI symptoms are common, but thrombocytopenia and peripheral neuropathy are significant side effects. Herpes zoster prophylaxis is required.

Eculizumab

s0150

Eculizumab is a humanized monoclonal antibody directed against p0180 complement protein C5 that prevents cleavage into C5a and C5b, thus

BOX 106.2
b0015

Prescribing Considerations for Immunosuppressive Medications

Tacrolimus
- Close monitoring of tacrolimus level is recommended in patients with diarrhea. Diarrhea elevates tacrolimus levels because of downregulation of (1) intestinal CYP450 and (2) p-glycoprotein, which normally transports drugs back into the intestinal lumen from enterocytes, thus increasing bioavailability.
- Hair loss associated with tacrolimus has been suggested to be dose-related and at times may respond to biotin supplementation; however, if persistent and severe, it may lead to poor compliance and a need for alternate therapy.
- Neurologic effects include night tremors, headaches, and tremors that can sometimes be alleviated with extended-release formulation.
- Urge cautious tacrolimus use with drugs that affect CYP450.
- Hypomagnesemia is common because tacrolimus downregulates TRPM6 and may also increase claudin-14 expression, which inhibits paracellular magnesium transport.
- Monitor for QT prolongation.
- It is associated with thrombotic microangiopathy and posttransplant diabetes.
- There is high interindividual variability on pharmacokinetics dependent on ethnicity; CYP3A5*1 polymorphism is high in African Americans and may lead to a higher tacrolimus dosage requirement.

Cyclosporine
- It is associated with hirsutism and gingival hyperplasia.

Mycophenolate
- Myelosuppression is a common side effect, and close complete blood count (CBC) monitoring is required.
- Gastrointestinal (GI) side effects are common. In cases of significant GI side effects, patients could be tried on enteric-coated mycophenolate mofetil (mycophenolic acid). Spacing out mycophenolic acid from twice daily to four times daily also sometimes helps.
- It is associated with teratogenicity; women of child-bearing age should be on dual contraception while on mycophenolate and should stop mycophenolate at least 6 weeks before conception.

Mammalian target of rapamycin inhibitors (mTORi)
- Routine monitoring of lipid panel and proteinuria is recommended.
- These are associated with pneumonitis.
- There is poor wound healing; these should not be used perioperatively.

Azathioprine
- Azathioprine has been associated with skin cancer with long-term use.
- Avoid use with allopurinol or febuxostat because it may increase serum concentrations of the active metabolite of azathioprine.
- Myelosuppression is a common side effect and close CBC monitoring is required, especially in those with low or absent thiopurine methyltransferase activity, often manifesting as macrocytic anemia.

blocking the subsequent formation of the terminal complex C5b-9 or membrane attack complex. Eculizumab prevents antibody-dependent complement-mediated cytotoxicity; therefore it has been used as an off-label treatment for antibody-mediated rejection. However, because of its experimental use and extreme cost, eculizumab is usually reserved as a rescue therapy for allografts resistant to other antirejection therapies. Eculizumab use in severe acute antibody-mediated rejection appears to be effective, but long-term follow-up of eculizumab-treated patients did not show prevention of chronic glomerular changes such as transplant glomerulopathy.[43–46] A phase II RCT in living-donor

- It is acceptable for use during pregnancy.

Belatacept

- There is a Black Box warning in Epstein-Barr virus–naive recipients, and it may increase post-transplant lymphoproliferative disorder risk.

kidney transplant recipients who required desensitization therapy showed that eculizimab did not reduce the risk of biopsy-proven acute antibody mediated rejection, graft loss, or death.47 As a result of increased incidence of meningococcal infections associated with eculizumab, meningococcal vaccine and antibiotic prophylaxis are required before starting therapy. Finally, eculizimab has been used successfully in the prevention of recurrence of certain complement-mediated glomerular diseases, such as atypical hemolytic syndrome.48

See Box 106.2 for a list of considerations when prescribing immu- p0185 nosuppressive medications.

SELF-ASSESSMENT QUESTIONS

o0010 1. What is the most common and vexing problem with cyclosporine and tacrolimus in kidney transplantation?
o0015
A. Nephrotoxicity
o0020
B. Hypertension
o0025
C. TMA
o0030
D. Alopecia
o0035 2. Belatacept offers patients a CNI alternative to maintenance immunosuppression and works by which mechanism of action?
o0040
A. Blocks complement C5 cleavage
o0045
B. Blocks CD25 on the IL-2 receptor
o0050
C. Blocks CD28-mediated costimulation of T cells
o0055
D. Inhibits B-cell proliferation by targeting CD20

3. Which immunosuppressive agent has been associated with teratogenicity in experimental animals and major fetal malformations?
A. Tacrolimus
B. Azathioprine
C. Corticosteroids
D. Mycophenolate
4. All of the following agents have been commonly used in the treatment of acute rejection except:
A. Antithymocyte globulin
B. Basiliximab
C. Rituximab
D. Intravenous immunoglobulins

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REFERENCES

1. Samaniego M, Becker BN, Djamali A. Drug insight: maintenance immunosuppression in kidney transplant recipients. Nat Clin Pract Nephrol. 2006;2:688–699.
2. Kuppe C, van Roeyen C, Leuchtle K, et al. Investigations of glucocorticoid action in GN. J Am Soc Nephrol. 2017;28(5):1408–1420.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(suppl 3):S1–S155.
4. Thomusch O, et al. Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet. 2016;388(10063):3006–3016.
5. Bae S, Garonzik Wang JM, Massie AB, et al. Early steroid withdrawal in deceased-donor kidney transplant recipients with delayed graft function. J Am Soc Nephrol. 2020;31(1):175–185.
6. Ho S, Clipstone N, Timmermann L, et al. The mechanism of action of cyclosporin A and FK506. Clin Immunol Immunopathol. 1996;80(Pt 2):S40–S45.
7. Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. Clin J Am Soc Nephrol. 2007;2:374–384.
8. Mancinelli LM, Frassetto L, Floren LC, et al. The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. Clin Pharmacol Ther. 2001;69(1):24–31.
9. Felipe CR, Silva HT, Machado PG, et al. The impact of ethnic miscegenation on tacrolimus clinical pharmacokinetics and therapeutic drug monitoring. Clin Transplant. 2002;16(4):262–272.
10. Vadivel N, Garg A, Holt DW, et al. Tacrolimus dose in black renal transplant recipients. Transplantation. 2007;83(7):997–999.
11. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. Clin J Am Soc Nephrol. 2007;2:184–191.
12. Gardiner KM, Tett SE, Staatz CE. Is conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium justifiable for gastrointestinal quality of life? Drugs R. 2018;18:271–282.
13. Budde K, Curtis J, Knoll G, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. Am J Transplant. 2004;4:237–243.
14. Salvadori M, Holzer H, de Mattos A, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant. 2004;4:231–236.
15. Morath C, Arns W, Schwenger V, et al. Sirolimus in renal transplantation. Nephrol Dial Transplant. 2007;22(suppl 8):viii61–viii65.
16. Sommerer C, Suwelack B, Dragun D, et al. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney Int. 2019;96(1):231–244.
17. Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet. 2011;377(9768):837–847.
18. Mulay AV, Cockfield S, Stryker R, Fergusson D, Knoll GA. Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. Transplantation. 2006;82(9):1153–1162.
19. Lim WH, Eris J, Kanellis J, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant. 2014;14(9):2106–2119.
20. de Fijter JW, Holdaas H, Oyen O, et al. Early Conversion from calcineurin inhibitor- to everolimus-based therapy following kidney transplantation: results of the randomized ELEVATE Trial. Am J Transplant. 2017;17:1853–1867.

21. 3C Study Collaborative Group. Campath, calcineurin inhibitor reduction, and chronic allograft nephropathy (the 3C Study): results of a randomized controlled clinical trial. Am J Transplant. 2018;18(6):1424–1434.
22. Tedesco-Silva H, Felipe C, Ferreira A, et al. Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving

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everolimus and reduced tacrolimus doses. Am J Transplant. 2015;15(10):2655–2664.
Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation. 2005;80(7):883–889.
Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med. 2015;4(9):1448–1459.
Campbell SB, Walker R, Tai SS, et al. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant. 2012;12(5):1146–1156.
Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367(4):329–339.
Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. Lancet. 1997;350:1193–1198.
Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade

with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med. 1998;338:161–165.

Salama AD, Pusey CD. Drug insight: rituximab in renal disease and transplantation. Nat Clin Pract Nephrol. 2006;2:221–230.

Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359:242–251.

Redfield RR, Jordan SC, Busque S, et al. Safety, pharmacokinetics, and pharmacodynamic activity of obinutuzumab, a type 2 anti-CD20 monoclonal antibody for the desensitization of candidates for renal transplant. Am J Transplant. 2019;19(11):3035–3045.

Sethi S, Najjar R, Peng A, et al. Outcomes of conversion from calcineurin inhibitor to belatacept-based immunosuppression in HLA-sensitized kidney transplant recipients. Transplantation. 2020;104(7):1500–1507.

Terrec F, Jouve T, Naciri-Bennani H, et al. Late conversion from calcineurin inhibitors to belatacept in kidney-transplant recipients has a significant beneficial impact on glycemic parameters. Transplant Direct. 2019;6(1):e517.

Pérez-Sáez MJ, Yu B, Uffing A, et al. Conversion from tacrolimus to belatacept improves renal function in kidney transplant patients with chronic vascular lesions in allograft biopsy. Clin Kidney J. 2018;12(4):586–591.

Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10:535–546.

Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med. 2016;374:333–343.

Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010;10:547–557.

Wen X, Casey MJ, Santos AH, et al. Comparison of utilization and clinical outcomes for belatacept- and tacrolimus- based immunosuppression in renal transplant recipients. Am J Transplant. 2016;16(11):3202–3211.

Walsh RC, Alloway RR, Girnita AL, et al. Proteasome inhibitor-based therapy for antibody-mediated rejection. Kidney Int. 2012;81:1067–1074.

Ejaz NS, Shields AR, Alloway RR, et al. Randomized controlled pilot study of B cell-targeted induction therapy in HLA sensitized kidney transplant recipients. Am J Transplant. 2013;13(12):3142–3154.

Lee J, Kim BS, Park Y, et al. The effect of bortezomib on antibodymediated rejection after kidney transplantation. Yonsei Med J. 2015;56(6):1638–1642.

Eskandary F, Bond G, Schwaiger E, et al. Bortezomib in late antibodymediated kidney transplant rejection (BORTEJECT study): study protocol for a randomized controlled trial. Trials. 2014;15:107.

Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011;11(11):2405–2413.

44. Cornell LD, Schinstock CA, Gandhi MJ, et al. Positive crossmatch kidney transplant recipients treated with eculizumab: outcomes beyond 1 year. Am J Transplant. 2015;15(5):1293–1302.
45. Kulkarni S, Kirkiles-Smith NC, Deng YH, et al. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. Am J Transplant. 2017;17(3):682–691.
46. Schinstock CA, Bentall AJ, Smith BH, et al. Long-term outcomes of eculizumab-treated positive crossmatch recipients: allograft survival, histologic findings, and natural history of the donor-specific antibodies. Am J Transplant. 2019;19(6):1671–1683.

47. Marks WH, Mamode N, Montgomery RA, et al. Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in livingdonor kidney transplant recipients requiring desensitization therapy: a randomized trial. Am J Transplant. 2019;19(10):2876–2888.
48. Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with eculizumab: a systematic review and meta-analysis. J Clin Med. 2019;8(7):919.

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c0107

Evaluation and Preoperative Management of Kidney Transplant Recipient and Donor

William R. Mulley, John Kanellis

p0010 Kidney transplantation provides superior long-term outcomes compared with dialysis, in both quantity and quality of life, although the benefit gained varies among individuals.[1] The better outcomes associated with transplantation coupled with the shortage of available organs has led to an expansion of donor criteria and an increasing tendency for centers to accept marginal donor kidneys. This chapter reviews the evaluation and preoperative management of both the kidney transplant recipient and the donor.

s0010

RECIPIENT EVALUATION

p0015 Many transplant centers now accept patients who were previously excluded from transplantation, such as those with human immunodeficiency virus (HIV) infection, obesity, and diabetes. This is because of the availability of newer treatment options for some conditions, a greater understanding of the impact of these conditions on patients and graft survival, and changing societal attitudes regarding equality of access to transplantation. Some absolute contraindications to transplantation remain (Box 107.1), including current infection or malignancy, noncompliance or substance abuse, and any condition likely to severely limit life expectancy (<1–2 years).[2–4]

p0020

Although the application of guidelines for transplant suitability may be relatively straightforward for patients with a single comorbidity, it is not as simple for those with multiple medical conditions, who represent a growing group of potential transplant recipients. Determination of suitability in such patients often requires input from specialists in a variety of medical and surgical disciplines along with allied health professionals. The final decision needs to be made by clinician and patient together after full discussion of the likely risks and benefits followed by regular reassessment of suitability while the patient awaits transplantation.

p0025

A summary of national and international guidelines[2–5] is presented in Box 107.2, and selected aspects are discussed.

s0015 Cardiovascular Disease

p0030 Cardiovascular (CV) disease is common in patients with end-stage kidney disease (ESKD) and is a major cause of death in transplant recipients. Hence, CV evaluation is critical in the evaluation of the potential transplant recipient.

s0020 Coronary Heart Disease and Left Ventricular Dysfunction

p0035 The role of pretransplantation investigation and intervention for coronary artery disease (CAD) is controversial. However, given the high incidence of cardiac events in the peri-transplantation period and its major contribution to posttransplantation mortality, we favor aggressive evaluation and intervention in at-risk patients while avoiding unnecessary tests and procedures in low-risk candidates. Patients may be risk-stratified using history and examination, resting

electrocardiography, and chest radiography. Further evaluation is unnecessary in asymptomatic patients without risk factors because of a very low incidence of coronary events.[6] Further investigation is recommended in patients with abnormal test results or significant risk factors, such as previous cardiac ischemic events, diabetes, smoking, age older than 50 years, hypertension, dialysis duration greater than 2 years, or a family history of CAD.2–4

p0040 Symptomatic patients should proceed directly to coronary angiography; noninvasive functional testing should be used to evaluate the need for angiography in asymptomatic patients.6,7 Exercise echocardiography or myocardial perfusion scintigraphy are preferred; both testing modalities have negative predictive values for myocardial infarction or cardiac death in excess of 90% in patients with kidney failure.8 If significant CAD is identified, treatment before transplantation is required. Treatment consists of aggressive risk factor modification, angioplasty, and stenting or coronary artery bypass grafting in patients with significant stenoses6,7 (Fig. 107.1).

In patients with evidence of left ventricular (LV) dysfunction, p0045 transthoracic echocardiography should be arranged; a cause should be sought and treated when possible. Severe LV dysfunction may improve significantly after transplantation, so is not an absolute contraindication to transplantation. However, because it is associated with reduced posttransplantation survival, it represents a contraindication in patients with significant comorbidities, unless combined heart and kidney transplantation is appropriate.2–4

Cerebrovascular Disease

s0025

Patients with recent transient ischemic attack or stroke are at greatest p0050 risk for recurrence early after the primary event; and because stroke after transplantation is associated with a high rate of mortality,9 a waiting time of 6 months is recommended. Meanwhile, aggressive risk factor modification is required to limit the likelihood of further stroke.

Risk factors for de novo stroke posttransplantation include older age, diabetes, and atrial fibrillation, although transplantation is associated with a reduced risk for stroke relative to remaining on the waiting list or maintenance dialysis. Routine testing for cerebrovascular disease is not advocated in asymptomatic patients. Patients with polycystic kidney disease (PCKD) should be offered investigation for cerebral aneurysm before transplantation, particularly those with additional risks for cerebral aneurysm rupture (e.g., personal or family history of cerebral hemorrhage). Risk for cerebral aneurysm in PCKD is discussed further in Chapter 46.

Peripheral Vascular Disease

s0030

p0055 Asymptomatic patients with strong femoral and peripheral pulses generally require no further investigation. Patients with diabetes, history of claudication, or reduced pulses require vascular imaging beginning with Doppler ultrasound. Significant disease involving the iliac vessels may make

CHAPTER 107 Evaluation and Preoperative Management of Kidney Transplant Recipient and Donor

Contraindications to Kidney Transplantation

BOX 107.1
b0010

Current Absolute Contraindications to Transplantation
- Active sepsis
- Current uncontrolled malignancy
- Uncontrolled psychosis
- Active drug dependence
- Any medical condition with a severely shortened life expectancy (<1–2 years)
- Positive T-cell CDC crossmatch

Assessment and Management of Cardiac Status in Potential Transplant Recipients

Potential kidney transplant recipient

High risk for CAD
(see text)

Historical Contraindications to Transplantation[a]
- HIV infection
- Hepatitis B and C infection
- Obesity
- Mood disorders
- Age > 60 years
- Previous malignancy
- Blood group incompatibility

[a] These conditions are now acceptable under certain circumstances (see text).

CDC, Complement-dependent cytotoxicity; HIV, human immunodeficiency virus.

BOX 107.2
b0015

Symptomatic

Low risk for CAD
(see text)

Asymptomatic

Positive Stress ecocardiography or Negative
Stress thallium scintigraphy

Coronary angiography

No significant
CAD

Significant CAD

Recipient Evaluation Checklist

History and Examination
- Cause of kidney failure and risk for recurrence
- Sensitization (transfusion, pregnancy, previous transplant)
- Past and current infections (TB, hepatitis, HIV)
- Immunization (especially hepatitis B)
- Malignancy
- Cardiovascular risks (smoking, hypertension, diabetes)
- Pulmonary, gastrointestinal disease
- Genitourinary tract
- Psychiatric, psychological history
- Surgical issues (weight, iliac vessels, abdomen, previous surgery)

Laboratory and Radiologic Investigations
- Viral serology (HIV, CMV, EBV, hepatitis B and C)
- Liver function tests
- Bone-related issues (PTH, calcium, phosphate)
- Chest radiograph
- Electrocardiogram
- Prostate-specific antigen (for men >50–60 years)
- Mammogram or breast ultrasound (women >50 years or with family history of breast cancer)
- Pap smear (sexually active women)

Immunologic Investigations
- ABO blood group and HLA typing
- Screening for HLA antibodies and autoreactive antibodies
- Crossmatching

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; PTH, parathyroid hormone; TB, tuberculosis.

transplantation difficult or impossible and may worsen ischemia in the distal leg. Although it is not an absolute contraindication to transplantation, peripheral vascular disease is associated with increased mortality and should be considered in conjunction with the patient’s other comorbidities.

Revascularization
or medical therapy

Transplant

f0010

Fig. 107.1 Assessment and management of coronary artery disease (CAD) in potential transplant recipients.

Cancer

s0035

Cancer is a major cause of death in kidney transplant recipients. Further p0060 increases in the incidence of malignancy are likely with increased graft survival and acceptance of older recipients. The incidence of malignancy is also increased in transplant recipients compared with the general population.10 However, the effect of transplantation on different types of cancer is not uniform, nor is the effect of different immunosuppressive agents.11 Some cancers, such as nonmelanoma skin cancers (61%–82% at 20 years) and lymphoma, have a markedly increased incidence in transplant recipients compared with the general population, in contrast to breast and prostate adenocarcinoma, which are not as substantially increased.

In patients with previous malignancy, guidelines for recom- p0065 mended waiting time are based on the likelihood of recurrence after transplantation (Box 107.3). In general, the longer the cancer-free interval before transplantation, the smaller the recurrence risk. For most malignancies, a period of 2 to 5 years is recommended.2–4 There are several exceptions: longer waiting time

(≥5 years) is recommended for breast cancer with nodal involvement, melanoma, and colorectal cancer worse than Duke’s stage B1; no waiting time is thought necessary for nonmelanocytic skin cancers confined to the skin, in situ cancers of bladder and cervix, focal microscopic low-grade prostate cancer, monoclonal gammopathy of uncertain significance (without evidence of multiple myeloma), and small (<7 cm) incidentally discovered and surgically removed kidney cell carcinomas. Waiting periods before transplantation should be individualized, taking into account the patient’s other comorbidities.

BOX 107.3 Guidelines for Transplantation in Patients With Previous Malignancy
b0020

Usual Wait Time of 2 Years
- Most cancers

No Wait Time Necessary
- Asymptomatic T1a (<4 cm) renal cell carcinoma without metastases or suspicious histologic features
- In situ carcinoma
- Focal neoplasm (defined as a localized tumor without metastases)
- Low-grade bladder cancer
- Basal cell skin cancer

Wait Time of >2 Years May Be Necessary
- Melanoma
- Breast cancer
- Colorectal cancer
- Uterine cancer

p0070

Chest radiography is performed as part of the routine assessment. Although extensive screening of all potential recipients is not warranted, potential recipients should be evaluated for breast, cervical, prostate, and colorectal cancer. More comprehensive and targeted evaluation is recommended in patients with a strong family history or suggestive clinical features of malignancy or conditions associated with an increased risk for malignant disease, such as kidney imaging in patients with acquired cystic disease of the kidney for possible kidney cell carcinoma.2 3

s0040 Infectious Complications

p0075 All patients are tested for previous exposure to Epstein-Barr virus (EBV) and cytomegalovirus (CMV) to assess the risk for infection, either primary or reactivation. This guides the appropriate use of prophylactic antiviral agents. For example, patients who are negative for CMV immunoglobulin G (IgG) who receive a kidney from a CMVpositive donor are at the highest risk for infection and may benefit from prolonged prophylaxis compared with the lower risk CMV-negative donor to a CMV-negative recipient (see Chapter 110). Testing for other infections should be tailored to geographic location; a guide is presented in Box 107.4. All potential recipients should be immunized against hepatitis B virus (HBV). Immunization against encapsulated organisms (pneumococci, Haemophilus influenzae, and meningococci) should be considered in patients at high risk for antibody-mediated rejection in case-rescue therapy (e.g., splenectomy) or when complement inhibition with eculizumab is required.

p0080

Centers experienced in managing HIV infection and transplantation report excellent patient and graft survival in carefully selected recipients.12 In the absence of an acquired immunodeficiency syndrome (AIDS)-defining illness, patients with sustained CD4 counts greater than 200/mL and undetectable HIV viral loads can be considered for transplantation.2 Patients with HBV infection may be considered for kidney transplantation if there is no evidence of active viral replication (HBV DNA or HBV early antigen [HBeAg] negative), advanced liver disease or cirrhosis (as determined by liver biopsy), or hepatocellular carcinoma (HCC).2–4 Immunosuppression can increase HBV replication; hence, treatment before transplantation is indicated in patients with active disease, and although data to support prophylactic antiviral therapy after transplantation are scarce, treatments such as entecavir are commonly used while immunosuppression is at its highest (first 12–24 months). Early reports suggested that mortality may be increased in HBV-positive patients after transplantation compared with HBVnegative recipients,13 but it is unclear whether this is true in the current era. We recommend frank disclosure of potential risks.2–4

BOX 107.4

Infection

Screening Tests for Occult

Routine Serology
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Hepatitis C virus
- HIV

b0025

Where Indicated, Tests for the Following Conditions and Infections
- HTLV
- Human herpesvirus 8
- Malaria
- Schistosomiasis
- Strongyloides stercoralis
- Trypanosoma cruzi
- Tuberculosis

Other Routine Investigations
- Chest radiograph
- Urine culture

HIV, Human immunodeficiency virus; HTLV, human T-lymphotropic virus.

p0085 Patients with hepatitis C should be assessed by measurement of hepatitis C virus (HCV) viral load and a liver biopsy. In patients without cirrhosis, transplantation should not be delayed by treatment because direct-acting antivirals can be safely used to treat HCV after transplantation,14 and mortality in HCV-positive patients is reduced by transplantation compared with remaining on dialysis.15 With informed consent, HCV-positive patients may receive a kidney from an HCV-positive donor because any possible increased risk for the latter is offset by a significantly reduced waiting time. Patients with HBV and HCV infection should be screened every 12 months for HCC by liver ultrasound and serum α-fetoprotein. Those with cirrhosis may be considered for combined kidney-liver transplantation.

p0090 Patients at high risk for tuberculosis (TB) reactivation after transplantation (previous TB, abnormal chest radiograph, or positive tuberculin skin test result; residence in an endemic area) who have not been previously treated should receive prophylactic isoniazid after transplantation (see Chapter 110). Interferon-γ (IFN-γ) release assays may replace or supplement the tuberculin skin test because they appear more sensitive for detecting latent TB infection.16 The need to evaluate patients for TB is determined by the likelihood of previous exposure.

p0095 Previous graft loss caused by polyoma (BK) viral nephropathy is not a contraindication to repeated transplantation. Waiting for serum and urine BK polymerase chain reaction test results to become negative appears to be preferable,17 whereas the value of graft nephrectomy before repeated transplantation is unclear. Vigilant evaluation for recurrence is recommended.4

Obesity

s0045

p0100 Transplantation in obese patients (body mass index [BMI] > 30 kg/ m2) generally improves survival compared with matched waiting list controls,18 but inferior outcomes for patient and graft survival, delayed graft function, wound healing, and infectious complications have been reported compared with nonobese patients, particularly those with BMI greater than 35 kg/m2 19 20 Additionally, overweight and obese patients are more likely to develop diabetes after transplantation, which can adversely affect graft and patient survival. Although not an absolute contraindication to transplantation, patients with obesity should be offered weight loss strategies (including bariatric surgery where appropriate) before transplantation to reduce their risk of mortality and morbidity.

s0050 Recurrent Disease

p0105 The risk for disease recurrence should be discussed as part of the informed consent process, particularly in primary kidney diseases with a high risk for recurrence (e.g., focal segmental glomerulosclerosis).21 Recurrent disease accounts for more than 5% of graft loss21 and is an increasingly important cause of graft dysfunction with increasing time posttransplantation. The risks and management of recurrent disease are discussed in Chapter 113

s0055 Gastrointestinal Disease

p0110 Investigations searching for gastrointestinal disease are not warranted in the asymptomatic patient.3 4 Patients with active acute or chronic pancreatitis should not undergo transplantation until they have been clear of symptoms for at least 3 months. Patients with active peptic ulcer disease should be treated before transplantation with proton pump inhibitors, and this should be continued to prevent ulceration after transplantation. Patients with symptomatic diverticular disease require colonoscopy and potential colonic resection in severe cases before transplantation because they are at increased risk for perforation on immunosuppressive medications.3 Although symptomatic cholecystitis should be treated surgically before transplantation, asymptomatic cholelithiasis does not require surgery before transplantation because cholecystectomy after transplantation is required in less than 10%, and results in no increased mortality or morbidity compared with pretransplantation cholecystectomy.22

s0060 Genitourinary Disorders

p0115 Testing for genitourinary tract disorders before transplantation is indicated in those with features suggestive of urinary obstruction, especially in children, in whom urologic problems are a major cause of ESKD. If obstruction is found, urologic assessment and/or voiding cystourethrography and urodynamic studies are indicated. Depending on the findings, intervention may be warranted to ensure bladder emptying and limit bladder pressures after transplantation; this may involve bladder augmentation, urinary diversion, or self-catheterization.

p0120

Native nephrectomy before transplantation should be considered in patients with recurrent or persistent kidney sepsis, particularly in the setting of nephrolithiasis. Very large polycystic kidneys may need to be removed to accommodate the transplant kidney. Whether previous grafts should be removed before repeated transplantation is controversial. Nephrectomy of a failed graft is commonly performed on withdrawal of immunosuppression in patients with early graft failure (<12 months) to alleviate symptoms such as pain, fever, and weight loss.23 Other indications include graft sepsis and allowance of room for the new graft. However, unless there is a convincing reason to remove the graft, it is generally left in situ In these circumstances the patient may need to stay on minimal immunosuppression, such as prednisolone for 3 to 6 months, to minimize graft tenderness and inflammation. Graft nephrectomy may be associated with an increased risk for human leukocyte antigen (HLA) sensitization,23 but this is not a universal finding. Another advantage of leaving the previous transplant in situ is preservation of any residual kidney function and urine output.

s0065 Pulmonary Disease

p0125 Physical examination and chest radiography are indicated for all potential recipients; pulmonary function tests or computed tomographic (CT) scanning are done if clinically indicated. Guidelines suggest that patients with a short life expectancy associated with pulmonary disease, such as cor pulmonale, uncontrolled asthma, and severe obstructive lung disease (FEV1 < 25% of predicted or Po2 < 60 mm Hg [8 kPa] on room air), or those needing home oxygen should be excluded from transplantation.4 Many centers require patients to cease smoking before acceptance because smokers have an increased risk for death and graft loss. Cessation of smoking demonstrates positive lifestyle behavior and good adherence, suggesting these factors will remain optimal after transplantation.

Psychosocial Issues

s0070
Psychosocial issues can have a major impact on transplant outcomes. p0130
Patients should be evaluated to judge capacity to consent and assess likely adherence to the transplant medication regimen. Predicting adherence can be challenging and may be based on pretransplantation adherence, such as to dialysis management regimens; transplantation should not proceed if the multidisciplinary assessment suggests that adherence is unlikely.2-4
Cognitive impairment is not an absolute contraindication to trans- p0135
plantation if appropriate supports and proxy arrangements are in place. Patients with serious psychiatric illnesses require assessment by a psychiatrist to determine transplant suitability and devise a management plan to cope with possible consequences of immunosuppressive medications such as corticosteroids.2-4 Drug and alcohol addiction should be addressed with rehabilitation and demonstrated abstinence before the patient is listed for transplantation.

Presence of Multiple Comorbidities

s0075
Increasingly, patients with multiple comorbidities are referred for con- p0140
sideration of transplantation. Each morbidity in itself often is not an absolute contraindication but taken together they may significantly affect prognosis. Controversially, some have suggested that patients must have specified long-term survival prospects—for example, an 80% chance of surviving 5 years—to be accepted for transplantation from a deceased donor. In addition, risk calculators have been devised based on registry data to allow such predictions (e.g., https://optn.transplant.hrsa.gov/resources/allocation-calculators/epts-calculator/).24

Reevaluation of Patients on the Waiting List

s0080
Patients may wait several years on the waiting list before an opportunity p0145
arises to undergo transplantation. It is vital that when their opportunity comes, they are still suitable candidates. Waiting list patients therefore should be reassessed at regular intervals (Box 107.5). General measures, such as cancer screening (e.g., skin, prostate, breast, and cervical), should be continued as indicated. Reassessment of cardiac status is advocated based on risk. Diabetic and other high-risk patients should be reassessed every 1 to 2 years.6 The value of reassessing low-risk patients is more questionable, but given that CKD is a strong risk factor for cardiac disease, repeated stress testing by exercise or pharmacologically driven echocardiography or myocardial perfusion scintigraphy at least every 3 years seems appropriate. Patients with preexisting medical conditions (e.g., HIV infection or viral hepatitis) require regular specialist reviews, with any issues arising brought to the attention of the transplant team. Surgical reassessment may be needed in patients with peripheral vascular disease, if patients gain weight, or if a complication such as peritonitis occurs while the patient awaits transplantation.

Patients should be temporarily removed from the waiting list if they develop a serious infection or other illness until it is resolved.

DONOR EVALUATION

Classification of the Deceased Donor

s0085

s0090

Deceased donors can be classified as either heart-beating donors with p0150 loss of brainstem function (donation after brain death [DBD]) or non–heart beating donors (donation after cardiac death [DCD]). In the last

b0030

BOX 107.5 Potential Recipient Reevaluation While Awaiting Transplantation

BOX 107.6 Classification of Donation After Cardiac Death Donors a

- Stress echocardiogram or thallium scan
- Angiography if indicated (see Fig. 107.1)

Uncontrolled
Category I: Dead on Arrival to Hospital
Cause of death is usually obvious (e.g., severe head injury), and no resuscitation is given.

Cancer Surveillance Relevant to Age, Sex, and Risk Factors
- Prostate-specific antigen
- Mammography
- Pap smear
- Colonoscopy if indicated
- Skin cancer check

Comorbidity Reassessment
- Viral hepatitis
- Liver function tests
- α-Fetoprotein
- Liver ultrasound
- HIV infection
- CD4 count
- AIDS-defining illness
- Other (see discussion of individual organ systems)
- Cardiac reevaluation every 1 to 2 years depending on risk factors (e.g., diabetes)

two decades the proportion of DCD donors has been increasing in many countries as a result of policies aiming to maximize the opportunities for donation.25

p0155

In the United States, DBD donors were previously divided into standard criteria donors (SCDs) and expanded-criteria donors (ECDs) for allocation purposes. ECD referred to heart-beating donors aged older than 60 years or 50 to 59 years with two or three of the following criteria: a history of hypertension, elevated serum creatinine at donation (>1.5 mg/dL or 130 μmol/L), or death from a cerebrovascular accident. In some jurisdictions, the term marginal donor is used to describe donors with significant underlying disease (hypertension, diabetes, vascular disease, kidney impairment) or advanced age (>65 years). In the last decade the United Network for Organ Sharing (UNOS) in the United States adopted a new system for classifying and allocating kidneys using a quality index.26 Other countries have also begun to use a similar system.27 The Kidney Donor Risk Index (KDRI) is a score that combines various donor factors to summarize the perceived quality of deceased donor kidneys. Factors in the calculation include age, creatinine, mode of death, donor pathway (brain death vs. circulatory death), history of hypertension or diabetes, race, and risk for HCV infection. A raw index score is converted to a percentile producing the Kidney Donor Profile Index (KDPI), rating from 0 (best) to 100 (worst).

p0160

The Maastricht classification defines DCD donors as controlled or uncontrolled (Box 107.6).28 Controlled donors are those who experience cardiac arrest after withdrawal of support or after brain death.
Uncontrolled donors are those who are deceased on arrival to the hospital or who had unsuccessful cardiopulmonary resuscitation. From a practical point of view, a system that uses controlled donors is easier to implement than one using uncontrolled donors. This is largely related to factors surrounding ethical considerations and the consent process involving relatives of the donor.

p0165

The survival of kidneys from ECD donors (loosely correlating with a KDPI > 85%) and from some categories of DCD donors is generally inferior to that of kidneys retrieved from SCD donors.28 Many matching schemes attempt to allocate these less ideal grafts to recipients who are predicted to have a lower than average overall

b0035

Category II: Unsuccessful Resuscitation

The patient is brought to the emergency department while being resuscitated, but this is not effective. Alternatively, cardiac arrest occurs in hospital and the patient cannot be resuscitated.

Controlled

Category III: Awaiting Cardiac Arrest

Severe brain injury without brain death. Patients are usually ventilator dependent. Cardiac arrest occurs once support is withdrawn.

Category IV: Cardiac Arrest While Brain Dead

Patient has a cardiac arrest after being declared brain dead. Alternatively, this occurs during brain death testing and the patient is not successfully resuscitated.

Category V: Unexpected Cardiac Arrest in a Critically Ill Patient

Example: unsuccessful resuscitation after unexpected cardiac arrest in intensive care.

a As per Maastricht classification 24 (also known as non–heart-beating donors).

From Indudhara R, Kenney PJ, Bueschen AJ, Burns JR. Live donor nephrectomy in patients with fibromuscular dysplasia of the renal arteries. J Urol. 1999;162:678–681.

survival, but practice varies considerably across countries.29 Simple age matching can be a part of this allocation process, or, alternatively, a more complex longevity-matching process can be performed using a recipient index.30 The Expected Post Transplant Survival (EPTS) score is the best known example, which incorporates factors such as age, diabetes, years on dialysis, and previous transplantation into the score.31

An attempt to better use kidneys from donors perceived to have an p0170 increased risk of viral infection (HBV, HCV, and HIV) despite negative nucleic acid testing (NAT) has been made in some countries in recent years.32 The issue here consists of a residual risk of viral transmission, related to a window period of possible infection in the donor, leaving the viral tests negative despite the presence of infection. In reality, the risk is low provided that results of NAT testing are negative.
Additionally, HCV can now be effectively treated, leading to some units actually transplanting organs known to be infected and then treating the recipient for HCV.33

Evaluation of the Deceased Donor

s0095

In most circumstances, organ donor coordinators screen potential p0175 deceased donors after referral from intensive care units (ICUs) or emergency departments (EDs). Patient records are assessed and relatives are interviewed about important aspects of the clinical history.
The assessment focuses on general health (including history of infections and cancer), social history (especially drug use and sexual history), and laboratory evidence of kidney impairment or other diseases
(Box 107.7). Patients with sepsis, acute hepatitis, or HIV infection are excluded from donation, as are those with a history of malignancy. Nonmelanoma skin cancers do not lead to exclusion, nor do primary brain tumors unless they are of a high grade or the donor has received

BOX 107.7

Checklist

b0040

Deceased Donor Evaluation

Medical History
- Hypertension, diabetes
- Malignancy
- Infections: Past and current (TB, hepatitis, HIV)
- Transfusions
- Trauma
- Surgical history
- Hospitalizations

Social History
- Intravenous drug use
- Alcohol, smoking
- Sexual behavior
- Tattoos, acupuncture
- Overseas travel
- Incarceration

Examination
- Blood pressure
- Cardiac, vascular
- Lymphadenopathy
- Abdominal

Laboratory and Technical
- Serum creatinine
- Urinalysis, urine culture
- Liver function tests
- Coagulation profile, complete blood count
- Blood culture
- Virology,[a] depending on geographic region: Antibodies to CMV, EBV, HSV-1 and HSV-2; HHV-6, -7, or -8; HCV, HBV (including HBsAg, anti-HBcAg, IgG, and IgM); HIV; West Nile virus; rabies; HTLV-1
- Parasites, depending on geographic region: malaria, babesiosis, toxoplasmosis, Chagas disease, syphilis
- Fungi in appropriate regions: Coccidioides, Histoplasma
- Tuberculosis (depending on geographic region)
- Chest radiograph
- Electrocardiogram
- Kidney biopsy if there is concern for chronic kidney disease

Operating Room Evaluation
- Intraabdominal examination to detect occult malignancy
- Macroscopic appearance of kidneys

[a] Choice of virologic investigations according to local risks.

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; TB, tuberculosis.

chemotherapy or had a craniotomy or cerebral shunt inserted.34 In some centers, donors potentially carrying HBV or HCV are accepted only for recipients who are seropositive for these viruses. The risk for an unknown donor malignant neoplasm is approximately 1.3%; however, the risk for transmitting a donor malignant neoplasm is lower at

approximately 0.2%.35
p0180
Evaluation of kidney function is determined by history, urinalysis, and serum creatinine concentration. In some patients a biopsy (often performed at retrieval) may provide useful information, particularly with ECDs or donors with a high KDPI. Estimated glomerular filtration

rate (eGFR) at admission should not be overtly reduced (>60 mL/min/1.73 m2), but a temporary decline in kidney function is acceptable if function is expected to recover. Proteinuria (>0.5 g/day) may indicate structural kidney damage and is a valid reason for nonacceptance.

The use of kidneys from very young donors varies among cen- p0185 ters. Donors aged younger than 5 or 6 years are associated with high risk for graft failure, especially from vascular thrombosis.36 For this reason, some centers occasionally transplant two kidneys in the one recipient en bloc, using the aorta and inferior vena cava as conduits.37

Deceased Donor Management Before Transplantation

s0100
In the DBD donor, maintenance of adequate blood pressure (BP) p0190 and oxygenation are important to prevent warm ischemic kidney injury. The use of pressor agents, volume resuscitation, and other conditioning strategies is complex and has been the subject of several guideline documents (see the Intensive Care Society website, www.ics.ac.uk). In this category of donor, the kidneys are generally not subject to significant warm ischemia at the time of organ retrieval unless the donor experiences prolonged hemodynamic compromise.

In DCD, once death is certified and deemed irreversible, either p0195 rapid surgical exposure of the great vessels with cooling of the organs followed by prompt retrieval is required, or, alternatively, the kidneys are cooled in situ by insertion of perfusion catheters through the femoral vessels (see also Chapter 108). Surgical retrieval can then take place after the following occur, as required: family counseling, donor assessment, or relocation from one hospital area to another (e.g., from the ICU or ED to the operating room). DCD is inevitably associated with warm ischemic kidney injury. This is responsible for the higher rate of delayed graft function that is seen in this group. The need for dialysis after transplantation is approximately 50% but varies from 30% to 90%, depending on the Maastricht category of donor.28

Living Donors

Live kidney donation is currently accepted in most countries based on the demand for deceased donor organs—which far outweighs the supply—and the apparent very low level of risk to the majority of healthy donors.38 Added to this are the detrimental effects for the recipient of waiting on dialysis and the generally superior results obtained through use of living donors.

Living donors may be related, unrelated, altruistic, or part of a donor exchange or list-exchange program. In many countries with well-established transplant programs, half or more of all transplants are now performed with living donors. In Japan, Brazil, and the Middle East, more than 80% of transplants use living donors. The superior outcomes of transplantation from living donors compared with that from deceased donors has supported the development of living donor paired exchange, in which living donors who are incompatible with their intended recipients are exchanged between recipients. Another approach is living donor–deceased donor exchange, in which the donor donates to the wait list in exchange for the intended recipient receiving priority on the list.39

In some countries, either a state-organized or a free-market system results in
the purchase of living donor kidneys.39 The Declaration
of Istanbul and the World Health Organization both condemn the
exploitation of living donors who are vulnerable (illiterate, impoverished,
undocumented immigrants, prisoners, and political or economic refugees).40
Many centers have extended their selection of donors to include
patients who are mildly hypertensive, overweight, or hyperlipidemic
or who have other abnormalities (such as isolated microhematuria or

s0105
p0200

p0205

p0210

p0215

Survival of Living Kidney Donors
98.3

1

97.0

94.7
86.4

92.7

0.9

81.8

0.8

66.2

0.7

63.7

0.6
Actual survival (n=481)
Expected survival (calculated)

0.5

0.4
35
15
20
25
30
Transplantation (year)
Fig. 107.2 Survival of Living Kidney Donors. Donor survival rates after living-donor kidney donation.
Retrieval rate was 80.0% (481/601). Expected survival was calculated using data for an age- and sex-matched normal population in Japan provided by the National Cancer Center. (From Okamoto M, Akioka K, Nobori S, et al. Short- and long-term donor outcomes after kidney donation: analysis of 601 cases over a 35-year period at Japanese single center. Transplantation. 2009;87[3]:419-423.)
0

f0015

5

10

previous nephrolithiasis).41 Although donation appears to be safe in the short- to medium-term for most of these patients, long-term risks have not been adequately assessed.

s0110 Mortality and Morbidity

p0220 Mortality related to living donation is a catastrophic and unexpected event; the perioperative risk for donor death is approximately 3 in

10,000.4 42 In the longer term, survival of donors appears to be similar to that of the general population (Fig. 107.2).

p0225

Physical and psychological function in living donors is higher than the community norm. Physical issues reported by donors after donation frequently include a temporary decrease from baseline in energy; some note a longer time to full recovery than anticipated and incision pain (after open nephrectomy) that lasts longer than expected. Psychological factors usually include an improved relationship with the recipient, an improved self-image, and frequently a positive effect on the donor’s life. Longer-term psychological morbidity appears minimal; however, some series have reported an association with anxiety, depression, or other psychological issues in a small proportion of the patients.43 Although most donors have a positive experience, a small number for a variety of reasons regret the decision to donate (0%–5%).44 Psychological evaluation before donation is therefore extremely important, as is support and counseling after donation, especially when the transplant does not go as well as anticipated.

s0115 Donor Evaluation: Living Donors

p0230 Several groups have developed guidelines for the evaluation and aftercare of living donors.45–47 An outline of the usual donor evaluation is shown in Boxes 107.8 and 107.9. An assessment of relevant anatomy may be achieved by CT angiography or magnetic resonance angiography, depending on the center. Kidney arteriography is not usually necessary, given the anatomic detail available from noninvasive techniques.

BOX 107.8 Living Donor Evaluation Checklist: History and Examination

History
- Hypertension
- Diabetes (including gestational)
- Infections
- Cancer (including skin lesions)
- Vascular disease
- Kidney calculi
- Gout
- Urinary tract
- Family history
- Medication use (including NSAIDs, herbs)
- Smoking
- Illicit and intravenous drug use
- Sexual history
- Vocation, sport interests
- Level of physical activity, exercise
- Psychiatric history, psychological factors
- Willingness to donate
- Relationship with recipient

Examination
- Blood pressure
- Weight and height, BMI
- Joints, skin
- Cancer (including skin lesions, breast)
- Lymph nodes
- Vascular disease
- Heart and lungs
- Abdomen

BMI, Body mass index; NSAIDs, nonsteroidal antiinflammatory drugs.

b0045

b0050

Laboratory and Radiologic Investigations

- Urinalysis (blood, protein)
- Urine microscopy and culture (blood, organisms)
- Serum electrolytes, urea, and creatinine
- Liver function tests
- Full blood examination
- Fasting blood glucose and/or oral glucose tolerance test
- Fasting lipids
- 24-Hour urine, creatinine clearance, or GFR measurement by iothalamate, Cr-EDTA, DTPA clearance, 24-hour urine protein, or protein excretion by other methods (e.g., protein-creatinine ratio)
- Serum uric acid, calcium, phosphate
- Viral screening: HBV, HCV, HIV, CMV, EBV serology
- Syphilis screening (RPR)
- TB screening (PPD)
- Electrocardiogram
- Chest radiograph
- Females: Pap smear, mammography (according to age and family history)
- Males: Prostate-specific antigen (according to age and family history)
- Additional cardiac investigations (where indicated by age, history, risk factors)
- Stress test
- Echocardiography
- Ambulatory blood pressure

Kidney Imaging (According to Local Expertise)

- Computed tomographic angiography
- Magnetic resonance imaging angiography
- Catheter angiography

CMV, Cytomegalovirus; Cr-EDTA, chromium-labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; EBV, Epstein-Barr virus; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PPD, purified protein derivative test; RPR, rapid plasmin reagent; TB, tuberculosis.

s0120 Assessment of Kidney Function

p0235 Most centers use GFR of 80 mL/min/1.73 m2 as the lower limit for donors. It is accepted that this threshold may be too low for donors younger than 40 years and too high for donors older than 60 to 65 years. An alternative approach is to consider the age-specific GFR and accept donors only if they fall within the average for this age range. This method has been recommended by the British Transplantation Society (guidelines available at www.bts.org.uk) and is presented in Fig. 107.3. An alternative approach uses the life expectancy of the donor.48 Based on these calculations, a 30-year-old donor would require a GFR of 123 mL/min/1.73 m2; the required GFR for a 70-year-old person would be 68 mL/min/1.73 m2

s0125 Hypertension and Proteinuria in the Living Donor

p0240 Donation may be acceptable for some hypertensive individuals if BP is well controlled, GFR is as expected for donation and age, and there are no features of end-organ involvement from hypertension.45–47 The evaluation for hypertension should include BP measurements on three separate occasions. Borderline elevated levels should be further evaluated with ambulatory BP monitoring. If elevated BP is detected and the prospective donor is still under consideration, echocardiography (looking for LV hypertrophy), ophthalmologic evaluation (looking for hypertensive retinal changes), and assessment for albuminuria

Acceptable GFR in Living Donors by Age
160
GFR (mL/min/1.73 m2)

Living Donor Evaluation
Checklist: Investigations

BOX 107.9

140

Mean 1 2 SD

120
Mean GFR
100
86 mL/min/1.73 m2
80

77
68

Mean – 2 SD

59

60

50

40
20

30

40

50

60

70

80

Age (years)

f0020

Fig. 107.3 Acceptable glomerular filtration rate (GFR) in living donors by age. Diagram explaining the minimum acceptable age–associated GFR in living donor candidates. The solid orange line shows the variation with age of mean GFR. The outer dashed lines show the +2 and −2 population standard deviation (SD) limits. GFR is constant up to the age of 40 years and then declines at the rate of 9 mL/min/1.73 m 2 per decade. The reference plot is based on an analysis of data for 428 living kidney transplant donors who had chromium-51–labeled ethylenediaminetetraacetic acid (51Cr-EDTA) GFR measurements. The solid blue line shows the acceptable lowest GFR for young adults, declining to 50 mL/min/1.73 m2 at age 80 years. For transplant donors with preoperative GFR values above the solid blue line, the GFR of the remaining kidney will still be above 37.5 mL/min/1.73 m2 at age 80 years. (Modified from the revised British Transplantation Society/Kidney Association U.K.

guidelines for living donor kidney transplantation. www.bts.org.uk/.)

(suggesting hypertensive kidney damage) should be undertaken. The prospective donor should be excluded if any of these features are present.

p0245 KDIGO (Kidney Disease: Improving Global Outcomes) recommends using the ratio of albumin to creatinine from a random urine sample with confirmation using an albumin excretion rate (AER) to assess donors for significant albuminuria (www.kdigo.org/guidelines/).47 49 An acceptable AER is less than 30 mg/day, with 30 to 100 mg/day requiring an individualized approach. An AER greater than 100 mg/day should exclude potential donors.

Obesity and Abnormal Glucose Tolerance in the Living Donor

s0130

p0250 Although many centers accept obese living donors, several issues must be addressed. These include the impact of obesity on perioperative complications, future kidney function, and CV health. In one study, obese (BMI > 30) patients had an increased rate of proteinuria and kidney impairment 10 to 20 years after nephrectomy.50 Obese individuals may therefore be more prone to development of kidney disease after donation, but this issue has not been carefully studied.

p0255 Future risk for diabetes is another important consideration. In addition to close assessment of those who are overweight, prospective donors with an abnormal fasting glucose concentration, a history of gestational diabetes, or a first-degree relative with diabetes should be evaluated with an oral glucose tolerance test. An abnormal glucose tolerance test result is a contraindication to donation. Patients often lose weight and otherwise change their lifestyle (exercise, diet), leading to an improvement in their results and eventual acceptance as donors. It is important that these lifestyle and risk modifications be sustained after donation occurs.

s0135 Kidney Abnormalities in the Living Donor

p0260 As well as factors identified in the history (e.g., previous calculi, urinary tract infections, prostatic disease), a variety of previously unidentified kidney abnormalities can be encountered in prospective donors during their assessment. These include microhematuria, kidney scarring (e.g., polar distortion suggesting reflux nephropathy), renovascular abnormalities, and kidney masses and cysts.

p0265

Isolated microhematuria in a prospective donor necessitates consideration of thin basement membrane nephropathy, Alport syndrome (carrier status in women may cause minor or moderate abnormalities), and IgA nephropathy, as well as urinary tract infection, malignancy, and nephrolithiasis. Persistent microhematuria is relatively common and is evident in approximately 3% of the general population.47 Among the possible disorders, IgA nephropathy is generally a contraindication to live donation, whereas thin basement membrane nephropathy may not necessarily be so.47 The implications of isolated mesangial IgA without other manifestations of glomerulonephritis requires further research, and donation should be decided in the context of family history, absolute kidney function, presence of interstitial disease, and age. If persistent isolated asymptomatic microhematuria is detected during living donor evaluation, a workup should include cystoscopy and urinary cytology. A kidney biopsy also should be considered because glomerular hematuria cannot otherwise be excluded.
If there is a possibility of familial disease (e.g., Alport syndrome, IgA nephropathy), this also helps clarify the prospective donor’s future risk for progressive kidney disease.5 47

p0270

Those with a history of bilateral or recurrent stones and those with systemic conditions associated with recurrent stone disease should not donate. An asymptomatic potential donor with a current single stone is suitable if the donor does not have a high risk for recurrence, if the stone is less than 1.5 mm, and especially if the stone is potentially removable during transplantation.47 The evaluation of an asymptomatic donor with a single prior episode of nephrolithiasis should include evaluation of serum calcium, creatinine, albumin, and parathyroid hormone levels; spot urine for cystine; urinalysis and urine culture; spiral CT scan; chemical analysis of the stone, if available; and 24-hour urine measurement of oxalate, uric acid, and creatinine.

p0275

Atherosclerotic kidney vascular disease is a relative contraindication to living donation. If it is discovered, the donor should be normotensive, have normal kidney function, and have only unilateral disease.
Careful evaluation for CAD and peripheral vascular disease should be undertaken, given the significant association of renovascular disease with atherosclerosis elsewhere. Fibromuscular dysplasia is found in 2% to 4% of prospective donors. Donors with severe and diffuse disease should not be accepted for donation. The age of the prospective donor should be considered, with the outcome in donors aged older than 50 years more benign than in younger donors.51

s0140 Malignancy

p0280 A history of certain malignancies is a contraindication to live kidney donation. These include melanoma, testicular cancer, kidney cell cancer, bronchial and breast cancer, choriocarcinoma, hematologic malignant neoplasm, and multiple myeloma.45–47 A history of malignancy may be acceptable for donation if prior treatment does not decrease kidney reserve, place the donor at increased risk for kidney disease, or increase the operative risk for nephrectomy. A history of malignancy may be acceptable if the specific cancer is curable and transmission of the cancer can be reasonably excluded; consultation with an oncologist may be required. Examples of cancers with low risk for transmission include certain mild forms of prostate, bladder, and cervical cancer. Consent to receive a kidney transplant must

include a discussion with the donor and the recipient indicating that risk for transmission of malignancy cannot be completely excluded.

Cardiovascular and Pulmonary Disease

s0145

In prospective donors, the cardiac assessment should be based on the p0285 history, risk factors, examination, and electrocardiographic findings.47 An exercise or pharmacologic stress test and echocardiography may be warranted in certain circumstances. Individuals with myocardial dysfunction or coronary ischemia are at increased perioperative risk and should generally not donate. Pulmonary contraindications to donation include chronic lung diseases that significantly increase the anesthetic risk. If indicated by history and examination, pulmonary function testing, echocardiography, or sleep studies should be performed.47 All donors should cease smoking for at least 8 to 12 weeks before surgery to minimize the risk for postoperative pneumonia.

COMPATIBILITY AND IMMUNOLOGIC CONSIDERATIONS

s0150

Blood Group Compatibility

s0155

Historically, transplantation across incompatible blood groups had p0290 been avoided because of the risk for hyperacute rejection mediated by preformed anti-A or anti-B antibodies to the carbohydrate blood group antigens, expressed by endothelial cells and by red blood cells. In the last two decades, ABO-incompatible transplantation has become more widespread, initially based on excellent outcomes described by Japanese centers.52 “Desensitizing” the recipient can avert hyperacute rejection. This involves removal of blood group antibodies by plasma exchange or immunoadsorption to achieve target titers. Preemptive splenectomy or rituximab administration (anti-CD20 monoclonal antibody) also is often used; however, the need for these measures is not clear. Rejection is predicted by high initial antibody titers and high rebound titers early after transplantation.53 A further period of plasma exchange or immunoadsorption after transplantation is commonly instituted, whereas other centers determine the need for these therapies preemptively based on posttransplantation antibody titers. With use of this protocol, patient and graft survival was initially reported as similar to that of blood group–compatible transplantation for the short to medium term (up to 9 years).52 A recent systematic review, including data on 7098 patients who underwent ABO-incompatible transplant, reports an increase in mortality, graft loss, and infection at 5-years posttransplantation relative to recipients of ABO-compatible transplants.54 Although the increase in absolute risk is small, these findings have prompted some to refer ABO-incompatible pairs to paired exchange programs (see www.bts.org.uk).

Human Leukocyte Antigen Compatibility

s0160

Tissue typing of recipient and donor determines their HLA match. p0295 HLA antigens are coded on chromosome 6, with half (one haplotype) inherited from each parent. The major histocompatibility class I

HLA-A and HLA-B and class II HLA-DR antigens have routinely been determined because rejection responses are thought to most commonly stem from mismatches at these alleles. However, an increasing awareness of the importance of immune responses to other HLA antigens has resulted in centers routinely looking for the presence of antibodies to HLA-C, HLA-DQ, and HLA-DP. A six-antigen (HLA-A, HLA-B, and HLA-DR) match confers a graft survival advantage compared with zero antigen matches for both deceased and living donor transplantation of 10% at 10 years.55 A further advance has been the description of the immunologically important antigenic subunits of HLA (epitopes) that rejection responses are directed against.56 Each HLA antigen has multiple epitopes that can be compared between donor and recipient to determine the degree of epitope matching, which also has implications for transplant outcomes.57 In addition to determination of HLA compatibility, crossmatching and screening for anti-HLA antibodies are performed to assess the risk for rejection.

s0165 Assessing Human Leukocyte Antigen Sensitization

p0300 Sensitization to HLA antigens generally occurs through blood transfusion, pregnancy, or prior transplantation. The extent of HLA sensitization in an individual can be measured using complement-dependent cytotoxicity (CDC), enzyme-linked immunosorbent assays (ELISA), and antigen-coated bead technology; the latter is most common. These assays determine the number and specificity of antibodies against HLA antigens present in sera from the potential recipient and compare them to the HLA of a panel of individuals from the recipient's prospective donor population. A panel reactive antibody (PRA) of 75% means that the recipient has anti-HLA antibodies that react with 75% of people from that population. To avoid donors against whom they have donor-specific antibodies, patients with higher PRAs typically wait longer for deceased donor transplantation.

p0305
Presence in the recipient of antibodies to donor-specific HLA antigens can result in hyperacute rejection. Crossmatching of donor lymphocytes with recipient serum allows screening for this possibility. Terasaki and coworkers pioneered the CDC crossmatch,58 which determines the presence of clinically significant antibodies by mixing donor T or B lymphocytes with recipient serum in the presence of complement. The sensitivity of the assay can be augmented by the addition of antihuman globulin. Presence of a positive T-cell CDC crossmatch to the donor is highly predictive of hyperacute rejection,58 whereas a B-cell CDC crossmatch is more subject to false-positive results but should prompt a search for donor-specific antibodies (Fig. 107.4).59,60 A positive T-cell CDC crossmatch is an absolute contraindication to transplantation. The CDC crossmatch has limitations in detecting low level and non–complement-fixing antibodies, high false-positive rates, and logistical issues with obtaining reagents and running the assays in a timely fashion.

p0310
The flow crossmatch is more sensitive than the CDC in detecting antibody capable of binding to donor T or B lymphocytes. Binding of antibody from donor serum is detected by flow cytometry after probing with a fluorescein-labeled anti-immunoglobulin antibody (Fig. 107.5).60 The strength of a positive flow crossmatch can be estimated by the degree of lymphocyte fluorescence that is measured in channel shifts. An increasing number of channel shifts is associated with an increasing risk of rejection. The predictive value of a positive flow crossmatch for rejection is less than that of a CDC crossmatch because of its increased sensitivity, and it does not assess the ability of the antibody to fix complement. Some deceased donor allocation systems now employ flow crossmatching, in conjunction with virtual crossmatching, in place of CDC crossmatching. Flow crossmatching is commonly performed in a living donor transplant workup. A positive flow crossmatch (with a negative CDC crossmatch) is not an absolute contraindication to proceeding; however, it may lead to alteration of the immunosuppressive regimen (e.g., use of a desensitization protocol) to decrease the risk or severity of antibody-mediated rejection.

Testing for anti-HLA antibodies in the recipient's serum is increasingly used as a means of predicting rejection. p0315 This virtual crossmatch compares the specificity of the antibodies identified with the prospective donor's HLA typing. Donor-specific anti-HLA antibodies correlate with worse graft survival even in the setting of a negative crossmatch.61

Although antibodies can be detected through a variety of techniques, including CDC panel reactive antibody testing and ELISA, the more sensitive antigen-coated bead technique is now almost exclusively employed. Multiple microscopic beads, each with a unique color that corresponds to a single HLA antigen that coats its surface, are mixed with recipient serum and probed with a fluorescein-labeled antiimmunoglobulin antibody (Fig. 107.6). Beads that bind antibody are identified as positive by fluorescence, and their HLA antigen specificity is detected by the unique coloring of the bead.[60] A positive virtual crossmatch is one in which a donor-specific antibody is detected. The strength of positivity of the virtual crossmatch can be estimated by the degree of fluorescence of the positive bead; however, this is not always accurate. The decision on whether to proceed with transplantation in the context of this information is complex. Recommendations for detection and characterization of clinically relevant antibodies in solid organ transplantation are summarized at www.bts.org.uk.

Complement-Dependent Cytotoxicity Crossmatch
A
Recipient
Serum

Donor
Lymphocytes

Complement

+

+
May contain
donor-specific
HLA antibodies

B

C

No donor-specific
HLA antibodies
in recipient serum:
No antibody binds

Negative
Crossmatch
(no cell lysis)

Donor-specific
HLA antibodies
in recipient serum:
Antibody binds
Complement activated

Positive
Crossmatch
(>20% of cells lysed)

f0025
Fig. 107.4 Complement-Dependent Cytotoxicity (CDC) Crossmatch. (A) Recipient serum potentially containing donor-specific anti–human leukocyte antigen (HLA) antibodies is added to donor T or B lymphocytes, along with complement. (B) If donor-specific antibodies are not present, no lysis occurs and the result is deemed negative. (C) If donor-specific anti-HLA antibodies bind to the lymphocytes and then activate complement, cell lysis will occur and the crossmatch result will be deemed positive. The proportion of lysed cells is assessed, and the crossmatch is graded as being weakly, moderately, or strongly positive. (From Mulley WR, Kanellis J. Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. Nephrology. 2011;16[2]:125–133.)

Flow Crossmatch
A

Donor
lymphocytes

Recipient
serum

May contain
donor-specific
HLA antibodies

+

B

Fluoresceinlabeled
antibodies
against
human IgG

+

No donor-specific
HLA antibodies
in recipient serum:
No antibody binds

Virtual Crossmatch
A

Donor-specific
HLA antibodies
in recipient serum:
Antibody binds

100 beads: each has a unique
dye signature and a unique
HLA antigen on its surface

Recipient
Serum

+
May contain
HLA antibodies

B

C

C

HLA antibody in
recipient serum binds
to specific bead

Detection antibody

binds and then captures
fluorescent reporter dye

D

f0030

Negative Crossmatch:
No binding of
fluorescein-labeled
antibody

Positive Crossmatch:
Binding of
fluorescein-labeled
antibody

Fig. 107.5 Flow Crossmatch. (A) Recipient serum potentially containing donor-specific anti–human leukocyte antigen (HLA) antibodies is added to donor T or B lymphocytes, along with fluorescein-labeled antibodies against human immunoglobulin G (IgG). (B) If donor-specific antibodies are not present, no binding occurs and the result is deemed negative. (C) If donor-specific anti-HLA antibodies bind to the lymphocytes, these can then bind the fluorescein-labeled antihuman IgG antibody, and this will be detectable by flow cytometry. The strength of the fluorescence can be measured and expressed as “channel shifts” above the control sample. (From Mulley WR, Kanellis J. Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. Nephrology. 2011;16(2):125–133.)

Dual-beam laser
One laser detects
bound reporter dye;
the other identifies
the specific bead

f0035

Fig. 107.6 Virtual Crossmatch. (A) Recipient serum potentially containing anti–human leukocyte antigen (HLA) antibodies is added to a mixture of synthetic beads. Each bead is coated with a set of antigens (screening beads) or, for more precise detail, with a single antigen (single antigen beads). A unique dye signature (up to 100) specifies the identity of each bead. (B) If anti-HLA antibodies are present, they will bind to the appropriate bead. (C) A detection antibody can subsequently bind and capture a reporter dye. (D) Each unique bead can then be interrogated for the presence of the reporter dye on its surface using a dual-beam laser. A profile of antibodies can thus be identified in the recipient and compared with the known HLA identity of any potential donor, allowing a prediction of the crossmatch result. (From Mulley WR, Kanellis J. Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. Nephrology. 2011;16[2];125–133.)

SELF-ASSESSMENT QUESTIONS

o0010 1. Which one of the following recipient factors is an absolute contraindication to transplantation?
o0015
A. Active sepsis
o0020
B. HIV infection
o0025
C. Obesity
o0030
D. Age older than 70 years

o0035
E. Previous malignancy

2. In predicting the risk for cardiac death in potential kidney transplant recipients, stress echocardiography performs best in terms of which of the following parameters?

A. Sensitivity
B. Specificity
C. Positive predictive value
D. Negative predictive value
E. A and B equally

o0040

o0045
o0050
o0055
o0060
o0065

o0070 3. Which one of the following brain-dead donors meets the definition for an expanded criteria deceased donor (as previously used in the United States)?

o0075

A. A previously well 53-year-old person with a serum creatinine at donation of 1.7 mg/dL (150 μmol/L)

o0080

B. A 48-year-old person with diabetes, hypertension, vascular disease, and smoking history

o0085

C. A 48-year-old person with hypertension and death from a cerebrovascular accident

o0090

D. A 62-year-old person with no significant medical history

o0095

E. A 58-year-old person with hepatitis

o0100 4. Which one of the following investigations would you not routinely perform on a 67-year-old man to assess his suitability to donate a kidney to his wife?

o0105

A. Urine microscopy

o0110

B. Colonoscopy

C. Hepatitis serology

D. Electrocardiogram

E. Kidney imaging

5. Which one of the following will best identify a high risk for hyperacute rejection?

A. Recipient tissue typing

B. Positive flow crossmatch

C. Positive T-cell cytotoxicity–dependent crossmatch

D. Positive virtual crossmatch

E. Donor O blood group

o0115
o0120
o0125
o0130
o0135
o0140
o0145
o0150
o0155

s0170

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725–1730.
2. Campbell S, Pilmore H, Gracey D, et al. KHA-CARI guideline: recipient assessment for transplantation. Nephrology. 2013;18(6):455–462.
3. Kasiske BL, Cangro CB, Hariharan S, et al. The evaluation of renal transplantation candidates: clinical practice guidelines. Am J Transplant. 2001;1(suppl 2):3–95.
4. Knoll G, Cockfield S, Blydt-Hansen T, et al. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. CMAJ (Can Med Assoc J). 2005;173:S1–S25.
5. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation. 2020;104(4S1 suppl 1):S11–S103.
6. Pilmore H. Cardiac assessment for renal transplantation. Am J Transplant. 2006;6:659–665.
7. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American heart association and the American college of cardiology foundation: endorsed by the American society of transplant surgeons, American society of transplantation, and national kidney foundation. Circulation. 2012;126(5):617–663.
8. Rabbat CG, Treleaven DJ, Russell JD, et al. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. J Am Soc Nephrol. 2003;14:431–439.
9. Lentine KL, Rocca Rey LA, Kolli S, et al. Variations in the risk for cerebrovascular events after kidney transplant compared with experience on the waiting list and after graft failure. Clin J Am Soc Nephrol. 2008;3(4):1090–1101.
10. Webster AC, Craig JC, Simpson JM, et al. Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. Am J Transplant. 2007;7:2140–2151.
11. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006;296:2823–2831.
12. Stock P, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. 2010;363:2004–2014.
13. Fabrizi F, Martin P, Dixit V, et al. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. Am J Transplant. 2005;5:2913–2921.
14. Lin MV, Sise ME, Pavlakis M, et al. Efficacy and safety of direct acting antivirals in kidney transplant recipients with chronic hepatitis C virus infection. PLoS One. 2016;11(7):e0158431.
15. Pereira BJ, Natov SN, Bouthot BA, et al. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The new england organ bank hepatitis C study group. Kidney Int. 1998;53:1374–1381.
16. Kim S, Lee S, Park J. A prospective longitudinal study evaluating the usefulness of a T-cell-based assay for latent tuberculosis infection in kidney transplant recipients. Am J Transplant. 2011;11:1927–1935.
17. Geetha D, Sozio S, Ghanta M, et al. Results of repeat renal transplantation after graft loss from BK virus nephropathy. Transplantation. 2011;92:781–786.
18. Gill JS, Lan J, Dong J, et al. The survival benefit of kidney transplantation in obese patients. Am J Transplant. 2013;13:2083–2090.
19. Naik AS, Sakhuja A, Cibrik DM, et al. The impact of obesity on allograft failure after kidney transplantation: a competing risks analysis. Transplantation. 2016;100(9):1963–1969.
20. Lafranca JA, IJermans JN, Betjes MG, et al. Body mass index and outcome in kidney transplant recipients: a systematic review and meta-analysis.

BMC Med. 2015;13:111.

21. Chadban S. Glomerulonephritis recurrence in the renal graft. J Am Soc Nephrol. 2001;12:394–402.
22. Kao LS, Flowers C, Flum DR. Prophylactic cholecystectomy in transplant patients: a decision analysis. J Gastrointest Surg. 2005;9:965–972.
23. Johnston O, Rose C, Landsberg D, et al. Nephrectomy after transplant failure: current practice and outcomes. Am J Transplant. 2007;7:1961–1967.
24. van Walraven C, Austin P, Knoll G. Predicting potential survival benefit of renal transplantation in patients with chronic kidney disease. CMAJ (Can Med Assoc J). 2010;182:666–672.
25. Kootstra G, van Heurn E. Non-heartbeating donation of kidneys for transplantation. Nat Clin Pract Nephrol. 2007;3:154–163.
26. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88:231–236.
27. Clayton PA, Dansie K, Sypek MP, et al. External validation of the US and UK kidney donor risk indices for deceased donor kidney transplant survival in the Australian and New Zealand population. Nephrol Dial Transplant. 2019;34(12):2127–2131.
28. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. Am J Kidney Dis. 2008;52:553–586.
29. Rege A, Irish B, Castleberry A, et al. Trends in usage and outcomes for expanded criteria donor kidney transplantation in the United States characterized by kidney donor profile index. Cureus. 2016;8(11):e887.
30. Bae S, Massie AB, Thomas AG, et al. Who can tolerate a marginal kidney? Predicting survival after deceased donor kidney transplant by donorrecipient combination. Am J Transplant. 2019 Feb;19(2):425–433.
31. Stegall MD, Stock PG, Andreoni K, Friedewald JJ, Leichtman AB. Why do we have the kidney allocation system we have today? A history of the 2014 kidney allocation system. Hum Immunol. 2017;78(1):4–8.
32. Brown CS, Wakam GK, Englesbe MJ. Increased-risk donors and solid organ transplantation: current practices and opportunities for improvement. Curr Opin Organ Transplant. 2020;25(2):139–143.
33. Terrault NA, Sher L. Expanding the use of hepatitis C-positive donors and keeping recipient safety at the forefront. Am J Transplant. 2020 Mar;20(3):627–628.
34. Morath C, Schwenger V, Schmidt J, Zeier M. Transmission of malignancy with solid organ transplants. Transplantation. 2005;80:S164–S166.
35. Buell JF, Trofe J, Sethuraman G, et al. Donors with central nervous system malignancies: are they truly safe? Transplantation. 2003;76:340–343.
36. Singh A, Stablein D, Tejani A. Risk factors for vascular thrombosis in pediatric renal transplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. Transplantation. 1997;63:1263–1267.
37. Foss A, Gunther A, Line PD, et al. Long-term clinical outcome of paediatric kidneys transplanted to adults. Nephrol Dial Transplant. 2008;23:726–729.
38. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. N Engl J Med. 2009;360:459–469.
39. Roth AE, Sönmez T, Unver MU, et al. Utilizing list exchange and nondirected donation through “chain” paired kidney donations. Am J Transplant. 2006;6:2694–2705.
40. Friedman EA, Friedman AL. Payment for donor kidneys: Pros and cons. Kidney Int. 2006;69:960–962.
41. The Declaration of Istanbul on organ trafficking and transplant tourism. Transplantation. 2008;86:1013–1018.
42. Davis CL, Delmonico FL. Living-donor kidney transplantation: a review of the current practices for the live donor. J Am Soc Nephrol. 2005;16:2098–2110.
43. Matas AJ, Bartlett ST, Leichtman AB, Delmonico FL. Morbidity and mortality after living kidney donation, 1999-2001: survey of United States

transplant centers. Am J Transplant. 2003;3:830–834.

44. Johnson EM, Anderson JK, Jacobs C, et al. Long-term follow-up of living kidney donors: quality of life after donation. Transplantation. 1999;67:717–721.
45. Andrews PA, Burnapp L. British transplantation society/kidney association UK guidelines for living donor kidney transplantation 2018: summary of updated guidance. Transplantation. 2018;107(7):e307.
46. Claisse G, Gaillard F, Mariat C. Living kidney donor evaluation. Transplantation. 2020;104(12):2487–2496.
47. Thiel GT, Nolte C, Tsinalis D. Living kidney donors with isolated medical abnormalities: the SOL-DHR experience. In: Gaston RS, Wadström J, eds. Living Donor Kidney Transplantation. London: Taylor & Francis; 2005:55–74.
48. Kidney Disease: Improving Global Outcomes. Guidelines. http://kdigo.org/guidelines/.
49. Praga M, Hernández E, Herrero JC, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. Kidney Int. 2000;58:2111–2118.
50. Lentine KL, Kasiske BL, Levey AS, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation. 2017;101(8S suppl 1):S1–S109.
51. Indudhara R, Kenney, Bueschen AJ, Burns JR. Live donor nephrectomy in patients with fibromuscular dysplasia of the renal arteries. J Urol. 1999;162:678–681.
52. Takahashi K, Saito K, Takahara S, et al. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. Am J Transplant. 2004;4:1089–1096.

53. Shimmura H, Tanabe K, Ishikawa N, et al. Role of anti-A/B antibody titers in results of ABO-incompatible kidney transplantation. Transplantation. 2000;70:1331–1335.
54. Scurt FG, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes after ABO-incompatible kidney transplantation: a systematic review and meta-analysis. Lancet. 2019;393(10185):2059–2072.
55. Opelz G, Wujciak T, Döhler B, et al. HLA compatibility and organ transplant survival. Collaborative Transplant Study. Rev Immunogenet. 1999;1:334–342.
56. Duquesnoy RJ. A structurally based approach to determine HLA compatibility at the humoral immune level. Hum. Immunol. 2006;67:847–862.
57. Mulley WR, Hudson F, Lee D, Holdsworth RF. Tissue typing for kidney transplantation for the general nephrologist. Nephrology. 2019;24(10):997–1000.
58. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. N Engl J Med. 1969;280(14):735–739.
59. Pollinger HS, Stegall MD, Gloor JM, et al. Kidney transplantation in patients with antibodies against donor HLA class II. Am J Transplant. 2007;7:857–863.
60. Mulley WR, Kanellis J. Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. Nephrology. 2011;16(2):125–133.
61. Lefaucheur C, Suberbielle-Boissel C, Hill GS, et al. Clinical relevance of preformed HLA donor-specific antibodies in kidney transplantation. Am J Transplant. 2008;8:324–331.

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Kidney Transplantation Surgery

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SOURCES OF KIDNEYS FOR TRANSPLANTATION

The usual and most frequent source of kidneys for transplantation has been donation after brain death (DBD), formerly known as donation from a heart-beating cadaveric donor. The increasing worldwide discrepancy between the availability of and the need for kidney allografts[1] has led to the increasing use of alternative sources of organs, including donation after cardiac death (DCD) donors (previously known as non–heart-beating donors) and living donors. The evaluation and selection of donors are discussed in Chapter 107. This chapter discusses surgical aspects of retrieval and transplantation of kidneys.

DONATION AFTER BRAIN DEATH DONORS

The potential DBD donor is maintained by artificial ventilation in a critical care setting until death has been diagnosed by brainstem death criteria,[2] the consent of the next of kin for donation has been given, and the necessary legal and institutional approvals have been obtained.

In the operating room some dissection is undertaken initially to define any aberrant anatomy and increase the speed and safety of organ retrieval after perfusion (warm dissection). Cannulation of the aorta and inferior vena cava is performed while the heart is still beating. This allows perfusion of the organs with cold preservative solution immediately before cardiac arrest, minimizing warm ischemia. The priorities of the organ retrieval team are influenced by the range of organs being donated. Heart, lung, liver, and pancreas retrieval take priority over kidney retrieval, which may significantly lengthen the ischemic time.

The kidneys are removed with a cuff of aorta (Carrel patch) attached to the renal artery, with the maximum achievable length of renal vein, and 10 to 15 cm of ureter. The length of the right renal vein should be maximized by including a portion of inferior vena cava in continuity. Care is taken to avoid damage to polar and other accessory arteries, especially the lower pole artery, which may supply the ureter. Stripping of adventitial tissue from the ureter must also be avoided, because this also may compromise its blood supply.

The kidneys are flushed with ice-cold preservation fluid until the effluent is clear and then are stored for transport in crushed ice or on a perfusion machine (see the discussion of kidney preservation).

DONATION AFTER CARDIAC DEATH DONORS

Before consensus was reached regarding the definition of brainstem death, DCD donors were the main source of transplant organs. These donors were intensive care unit based and had sustained head injuries or cerebrovascular accidents deemed irrecoverable, but organ retrieval could proceed only after cardiorespiratory death. This changed with the introduction of brainstem death legislation, but the use of DCD kidneys has recently increased again in response to the shortage of suitable organs for transplantation. An international consensus has defined categories of DCD donors[3] to facilitate legal and ethical discussion and to highlight possible differences in organ viability (see Chapter 107, Box 107.6). DCD kidneys sustain a period of warm ischemia, the period between cardiac arrest and the time that in situ cold perfusion is started. The duration of ischemia correlates with rates of primary nonfunction, delayed graft function, acute rejection, allograft, and patient survival. The main requirement of organ procurement from DCD donors is therefore to achieve rapid in situ perfusion of the kidneys to limit warm ischemia. This requires an emergency response team of surgeons and transplant coordinators, with considerable oncall and logistic commitments.

DCD donors may be either uncontrolled (Maastricht categories I and II) or controlled (Maastricht categories III through V). In controlled donors, cardiac arrest is expected, and it is therefore possible to reduce the warm ischemia time to only a few minutes because the surgical retrieval team will be on standby. Unexpected donor cardiac arrest may result in prolonged warm ischemia times. The duration of reversible warm ischemia time that the human kidney can sustain is unknown, but DCD kidneys with warm ischemia exceeding 60 minutes are considered by many to be of marginal suitability.

Donation After Cardiac Death Protocol

Centers involved with DCD donation should adhere to the Maastricht protocol,4 which includes the following principles:

✓•✓ Approval by the local medical ethics committee
✓•✓ Diagnosis of death by doctors who are independent of the transplantation team
✓•✓ Five-minute rule (after declaration of cardiac death, the body is left untouched for a period of at least 5 minutes before intervention)
✓•✓ Rapid in situ cooling with use of a catheter inserted into the aorta
✓•✓ Organ retrieval by standard surgical techniques

Uncontrolled Donation After Cardiac Death Donors

After a period of unsuccessful resuscitation, confirmation of cardiac death, and observation of the 5-minute rule, cardiac massage and ventilation with 100% oxygen are recommenced in an attempt to deliver oxygenated blood to the kidneys. A mechanical resuscitation device may be used. In situ renal cooling is achieved by placing a doubleballoon, triple-lumen perfusion catheter into the aorta via a femoral artery cut-down (Fig. 108.1) with instillation of preservation solution. Alternatively, the donor can be moved to an operating room as soon as death has occurred, and the aortic perfusion catheter placed directly at laparotomy rather than via a femoral artery cutdown.

Controlled Donation After Cardiac Death Donors

For controlled DCD donors, the transplantation team awaits cardiac arrest following withdrawal of life sustaining treatment. This usually

In Situ Perfusion of Non–Heart-Beating
Donor Kidneys
Ice-cold perfusion
fluid
Vena
cava

Aorta

A

Venous
vent

Fig. 108.1 Technique for in Situ Perfusion of Donation After Cardiac Death Kidneys. A double-lumen, double-balloon arterial catheter is introduced through the femoral artery and the lower balloon inflated at the aortic bifurcation and the upper balloon above the renal arteries. Icecold perfusion fluid is introduced and vented through the femoral vein until the effluent becomes clear.

takes place in the theatre anesthetic room or intensive care unit if it is close to the operating theatre. Withdrawal involves cessation of mechanical ventilation, extubation, and cessation of inotropic medications. Following asystole and confirmation of death, the 5-minute rule is observed and the patient is transferred to the operating theatre. A rapid laparotomy is performed and the perfusion catheter is inserted via the aorta or iliac artery.

LIVING KIDNEY DONORS

In the United States in 2018, 29% of kidney transplants were from living donors[5] compared with 28% in the United Kingdom in 2018–19.[6] After a rapid increase in living donor transplantation at the beginning of this decade, rates have become more static. Superior recipient posttransplantation outcome compared with use of kidneys from deceased donors,[7] the potential for preemptive transplantation before dialysis, and the ability to plan the procedure (allowing optimization of recipient condition) are major advantages and justify continued efforts to expand use of living donors. The medical evaluation of the living donor is discussed in Chapter 107

Preoperative Imaging

Preoperative imaging of living donors confirms the presence of two functioning kidneys, indicates pathology that would preclude donation, and provides anatomic information necessary for planning the procedure. Imaging assumes paramount importance before minimal access donor nephrectomy because of the reduced operative exposure

B

Fig. 108.2 Living Donor Preoperative Computed Tomographic Angiogram. (A) Three-dimensional reconstruction of arterial supply. Note the lower pole artery to the right kidney (arrow), which may supply the ureter as well as the lower pole parenchyma. (B) Conventional image showing single artery and vein to the left kidney.

and particular difficulties in the identification of complex vascular anatomy. The location, size, and number of renal arteries and veins needs to be accurately described preoperatively. Angiography combined with excretion urography is now obsolete. For preoperative description of the main renal artery and vein anatomy, magnetic resonance angiography and computed tomographic angiography are comparable,[8] but computed tomographic angiography is more sensitive and specific for complex vascular anatomy and provides excellent correlation between imaging and surgical findings9 (Fig. 108.2).

Minimal Access (Laparoscopic) Donor Nephrectomy

Living donor nephrectomy was traditionally performed through an open incision, necessitating a prolonged period of recovery. This and the cosmetic implications of a large flank wound may discourage potential donors (Fig. 108.3). To reduce such disincentives, there was

3

2
4
1
5

Fig. 108.3 Flank wound from open nephrectomy.

A

BOX 108.1 Donor Benefits of Minimally Invasive Donor Nephrectomy

- Shorter incisions
- Less pain
- Shorter hospital stay
- Shorter recovery
- Better cosmetic appearance

a move in the late 1990s and early 2000s toward minimally invasive donor nephrectomy, first performed as a transperitoneal laparoscopic procedure (laparoscopic donor nephrectomy [LapDN]).[10] LapDN is associated with decreased severity and duration of postoperative pain, shorter inpatient stay, quicker return to work and normal activities, and improved cosmetic result compared with open donor nephrectomy[11] (Box 108.1). Furthermore, the overall societal cost of LapDN is lower,[12] and recipient quality-of-life scores are higher.[13] The procedure is, however, technically demanding, and there is potential for damage to the kidney parenchyma, vessels, and ureter during dissection. It takes longer than open nephrectomy and exposes the allograft to a longer period of warm ischemia, albeit only of a few minutes.[11,14] Nevertheless, retrospective data suggest that minimal access donor nephrectomy not only offers postoperative advantages to the donor but also increases the number of transplants performed by reducing donor disincentives; estimates range from a 25% to a 100%[15] increase in transplantation activity. The widespread introduction of LapDN at the beginning of the 2000s saw an initial dramatic increase in the number of live kidney donors. However, rates have been static in both the United States and the United Kingdom over the last 5 years, suggesting that we may have seen the maximum benefits of this effect. Three minimal-access approaches have been described: transperitoneal, extraperitoneal, and hand-assisted living donor nephrectomy.

Transperitoneal LapDN

Pneumoperitoneum is established, and four laparoscopic ports are usually required (Fig. 108.4). After laparoscopic dissection a Pfannenstiel or iliac fossa incision is made through which the kidney is brought out within an endoscopy retrieval bag after control and division of the artery vein and ureter.

B

C

Fig. 108.4 Technique for Laparoscopic Donor Nephrectomy. (A) Positions for four laparoscopic ports (1–4) and Pfannenstiel incision (5), through which the kidney is removed. (B) Intraoperative view showing left renal artery (short arrow) and vein (long arrow) prepared for control and division. (C) Intraoperative view showing the kidney (arrows mark lateral margin) placed in the endoscopic retrieval bag (arrowheads mark the edge of the bag).

Hand-Assisted LapDN

The hand-assisted technique allows tactile sense to facilitate dissection, retraction, and exposure. It is said to be easier to learn and can be safely and efficiently performed by surgeons with less laparoscopic experience. The hand-assist device allows the operator’s nondominant hand to enter the abdomen through an airtight system.

Retroperitoneoscopic Operative Technique

The retroperitoneal approach avoids breaching the peritoneum, displays the kidney anatomy in a very different manner, and may be easier for retrieving the full length of the vessels, especially on the right side. The disadvantage is that a more limited operating space is available than with the transperitoneal or hand-assisted laparoscopic techniques.

Robotic Live Donor Nephrectomy

All of the earlier minimally invasive techniques can be undertaken using robotic assistance, and this has been adopted by a number of centers worldwide. However, there is no high-level evidence of clinical benefit over laparoscopic-assisted approaches, and it is difficult to justify the additional costs and infrastructure required, given the excellent outcomes of the current minimally invasive techniques.

Contraindications to Minimal Access Donor Nephrectomy

There are no absolute contraindications other than those applying to the open operation. The relative contraindications are dictated by donor factors and the experience of the surgeon. The donor must be fit for anesthesia, including the physiologic stress of pneumoperitoneum. Obesity is a relative contraindication for both open and laparoscopic surgery, and the hand-assisted approach may be better suited in such patients. Previous abdominal surgery is a further relative contraindication because of the potential for adhesions. Multiplicity of renal vessels should not hinder LapDN.

Effect of Pneumoperitoneum

Transient intraoperative oliguria secondary to decreased renal blood flow is a frequent occurrence during laparoscopic procedures. Proposed mechanisms include decreased cardiac output, renal vein compression, ureteral obstruction, renal parenchymal compression, and systemic hormonal effects. Intracranial pressure increases during pneumoperitoneum, with release of vasoconstrictor agents that decrease renal blood flow. Use of a lower pressure reduces the adverse effects of pneumoperitoneum on kidney perfusion. In donor nephrectomy, impaired renal blood flow may compromise early allograft function and compound the damaging effects of warm and cold ischemia and operative manipulation of the kidney. The pioneers of LapDN used high volumes of crystalloid preoperatively and intraoperatively to maintain kidney perfusion in the presence of pneumoperitoneum. However, this was associated with episodes of unilateral pulmonary edema in the dependent lung, and we now recommend no additional volume loading in the donor beyond standard perioperative fluid replacement. The revised protocol has not apparently reduced the likelihood of good graft function.

Graft Function and Acute Rejection

There is no consistent evidence that graft function differs among kidneys retrieved by open, laparoscopic, or hand-assisted donor nephrectomy. The exception is that rates of delayed graft function and acute rejection may be higher in pediatric recipients, especially the 0- to 5-year age group.

Pretransplantation ischemia could, in theory, render the donor kidney more immunogenic by inducing major histocompatibility complex (MHC) class II expression. However, despite the longer warm

ischemia time, acute rejection rates and severity of rejection are not higher in laparoscopic than in openly retrieved living donor kidneys.

Technical Issues

Ureteral ischemia was more common in early experience of LapDN but can be avoided if care is taken to ensure that sufficient periureteral tissue is taken and that the dissection does not occur too close to the renal pelvis.

Multiple arteries need not be a barrier to successful use of grafts from laparoscopic donors. In open donor nephrectomy, the right kidney is retrieved in 20% to 30% of procedures, whereas LapDN uses the right kidney in fewer than 10%,16 reflecting concern over the operative safety of the right-sided laparoscopic operation, principally the difficulties involved in obtaining an adequate length of renal vein. It has been argued that this practice has led to compromise of the principle that the better kidney should remain with the donor.

Postoperative Recovery

After uneventful open nephrectomy, the donor can expect to be discharged from the hospital in 5 or 6 days and is able to return to work after 3 to 6 weeks, although return to work has been shown to be 2 to 3 weeks later in open nephrectomy compared with LapDN.11 After LapDN the donor usually leaves the hospital in 1 to 2 days and can return to work in 3 to 6 weeks.

Choice of Donor Operative Technique

The choice of operative procedure depends on the local expertise of the surgeons. There is accumulating evidence that the laparoscopic operation removes some of the disincentives to donation, and this approach has now been widely adopted around the world.

KIDNEY PRESERVATION

Preservation of deceased donor organs is crucial to allow time for matching, sharing of organs, and preparation of the recipient. Damage from hypothermia and reperfusion must be minimized. There is little standardization of the type of preservation solution used. Marshall’s hyperosmolar citrate solution and histidine-tryptophan-ketoglutarate are popular choices in Europe, but University of Wisconsin solution is more commonly used in the United States, where extended preservation times are more often required.

Organs can be preserved by cold storage (kept in crushed ice after flushing with preservation solution) or by machine-driven pulsatile perfusion. The proposed benefits of machine perfusion come from allowing aerobic function through provision of oxygen and substrate and removal of metabolic end-products. Although hypothermic machine perfusion has been used for many years, there is still no consensus about its superiority to cold storage nor about the best perfusion parameters. However, recent meta-analyses have suggested benefits of machine perfusion in improved delayed graft function rates and graft survival.17,18 This effect seems to be similar for kidneys from both DCD and DBD donors and to have cost benefits over static cold storage.18

Further developments in hypothermic machine perfusion have led to the addition of oxygen to the perfusion fluid. Clinical trials are ongoing to assess the benefits of hypothermic oxygenated perfusion over both static cold storage and standard hypothermic machine perfusion, with one recent RCT suggesting a reduction in severe complications and graft failure with the addition of oxygen to hypothermic machine perfusion.19

A novel approach to kidney preservation, only recently introduced into clinical practice, is ex vivo normothermic perfusion. Early results

are promising,20 but the technique needs to be studied in larger clinical trials, one of which is ongoing in the United Kingdom.21

Decisions on the use of a kidney from a marginal donor can be supported by data from machine or normothermic perfusion; high perfusion pressures are associated with primary nonfunction and delayed graft function.

KIDNEY TRANSPLANTATION PROCEDURE

The transplanted kidney is placed heterotopically in one or another iliac fossa. The right side is usually preferred for first-time kidney transplant as the external iliac vessels, particularly the vein, lie more superficially than on the left. The inferior epigastric vessels are ligated, as is the round ligament of the uterus in female patients. Occasionally the inferior epigastric artery may be preserved and used for revascularization of small polar arteries. In male patients the spermatic cord is mobilized and preserved. The peritoneum should not be breached but instead swept superiorly to reveal the extraperitoneal bed into which the transplanted kidney will be placed. The external iliac blood vessels are then mobilized, with care taken to meticulously ligate all the associated lymphatic channels to reduce the risk for posttransplantation lymphatic leak.

Vascular Anastomosis

The renal vein is anastomosed end to side to the external iliac vein. The arterial anastomosis can be performed either end to side to the external iliac artery or end to end to the divided internal iliac artery (Fig. 108.5). The end-to-side anastomosis is technically easier and is the usual method used in cadaveric transplantation, where it is possible to include a Carrel aortic patch with the renal artery.

With living donor kidneys it is not possible to include a Carrel patch, and occasionally a cadaveric kidney may be provided without a useable patch. In these circumstances the options are to anastomose the renal artery end to end to the divided internal iliac artery or end to side to the external iliac artery. Use of an aortic punch to create a circular arteriotomy may facilitate the latter technique. For living donor kidneys, most surgeons use the external iliac artery. It is our experience that positioning the kidney is often easier if the internal iliac artery has been used for the anastomosis, but this does risk buttock claudication and potentially increases the risk for erectile dysfunction in male recipients.

After completion of the vascular anastomoses, the kidney must sit in such a position that the renal vessels are not kinked. The transplanted kidney can be placed laterally in the iliac fossa or may be placed in a subrectus pouch fashioned specifically for the purpose.22 In the latter case the renal vessels run laterally from the kidney, and this should be noted when a posttransplantation biopsy is performed. An operative diagram of the position of the kidney and vessels is therefore an important component of the clinical notes.

If there are multiple renal vessels, the number of anastomoses should be minimized. This usually can be achieved by careful bench surgery before implantation. If there are two or more renal arteries, their aortic patches are joined in such a way that a single arterial anastomosis is required. If necessary, recipient iliac artery or saphenous vein is used to facilitate reconstruction. Occasionally, small polar arteries will be recognized only after a kidney has been retrieved, and it is particularly important to reanastomose lower polar arteries accurately because these may provide all the ureteral blood supply. In the case of double renal veins, the most common course of action is simply to ligate the smaller vein; the larger one is usually sufficient to drain the whole kidney. If there are two equally sized veins, both may need to be anastomosed, either separately to the external iliac vein or joined and anastomosed together.

End-to-Side Arterial Anastomosis

A

End-to-End Arterial Anastomosis

B

Fig. 108.5 Vascular Anastomosis Techniques for kidney Transplantation. (A) End-to-side anastomosis to the external iliac artery. (B) End-to-end anastomosis to the divided internal iliac artery, suitable for living donor transplantation in which no aortic patch is available.

Urinary Drainage

The traditional method of ureteral anastomosis is the PolitanoLeadbetter technique, involving a transvesical ureteroneocystostomy with creation of a submucosal antireflux tunnel. The end of the transplanted ureter is drawn through a submucosal tunnel from outside to inside and sutured to the bladder mucosa. The majority of surgeons now prefer the technically simpler extravesical ureteroneocystostomy onlay, in which the spatulated end of the ureter is anastomosed to the cystostomy and the divided muscle layer is then resutured over the ureter to create a short antireflux muscle tunnel. The onlay method has the advantage of being possible with only a short length of ureter. The shorter the ureter, the less likely it is that there will be an inadequate blood supply to the distal end, thereby reducing the risks for ischemic ureteral leaks or stenosis. A temporary double-J ureteral stent is usually placed. Stents reduce the impact of small technical errors while the ureter is healing and reduce major urologic complications to an incidence of 1.5%.23 However, they are a potential source of urinary tract infection, can become encrusted or blocked by debris, and can migrate or fragment. Nevertheless, antibiotic prophylaxis is not justified because it increases the risk for infection with multiresistant organisms. A further danger is the forgotten stent that has not been removed, which should always be considered in patients with unexplained and persistent lower urinary tract symptoms after transplantation. Stents are usually removed 4 to 6 weeks posttransplantation, and this can be performed without general anesthesia with use of a flexible cystoscope.

immunosuppressive agents are given orally, except in the presence of a prolonged postoperative ileus with high volumes of nasogastric drainage, when they should be administered intravenously. If recovery is straightforward, the bladder catheter and wound drains are usually removed by day 5, and the recipient is fit for discharge after 7 to 10 days to be kept under close outpatient monitoring.

SURGICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

There is a small but significant incidence of technical complications, which can be minimized by avoiding damage to the kidneys at the time of the retrieval. Nonetheless, the presence of multiple renal vessels and donor atherosclerotic disease does increase the likelihood of technical problems in the recipient, as do recipient obesity, atherosclerosis, and previous transplantation. Algorithms to aid in the management of complications in the early posttransplant period can be found in Figs. 108.6 and 108.7.

Wound Infection

The use of preoperative prophylactic antibiotics, commonly amoxicillin–clavulanic acid, has reduced the incidence of wound infection

Management of Sudden Oliguria or Anuria in the Early Posttransplant Period

Alternative Techniques of Urinary Reconstruction

Kidney transplantation is quite commonly performed in patients who have abnormal bladders. In many patients it is possible to anastomose the transplanted ureter to the bladder in the hope that the bladder can be rehabilitated, if necessary, with use of posttransplantation intermittent self-catheterization. Nonetheless, some patients require urinary diversion with an ileal conduit. The conduit should be fashioned at least 6 weeks before transplantation, but it may have been present for many years. If so, a contrast study (a conduitogram) should be performed before transplantation to exclude the development of conduit stenosis, although this is rare. The transplanted kidney is best placed in the ipsilateral iliac fossa to avoid tension in the ureter, and it may be preferable to deliberately place the transplanted kidney upside down so that the ureter runs cranially and has a more direct route to the conduit. After revascularization, the peritoneum is opened, and the ureter is anastomosed to the conduit over a double-J stent. Excellent longterm results have been achieved with this technique.24

Drainage and Wound Closure

Both the transplant bed and the subcutaneous tissues may be drained to prevent the accumulation of serosanguineous fluid or lymph around the transplanted kidney, although many surgeons no longer routinely place drains. The skin is best closed with a subcuticular absorbable suture and then dressed with a clear adhesive dressing so ultrasound scanning can be performed early without disturbing the wound. For this reason, metal clips are rarely used for the skin.

Postoperative Course

The recipient is nursed in a general ward with standard precautions and no need for reverse barrier nursing. There is no benefit to continuing prophylactic antibiotics beyond a single dose given at induction of anesthesia. Prophylaxis against thromboembolic disease is in the form of thromboembolic deterrent stockings, and low-molecular-weight heparin (LMWH) is continued until discharge. Oral fluids and diet are commenced as tolerated immediately after surgery. Maintenance

Oliguria or anuria
? Blocked urinary
catheter
Flush catheter

? Hypovolemia

No

Urine output
resolved?

No further action
Yes

Dry
Assess fluid status

Yes

Fluid challenge

Urine output
resolved?

Hydrated
Urgent ultrasound
with duplex ultrasound

No

Vascular
thrombosis

Surgical
exploration

Hydronephrosis

See Fig. 108.10

Normal
Poor peripheral
perfusion
Loss of CMD

Treat

Acute rejection
Transplant biopsy

ATN
Monitor

Fig. 108.6 Management of sudden oliguria or anuria in the early posttransplant period. ATN, Acute tubular necrosis; CMD, corticomedullary differentiation.

Management of Transplant Pain or Swelling
in the Early Posttransplant Period
Pain and/or swelling over transplant
Renal vein
thrombosis

Urgent duplex ultrasound

Surgical exploration

Hematoma

Hb fall?

Fluid collection
No

Graft edema
Transplant biopsy

Conservative
management

Yes

Rejection

Surgical
exploration

Aspirate sample
for biochemistry

Abscess

Urinoma

Treat

Lymphocele
Asymptomatic

Symptomatic

Conservative
treatment

Surgical or
radiologic
drainage

Cystogram or
pyelogram

Aspirate
Recurrent

Surgical
repair

Conservative
management
with double-J

Surgical drainage
(fenestration procedure)

Fig. 108.7 Management of transplant pain or swelling in the early posttransplant period. Hb, Hemoglobin.

to less than 1%. If a wound infection does occur, treatment is with antibiotics, guided by microbiologic wound swabs, and drainage of collections as necessary.

Wound Dehiscence

The risk for wound dehiscence is increased in obese and diabetic patients and those receiving sirolimus. Identification and treatment of any infection are mandatory. Resuturing of the wound is rarely justified. Large areas of dehiscence often benefit from vacuum-assisted closure, but the majority require only frequent dressing.

Vascular Complications

Transplant vascular thrombosis is a feared complication that may cause early and irreversible graft failure. Although there are also significant hemorrhagic risks, routine perioperative prophylaxis should be given with subcutaneous LMWH, and some units prescribe aspirin for the first few postoperative months.

Bleeding From Vessels in the Renal Hilum

Careful postoperative observation and regular hemoglobin and hematocrit measurements are crucial for the early detection of bleeding. Output from the transplant drains may give an early indication of heavy blood loss. Unsecured small vessels in the renal hilum may not be obvious during surgery, but they may start bleeding postoperatively.

This form of blood loss can be slow, persistent, and serious. If the patient’s condition allows, urgent imaging may be performed to secure a diagnosis, but the best course of action is usually emergency exploration of the transplant under general anesthesia.

Anastomotic Hemorrhage

Anastomotic hemorrhage is a rare occurrence, usually caused by a technical surgical error, and is more common with multiple arteries and the use of antiplatelet agents.[25,26] Early after transplantation, the patient may report pain over the graft. This symptom always should be taken seriously. There also may be pain in the back or the rectum caused by a tension hematoma in the retroperitoneum or pelvis. Significant hemorrhage will be attended by circulatory collapse, with tachycardia and hypotension. There will be a decrease in the hemoglobin and hematocrit, sometimes to alarmingly low levels. The patient must be returned to the operating room immediately and the transplant reexplored.

Hemorrhage also can occur some weeks after transplantation because of the development of a mycotic aneurysm of the renal artery. In the rare case of a ruptured mycotic aneurysm, an immediate graft nephrectomy is required, but the mortality is high.

Renal Artery Thrombosis

Renal artery thrombosis is a rare event, occurring in less than 1% of transplants. The usual outcome is loss of the kidney. Acute arterial thrombosis may occur intraoperatively or during the first days or weeks after transplantation. Potential causes include hyperacute rejection or a procoagulant state, but most cases are caused by a technical error during the anastomosis of small or atheromatous vessels.26 Successful vascular anastomosis requires that the vessels are not under tension and that there is a smooth transition between the two endothelial surfaces; sutures must be placed through all layers of the vessel walls, so an intimal flap is avoided. Vascular adventitia is thrombogenic and must be excluded from the lumen of the anastomosis. The risk for renal artery thrombosis is increased in the presence of atherosclerosis, persistent hypotension, volume depletion (e.g., diarrhea, excessive preoperative dialysis), and prothrombotic states, including diabetes.

Renal arterial thrombosis manifests with sudden anuria, the differential diagnoses being a blocked urinary catheter, dehydration, acute tubular necrosis, or a urologic complication. A high index of suspicion is required to make this diagnosis, particularly in the immediate postoperative period. The only worthwhile investigation is an urgent duplex ultrasound scan, but if the diagnosis is seriously entertained, the only hope of saving the transplant is to reexplore it immediately in the hope that a correctable cause can be found. The reality is that unless the acute arterial thrombosis occurs during surgery, there is little chance of saving the transplanted kidney. Acutely thrombosed grafts must nevertheless be explored and removed to avoid the development of sepsis in a necrotic graft, a potentially fatal complication.

Renal Vein Thrombosis

Renal vein thrombosis is more common than arterial thrombosis and occurs in 1% to 6% of renal transplants.26,27 Although it may result from a technical error at the time of surgery, its cause is usually less certain. The renal vein can certainly be twisted or kinked if it is not correctly placed after completion of the vascular and ureteral anastomoses. The peak incidence of renal vein thrombosis is 3 to 9 days after transplantation;28 transplant patients with good initial graft function will have a sudden loss of urine output, which is often markedly bloodstained, associated with severe pain arising from swelling and (very rarely) rupture of the allograft. The ipsilateral leg may swell if there is involvement of the iliac venous system. Renal vein thrombosis also may be occult and is one differential diagnosis of delayed graft function. Duplex ultrasound scanning is the best investigation. In an established renal vein thrombosis this may show an obviously swollen allograft with surrounding hematoma and an absence of renal perfusion. Lesser degrees of thrombosis, or indeed incipient thrombosis, may be highlighted by an absence of arterial flow in diastole. An even later development is a reversal of flow in diastole.

As with arterial thrombosis, if this diagnosis is entertained, the best course of action is to reexplore the transplant as an emergency. The renal vein anastomosis can be opened to allow the clot to be extracted, and the venotomy is then closed and the kidney observed for improvement. A more radical alternative is to immediately explant the kidney by taking down the arterial, venous, and ureteral anastomoses. The kidney can then be reflushed with cold perfusion fluid on the back table and held in preservation fluid at 4°C. This allows much more time to assess the cause of the venous thrombosis, and if the kidney remains viable, the transplant operation can be repeated. If the transplant is already infarcted or cannot be adequately flushed with preservation fluid, the organ will need to be discarded anyway and nothing is lost by immediate explantation. Successful emergency surgical exploration with subsequent long-term function is rare. Interventional radiographic techniques offer an alternative to surgery. The renal vein can be selectively catheterized via the ipsilateral femoral vein, and graft thrombolysis then may be attempted. This technique is particularly useful when renal vein thrombosis occurs late after transplant and the

risk for systemic anticoagulation is low. The use of various thrombolytic agents has been reported, including heparin, urokinase, streptokinase, and tissue plasminogen activator, with no consensus as to which is the most appropriate.

Transplant Renal Artery Stenosis

Transplant renal artery stenosis is a later complication occurring 3 to 48 months after transplantation. Not all stenoses are of functional or clinical significance, as shown by studies in which all functioning transplants have undergone angiography.29 Causal factors include donor and recipient atherosclerosis, factors associated with surgical technique, and severe acute rejection.30 The presentation and management of transplant renal artery stenosis are discussed in Chapter 43.

Lymphocele

Small, clinically insignificant lymphatic collections can be demonstrated by ultrasound scan in up to 50% of kidney transplants.31 Larger lymphoceles that cause complications or require treatment occur in 2% to 10% of patients.32 The source of peritransplant lymph leaks is the lymphatic channels around the iliac arterial system rather than the lymphatics of the transplanted kidney itself.33 Therefore, during the dissection of the iliac arterial system, all the surrounding lymphatic channels must be meticulously secured with nonabsorbable ligatures or metal clips. Wound suction drains should not be removed postoperatively until less than 30 mL of fluid is produced on 2 consecutive days. It is safe to leave drains in place for several weeks posttransplantation to allow a low-volume lymphatic leak to seal by gradual fibrosis. Despite the theoretical risk for infection, this does not seem to be a problem in practice. If necessary, the patient can be discharged from the hospital with the drain in situ.

Compression of the transplanted ureter leading to kidney dysfunction is produced only by very large lymphoceles (volume > 300 mL). The peak incidence is at 6 weeks, but a lymphatic collection may manifest 2 weeks to 6 months after transplantation.31 Most lymphatic collections are found anterior to the iliac vessels and lying between the transplant and the bladder (Fig. 108.8). Presenting features may include wound or ipsilateral thigh swelling in association with suprapubic discomfort and urinary frequency caused by bladder compression. Other presentations include pain over the transplanted kidney, sometimes associated with fever, ureteral obstruction with graft dysfunction, and ipsilateral thrombophlebitis. However, the vast majority are asymptomatic and manifest as an incidental finding during an ultrasound scan being performed for another reason. It is important to aspirate all peritransplant fluid collections under ultrasound control to aid diagnosis. Macroscopic findings are usually sufficient to differentiate infected from noninfected lymph, and biochemical analysis of the fluid allows a urine leak to be excluded. Computed tomography or magnetic resonance imaging is an essential investigation if surgery is being contemplated, particularly if a laparoscopic procedure is planned. This allows accurate definition of the relationship between the lymphocele and the transplanted ureter. If the ureter is bow-strung across the superior surface of the lymphocele, it could be damaged during a laparoscopic fenestration procedure.

Many small lymphoceles are asymptomatic and will resolve spontaneously given enough time. If action is deemed necessary, first-line treatment is aspiration under ultrasound control. If there is a recurrence, further aspirations can be performed or an external drain can be placed with ultrasound guidance. If these simple measures fail, open or laparoscopic surgical drainage may be required. A 5-cm-diameter disk of the lymphocele wall is removed to create a large opening into the peritoneal cavity, allowing reabsorption of the lymph through the abdominal lymphatic drainage system. These peritoneal fenestrations

A

B

Fig. 108.8 Posttransplantation Lymphocele. (A) Ultrasound appearance. A large, echolucent lymphocele can be seen inferior to the transplanted (marked by crosses). (B) Computed tomography appearance. A 5 × 5 cm lymphocele (arrowheads) is present under the transplanted kidney (arrows).

tend to heal before the lymphocele is completely reabsorbed, leading to early recurrence; a metal or omental plug may prevent this.

Urologic Complications

Urinary tract complications are relatively common after kidney transplantation, with an incidence of 5% to 14%.34 Although they can be difficult to manage, they only rarely cause graft loss or mortality. The relatively high incidence of urologic problems is a consequence of the tenuous blood supply of the transplanted ureter. After kidney retrieval, the only ureteral blood supply that is preserved is derived from the renal artery near the hilum of the kidney, and this can be easily damaged during retrieval.

Urinary Leaks

Urinary leaks most commonly occur because of ischemic necrosis in any part of the transplanted urinary collecting system. The distal ureter has the poorest blood supply and is therefore the most common site. Less commonly, leaks occur from the renal pelvis or the midportion of the ureter, which may be a result of unrecognized direct damage to the ureter during organ retrieval. Urinary leaks tend to occur in the first few days after transplantation but can manifest much later. The usual presentation is with straw-colored fluid leaking directly from the transplant wound or accumulating in the drains in association with oliguria. Alternatively, extravasating urine may accumulate as a peritransplant fluid collection. This manifests as a painful swelling of the wound, and the patient may have a fever. In either case, the extravasated fluid must be differentiated from lymph by biochemical analysis of the fluid and a simultaneous serum sample. Urine will have markedly elevated

urea and creatinine levels compared with the patient’s serum, whereas lymph will have a similar biochemical profile.

The presence of a urinary fistula should be confirmed by antegrade or retrograde pyelography. Both techniques present challenges.

Antegrade puncture of a nondilated pelvicaliceal system is technically difficult but usually possible. Retrograde cannulation of the transplanted ureteral orifice can be attempted with a flexible cystoscope.

This is also a difficult maneuver because the transplanted ureter is implanted into the dome of the bladder rather than at its base. If the urine leak is contained as a urinoma, ultrasound will demonstrate a fluid collection between the transplanted kidney and the bladder, which can be sampled by needling or drained by the placement of a suitable percutaneous catheter.

The management of urinary leaks has changed significantly in recent years. The former practice of early reexploration and surgical reconstruction35 is no longer always necessary. Interventional radiographic techniques offer an alternative, at least for initial treatment.

The aim is to place a double-J (pigtail) ureteral stent across the region of damage via an antegrade nephrostomy; this may allow time for the urinary fistula to heal.36 This technique, however, is unlikely to be successful if there is significant ischemic necrosis of the ureter, in which case surgery still has a role. Reexploration of kidney transplants is straightforward in the early postoperative period but may be a considerable challenge later because of the development of an intense peritransplant fibrotic reaction. The choice of operative procedure for a necrotic distal ureter depends on the length of remaining viable ureter. If there is sufficient length after excision of the necrotic distal portion, the transplanted ureter may simply be reimplanted into the bladder. If this is not possible, the urinary tract should be reconstructed with use of the patient’s native ureter. Depending on length of viable transplanted ureter, there is a choice between anastomosing the native ureter to the transplanted ureter proximal to the ischemic segment (ureteroureterostomy) or to the transplanted renal pelvis (ureteropyelostomy; Fig. 108.9). Whichever technique is chosen, the anastomosis should be protected with a double-J stent. Although these techniques require the native ureter to be ligated proximally, there is usually no need to perform an ipsilateral nephrectomy.[37] Postoperatively, the antegrade nephrostomy can be left in situ so a contrast study can be performed after 7 to 10 days to confirm healing of the new anastomosis. If the transplant recipient has undergone an ipsilateral nephrectomy in the past or the native ureter is too diseased to be used for reconstruction, a Boari bladder flap can be used to reconstruct the urinary tract.

Ureteral Obstruction

Obstruction of the transplanted ureter may occur at any time after transplantation. It should always be considered in the differential diagnosis of acute transplant dysfunction and excluded by ultrasound examination. The management of transplant ureteral obstruction is summarized in Fig. 108.10. Early obstruction is uncommon and suggestive of a technical error, such as creating a submucosal bladder tunnel that is too tight, kinking of a redundant length of ureter, and incorrect suture placement during anastomosis. Early obstruction may be caused by a blood clot in the ureter, bladder, or catheter. Bleeding may occur from the ureterovesical anastomosis or cystostomy or after a transplant biopsy. It is common practice to drain the urinary bladder using a three-way irrigating catheter because small-diameter two-way Foley catheters are easily blocked by blood clot.

Late ureteral obstruction may occur at the vesicoureteral or pelviureteral junctions. Ischemia that is not severe enough to cause necrosis is presumed to be the cause of most vesicoureteral obstructions.[38]

Kidney transplants invariably excite a pronounced perigraft fibrotic response, and this is more likely to be the cause of an obstruction at the

Ureteral Reconstruction Using
Native Ureter
Proximal
native
ureter

Renal
transplant

Stenosed
transplant
ureter

Native
ureter

Fig. 108.9 Ureteral reconstruction using native ureter.

level of the pelviureteral junction. It is also possible that acute rejection episodes contribute to subsequent fibrosis.36 BK polyoma virus also can cause late ureteric obstruction because of hypertrophy of ureteric epithelial cells in combination with infiltration of inflammatory cells.

An ultrasound scan will demonstrate a dilated pelvicaliceal system. However, long-standing kidney transplants may have quite marked pelvicaliceal dilation without being obstructed. This most commonly causes uncertainty in assessment of whether obstruction may be contributing to chronic allograft dysfunction in a patient with biopsyproven chronic allograft nephropathy. Further investigation is needed to confirm or refute the presence of obstruction and define its anatomy. Retrograde pyelography has a low success rate because of the difficulty of catheterizing the transplanted ureteral orifice at cystoscopy. Therefore, percutaneous nephrostomy followed by antegrade pyelography is the investigation of choice in suspected transplant ureteral obstruction. The nephrostomy is performed under antibiotic cover using ultrasound control, and the nephrostomy tube should be left in place for a few days. If serum creatinine decreases during this period, obstruction is confirmed. If there is no improvement in kidney function, significant obstruction can be confidently excluded. This simple observation avoids the need for an antegrade pressure study (Whitaker test), which may be difficult to interpret in transplanted kidneys. After external decompression of the transplanted kidney for a few days, an antegrade pyelogram is obtained to accurately define the anatomy of the obstructing lesion.

Nonoperative approaches for the treatment of transplant ureteral stricture are often preferred.39 The simplest approach is to place a double-J stent across the stricture via a percutaneous nephrostomy. This may require initial balloon dilation.40 The stent can be removed after 6 weeks, but the restenosis rate is high. An alternative is long-term

Management of Transplant Ureteral Obstruction
Graft dysfunction

PC dilation

Ultrasound

Nephrostomy

No improvement in
graft function

Improvement in
graft function

Antegrade
pyelogram

Place double-J
ureteral stent

Ureteral stenosis
identified

Permanent
double-J ureteral stent
(change every 6 mo)

No PC dilation

Not obstructed—
Remove nephrostomy

No ureteral
stenosis identified

No further action
Monitor graft function

Clamp and remove
nephrostomy

Persistent
ureteral stenosis

If sufficient
transplant ureter,
surgical reimplantation

If insufficient
transplant ureter,
ureterostomy
or ureteropyelostomy
using native ureter

Fig. 108.10 Management of transplant ureteral obstruction. PC, Pelvicaliceal.

stenting, changing the stent every 6 months. The disadvantage of this method is a high incidence of urinary tract infection, with potential severe consequences for immunosuppressed patients, and long-term antibiotic prophylaxis is a sensible precaution. Open surgical management still has a place in the management of ureteral obstruction. The operation performed depends on the site of obstruction and remaining length of healthy transplanted ureter proximal to the obstruction (see discussion of urinary leaks). Not all cases of obstruction require intervention. When there is a mild degree of obstruction not associated with urinary tract infection and in a long-standing kidney that is affected by chronic allograft nephropathy, it may be better to simply monitor transplant function, reserving intervention for a later date should it become necessary.

Complications in the Transplant Bed

A number of nerves may be encountered in the retroperitoneal dissection required for kidney transplantation. These include the lateral femoral cutaneous nerve and the femoral, obturator, and sacral nerves. Each of these may be damaged by a traction injury, particularly when modern fixed wound retraction systems are used, because these can exert a great deal of pressure on the surrounding tissues. Patients with such neurapraxias should recover completely, but this may take some months, and the condition can be very disabling.

In male transplant recipients, the spermatic cord must be mobilized during the dissection to gain access to the retroperitoneal space. Damage to the testicular artery in the cord can result in testicular atrophy.

TRANSPLANT NEPHRECTOMY

The optimal management strategy for patients with a failed kidney transplant remains unclear, with a lack of good-quality evidence.

Transplant nephrectomy is mandatory for early graft failure caused by vascular thrombosis, capsular rupture, and irreversible rejection. However, the management of a kidney transplant that has chronically failed is more challenging. The options are transplant nephrectomy or leaving the graft in situ, with or without continuation of immunosuppression. Mortality from both infection and cardiovascular disease has been shown to be higher in patients with failed grafts continuing immunosuppression.41 However, weaning and discontinuation of immunosuppression also have been shown to increase the risk for transplant nephrectomy and allosensitization.42

If the graft remains in situ without immunosuppression, signs and symptoms such as pain, fever, hematuria, and thrombocytopenia may prompt transplant nephrectomy, although the patient also can be treated initially with corticosteroids.

Historically, transplant nephrectomy was advocated to remove antigenic stimulation for anti–human leukocyte antigen (antiHLA) antibody production, which might adversely affect the possibility of retransplantation. However, there is some evidence that transplant nephrectomy, particularly late after transplantation, may actually increase allosensitization.43 The suggestion is that the graft may act as an “immunologic sponge” to absorb antibody or may regulate the production of antidonor antibody by the recipient’s immune system.

Early graft nephrectomy is straightforward, but after the first few weeks kidney transplants usually develop quite intense perigraft fibrosis, and this can make late allograft nephrectomy a difficult technical challenge. A subcapsular dissection is preferred, and after removal of the kidney, the hilum is sutured, leaving a cuff of donor vessels in place. Careful hemostasis is required, and the whole raw capsular bed should be cauterized. The wound is usually closed without drains.

SELF-ASSESSMENT QUESTIONS

1. Which of the following statements are false regarding organ donation and retrieval?

A. For donation after brain death, the aorta is cannulated after cardiac arrest.

B. Kidneys to be obtained by donation after cardiac death sustain a period of warm ischemia during retrieval.

C. Approximately 30% of kidney transplants in the United Kingdom are currently from living donors.

D. Laparoscopic donor nephrectomy is contraindicated with multiple renal arteries.

E. The usual hospital stay after laparoscopic donor nephrectomy is 1 to 2 days.

2. Which of the following statements are true regarding the kidney transplant surgical procedure?

A. The kidney is placed in an extraperitoneal position in one or the other iliac fossa.

B. For cadaveric kidney transplants, the renal artery is usually anastomosed to the internal iliac artery.

C. Lower-pole renal arteries can be sacrificed without increasing the risk for ureteral complications.

D. The transplant ureter is anastomosed directly to the bladder.

E. Transplant ureteral stents should remain in place for 3 months.

3. Which of the following are not risk factors for transplant renal artery thrombosis?

A. Atherosclerosis

B. Dehydration

C. von Willebrand disease

D. Diabetes

E. Protein C deficiency

4. Which of the following statements are true regarding urologic complications after kidney transplantation?

A. Urologic complications are less common than vascular complications.

B. Urologic complications invariably manifest early.

C. Urine leaks are diagnosed by markedly raised urea and creatinine levels in the fluid compared with serum.

D. Reexploration and surgical reconstruction are always required for urine leaks.

E. Transplant ureteral stenosis is associated with BK polyoma virus infection.

5. Which of the following statements are true regarding transplant nephrectomy?

A. Transplant nephrectomy is mandatory for early graft failure caused by thrombosis.

B. Transplant nephrectomy reduces allosensitization.

C. Mortality is higher in patients with failed grafts weaned from immunosuppression.

D. Graft nephrectomy, particularly late after transplantation, is straightforward.

E. All failed kidney transplants should be removed.

REFERENCES

1. Wu DA, Watson CJ, Bradley JA, et al. Global trends and challenges in deceased donor kidney allocation. Kidney Int. 2017;9:1287–1299.

✓ 2. ✓ Criteria for the diagnosis of brain stem death. Review by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom. J R Coll Physicians Lond. 1995;29:381–382.

✓ 3. ✓ Kootstra G, Daemen JH, Oomen AP. Categories of non–heart-beating donors. Transplant Proc. 1995;27:2893–2894.

4. Daemen JW, Kootstra G, Wijnen RM, et al. Nonheart-beating donors: the Maastricht experience. Clin Transpl. 1994:303–316.

5. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 annual data report: kidney. Am J Transplant. 2020;20(suppl 1):20–130.

✓ 6. ✓ Statistics and Clinical Studies, NHS Blood and Transplant. Annual Report on Kidney Transplantation: Report for 2020-2021. https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/.

✓ 7. ✓ Foroutan F, Friesen EL, Clark KE, et al. Risk factors for 1-year graft loss after kidney transplantation: systematic review and meta-analysis. Clin J Am Soc Nephrol. 2019;14(11):1642–1650.

✓ 8. ✓ Rankin SC, Jan W, Koffman CG. Noninvasive imaging of living related kidney donors: evaluation with CT angiography and gadoliniumenhanced MR angiography. AJR Am J Roentgenol. 2001;177:349–355.

✓ 9. ✓ Namasivayam S, Small WC, Kalra MK, et al. Multidetector-row CT angiography for preoperative evaluation of potential laparoscopic renal donors: how accurate are we? Clin Imaging. 2006;30:120–126.

✓10. ✓ Ratner LE, Ciseck LJ, Moore RG, et al. Laparoscopic live donor nephrectomy. Transplantation. 1995;60:1047–1049.

11. Nanidis TG, Antcliffe D, Kokkinos C, et al. Laparoscopic versus open live donor nephrectomy in renal transplantation: a meta-analysis. Ann Surg. 2008;247:58–70.

✓12. ✓ Pace KT, Dyer SJ, Phan V, et al. Laparoscopic v open donor nephrectomy: a cost-utility analysis of the initial experience at a tertiary-care center. J Endourol. 2002;16:495–508.

13. Nicholson ML, Elwell R, Kaushik M, et al. Health-related quality of life after living donor nephrectomy: a randomized controlled trial of laparoscopic versus open nephrectomy. Transplantation. 2011;91:457–461.

14. Xiao Q, Fu B, Song K, et al. Comparison of surgical techniques in living donor nephrectomy: a systematic review and Bayesian network metaanalysis. Ann Transplant. 2020;25:e926677.

✓15. ✓ Ratner LE, Buell JF, Kuo PC. Laparoscopic donor nephrectomy: pro. Transplantation. 2000;70:1544–1546.

16. Brook NR, Nicholson ML. An audit over 2 years’ practice of open and laparoscopic live-donor nephrectomy at renal transplant centres in the UK and Ireland. BJU Int. 2004;93:1027–1031.

17. Peng P, Ding Z, He Y, et al. Hypothermic machine perfusion versus static cold storage in deceased donor kidney transplantation: a systematic review and meta-analysis of randomized controlled trials. Artif Organs. 2019;43:478–489.

✓18. ✓ Tingle SJ, Figueiredo RS, Moir JA, et al. Hypothermic machine perfusion is superior to static cold storage in deceased donor kidney transplantation: a meta-analysis. Clin Transplant. 2020;34(4):e13814.

✓19. ✓ Jochmans I, Brat A, Davies L, et al. Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised, doubleblind, paired, phase 3 trial. Lancet. 2020;396:1653–1662.

20. Nicholson ML, Hosgood SA. Renal transplantation after ex vivo normothermic perfusion: the first clinical study. Am J Transplant. 2013;13:1246–1252.

21. Hosgood SA, Saeb-Parsy K, Wilson C, et al. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion

versus static cold storage in donation after circulatory death renal

transplantation. BMJ Open. 2017;7:e012237.
22. Wheatley TJ, Doughman TM, Veitch PS, Nicholson ML. Subrectus pouch for renal transplantation. Br J Surg. 1996;83:419.
23. Wilson CH, Bhatti AA, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2005;(4):CD004925.
2✓ 4.✓ Abusin K, Rix D, Mohammed M, et al. Long-term adult renal graft outcome after ureteric drainage into an augmented bladder or ileal conduit. Transpl Int. 1998;11(suppl 1):S147–S149.
2✓ 5.✓ Osman Y, Shokeir A, Ali-el-Dein B, et al. Vascular complications after live donor renal transplantation: study of risk factors and effects on graft and patient survival. J Urol. 2003;169:859–862.
26. Hernández D, Rufino M, Armas S, et al. Retrospective analysis of surgical complications following cadaveric kidney transplantation in the modern transplant era. Nephrol Dial Transplant. 2006;21:2908–2915.
27. Granata A, Clementi S, Londrino F, et al. Renal transplant vascular complications: the role of doppler ultrasound. J Ultrasound. 2014;18:101–107.
2✓ 8.✓ Beyga ZT, Kahan BD. Surgical complications of kidney transplantation. J Nephrol. 1998;11:137–145.
2✓ 9.✓ Lacombe M. Arterial stenosis complicating renal allotransplantation in man: a study of 38 cases. Ann Surg. 1975;181:283–288.
30. Bruno S, Remuzzi G, Ruggenenti P. Transplant renal artery stenosis. J Am Soc Nephrol. 2004;15:134–141.
3✓ 1.✓ Pollak R, Veremis SA, Maddux MS, Mozes MF. The natural history of and therapy for perirenal fluid collections following renal transplantation. J Urol. 1988;140:716–720.
32. Zincke H, Woods JE, Leary FJ, et al. Experience with lymphoceles after renal transplantation. Surgery. 1975;77:444–450.
3✓ 3.✓ Ward K, Klingensmith 3rd WC, Sterioff S, Wagner HN Jr. The origin of lymphoceles following renal transplantation. Transplantation. 1978;25:346–347.
34. Mundy AR, Podesta ML, Bewick M, et al. The urological complications of 1000 renal transplants. Br J Urol. 1981;53:397–402.
35. Palmer JM, Chatterjee SN. Urologic complications in renal transplantation. Surg Clin North Am. 1978;58:305–319.
36. Nicholson ML, Veitch PS, Donnelly PK, Bell PR. Urological complications of renal transplantation: the impact of double J ureteric stents. Ann R Coll Surg Engl. 1991;73:316–321.
3✓ 7.✓ Lord RH, Pepera T, Williams G. Ureteroureterostomy and pyeloureterostomy without native nephrectomy in renal transplantation. Br J Urol. 1991;67:349–351.
3✓ 8.✓ Brook NR, Waller JR, Pattenden CJ, Nicholson ML. Ureteric stenosis after renal transplantation: no effect of acute rejection or immunosuppression. Transplant Proc. 2002;34:3007–3008.
3✓ 9.✓ Goldstein I, Cho SI, Olsson CA. Nephrostomy drainage for renal transplant complications. J Urol. 1981;126:159–163.
4✓ 0.✓ Ooms LSS, Moelker A, Roodnat JI, et al. Antegrade balloon dilatation as a treatment option for posttransplant ureteral strictures: case series of 50 patients. Exp Clin Transplant. 2018;16:150–155.
41. Smak Gregor PJ, Zietse R, van Saase JL, et al. Immunosuppression should be stopped in patients with renal allograft failure. Clin Transplant. 2001;15:397–401.
42. Augustine JJ, Woodside KJ, Padiyar A, et al. Independent of nephrectomy, weaning immunosuppression leads to late sensitization after kidney transplant failure. Transplantation. 2012;94:738–743.
43. Sener A, Khakhar AK, Nguan CY, et al. Early but not late allograft nephrectomy reduces allosensitization after transplant failure. Can Urol Assoc J. 2011;5:E142–E147.

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109

Prophylaxis and Treatment of Kidney Transplant Rejection

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The clinical presentation of the immune response to transplanted tissue (referred to as rejection) became apparent in 1960 when, after successful proof-of-principle kidney transplants were performed in identical twins, kidney transplantation was attempted between immunologically dissimilar individuals.[1] Eleven patients underwent lymphoid irradiation to prevent rejection after kidney transplant from nonidentical donors. Although 10 of 11 died of overwhelming infection, illustrating the potential consequences of immunosuppression, the lone surviving patient from this series subsequently experienced two episodes of acute rejection, both of which were treated with corticosteroids, and recovered good graft function. Thus, began the development of immunosuppressive agents that could prevent and treat rejection while not inducing severe life-threatening side effects. As a result of the development of newer immunosuppression medications, the incidence of acute rejection in the first year after transplant has significantly decreased over time and is now approximately 10% to 15%[2] (Fig. 109.1). However, the management of chronic rejection has remained a challenge, with continued attempts to better define the nature of injury and methods to prevent or reverse this process. As attention shifts to limiting the toxicity of immunosuppression medications (e.g., withdrawal of corticosteroids or calcineurin inhibitors [CNIs]) and attempts to increase access to transplant (e.g., performing transplants across human leukocyte antigen [HLA] and blood type barriers), management of acute rejection continues to be an important clinical issue.

DEFINITION

Rejection (both acute and chronic) is defined by histologic findings after kidney transplant biopsy. An adequate biopsy specimen contains at least 10 glomeruli and 2 small arteries, stained for hematoxylineosin (HE), periodic acid–Schiff (PAS) or methenamine silver, and Masson trichrome, and a specimen with seven to nine glomeruli and one artery is considered of marginal adequacy. When performed for clinical indications (kidney dysfunction), two separate cores should be obtained because the findings of rejection are often patchy in distribution (Fig. 109.2).[3]

The Banff Working Classification of Renal Allograft Pathology forms the basis of the histologic definition of rejection and is updated biannually (Boxes 109.1 and 109.2). First developed in 1993 with a primary focus on T-cell–mediated acute inflammatory infiltrates to classify the degree of rejection, updates in the classification differentiated humoral (antibody-mediated) and T-cell responses and further distinguished a chronic humoral form of injury previously classified as chronic allograft nephropathy (see Chapter 112).[4] This was based on the indirect identification of antibody-mediated injury by evidence of complement (C4d) deposition. C4d is a fragment of C4b that is generated after immunoglobulin G (IgG) and IgM binding to host antigens with activation of the classical complement pathway. C4b/C4d forms a covalent bond with proteins on tissue such as capillary endothelial cells via a sulfhydryl group and remains bound to tissue after immunoglobulin and other complement products have been released.[5] Staining for C4d, either by immunohistochemistry or immunofluorescence, indicates that an antibody-mediated process may be involved.

Although C4d remains a specific marker for antibody-mediated graft pathology, it has limited sensitivity.[6] Studies of endothelialassociated transcript (ENDAT) expression[7,8] and C4d-negative histologic findings from protocol biopsy studies in patients with microvascular inflammation[9] helped identify the clinical importance of C4d-negative antibody–mediated rejection, which led to these updated Banff criteria.

Antibody-Mediated Rejection

Acute antibody-mediated (humoral) rejection occurs in 5% to 7% of all transplants and is present in 20% to 30% of episodes of acute rejection[10] in patients with ABO- and HLA-compatible transplants, occurring typically within the first few weeks of transplantation or in association with a change or poor adherence to immunosuppression. Although patients who have preexisting donor-specific HLA alloantibodies (donor-specific antibodies) are at higher risk for acute humoral rejection, the identification of de novo donor-specific antibodies at the time of graft dysfunction is common. There is also increasing recognition of the pathologic role of non-HLA antibodies directed against autoantigens on the vascular endothelium. The diagnosis of acute humoral rejection requires (1) identification of circulating donor-specific antibodies, (2) evidence that those antibodies are interacting with the vascular endothelium, and (3) evidence that this interaction is causing tissue injury (Box 109.1 and Fig. 109.3).[6] Patterns of injury associated with acute humoral rejection range from acute tubular cell injury to thrombotic microangiopathy, but neutrophils and/or macrophages are typically present in peritubular capillaries. The requirement for evidence of antibody/endothelial interaction has been expanded beyond C4d staining and now includes at least moderate microvascular inflammation or evidence of increased ENDAT expression if using a validated assay.

Chronic active antibody-mediated rejection has been identified as a leading cause of late allograft loss[7,11] and is likely the result of an indolent alloimmune response that can result in transplant glomerulopathy and microcirculatory inflammation. Although transplant glomerulopathy is often associated with circulating donor-specific antibodies and C4d deposition, these diagnostic markers are not detected in 30% to 50% of cases.[12] One possibility is that transplant glomerulopathy is not solely due to a humoral response. Alternatively, the failure to detect donor-specific antibodies and C4d deposition could be due to non–complement-fixing antibodies and/or the waxing/waning nature of the humoral response.

The current Banff diagnostic criteria for chronic humoral rejection require (1) evidence of donor-specific antibodies, (2) evidence of current/recent antibody interaction with vascular endothelium, and (3)

One-Year Incidence of Acute Rejection Over Time
Associated With Immunosuppressive Agents

1-year acute rejection (%)

80
Atgam

60

Radiation
Prednisone

Cyclosporine (unmodified)

Mercaptopurine
OKT3

40

Cyclosporine (modified)
Tacrolimus
MMF
Thymoglobulin
Basiliximab

MPA

20

Sirolimus
Rituximab

Belatacept
Everolimus

0
1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020
Year

Fig. 109.1 One-year incidence of acute rejection over time as associated with the introduction of new immunosuppressive agents. MMF, Mycophenolate mofetil; MPA, mycophenolate sodium. (From Cooper JE. Evaluation and treatment of acute rejection in kidney allografts. Clin J Am Soc Nephrol. 2020;15[3]:430–438.)

Effect of Sample Site
on the Diagnosis of Rejection
Biopsy 1

Biopsy 2

Fig. 109.2 Biopsy Technique. Acute rejection begins as patchy, focal infiltrates and becomes homogeneous only in advanced stages. The intensity of mononuclear infiltrate seen on the biopsy sample would differ between core 1 and core 2. Routinely taking two core biopsy samples can help decrease the sampling errors, which can affect the histologic interpretation of rejection.

evidence of chronic tissue injury such as transplant glomerulopathy, multilamination of the peritubular capillary basement membrane, and/or arterial intimal fibrosis (Fig. 109.4).

T-Cell–Mediated Rejection

The original pathologic description of rejection is now referred to as T-cell–mediated rejection. The classification of acute T-cell–mediated

rejection (acute cellular rejection [ACR]) is based on the degree and location of mononuclear cell inflammation. Because interstitial inflammation and tubulitis are frequently present immediately beneath the kidney capsule (subcapsular inflammation) in stable allografts, this finding is not considered when interpreting an allograft biopsy result for the presence of rejection. When severe, interstitial inflammation may extend into tubules via injury to the tubular basement membrane (tubulitis).

The predominant phenotype of these infiltrates is a mixture of CD4+ and CD8+ T-cells; however, B-cells, eosinophils, and macrophages also may be present. Less commonly, endarteritis (endothelialitis) may be present in which T-cells and macrophages extend under the arterial endothelium, a phenomenon that may or may not be accompanied by interstitial inflammation or tubulitis. The finding of interstitial infiltrates and tubulitis in a kidney transplant biopsy is not specific to ACR, and other causes such as viral nephropathy (BK virus, less commonly cytomegalovirus), pyelonephritis, or posttransplant lymphoproliferative disease should be considered. In contrast, histologic evidence of endothelialitis is pathognomonic of rejection and may overlap with antibody-mediated injury.

Acute T-cell–mediated rejection is histologically classified in the Banff criteria by the degree of interstitial inflammation, the quantity of cells infiltrating into tubules, or by endothelialitis of the small arterioles. Type I ACR is characterized by the absence of endothelialitis, with interstitial inflammation of at least 25% of the parenchyma, and tubulitis (Box 109.2 and Fig. 109.5). Type II ACR is characterized by vascular involvement/endothelialitis (Fig. 109.6). Type III ACR is characterized by vascular inflammation that extends to the media (transmural) and may be accompanied by fibrinoid change and necrosis of the smooth muscle cells (Fig. 109.7). Types II and III ACR may or may not be associated with elements of type I ACR; thus the pathologic description of rejection should not be viewed as a pathogenic continuum. However, types II and III ACR often require different therapeutic interventions and carry different prognostic implications than type I ACR (see later sections).

Chronic active T-cell–mediated rejection is a histologic diagnosis that refers to arterial intimal fibrosis specifically with evidence of mononuclear cell infiltration and formation of neointima (Fig. 109.8). This is distinguished from chronic humoral rejection by the location of vascular injury and lack of evidence of pathogenic antibody; it is

BOX 109.1 Banff Classification of Antibody-Mediated Rejection

BOX 109.2 Banff Classification of T-Cell–Mediated Rejection

Active (All Three Criteria Must Be Met for Diagnosis)

1. Acute tissue injury with 1 or more of the following:
   - Microvascular inflammation (g > 0, ptc > 0)
   - Intimal or transmural arteritis (v > 0)
   - Acute thrombotic microangiopathy
   - Acute tubular injury
2. Evidence of current/recent antibody interaction with vascular endothelium with one or more of the following:
   - Linear peritubular capillary C4d staining
   - Moderate microvascular inflammation (g + ptc ≥ 2)
   - Increased expression of validated gene transcripts/classifiers in the biopsy tissue strongly associated with antibody-mediated rejection
3. Serologic evidence of donor-specific antibodies, including antibodies to human leukocyte antigens and nonhuman leukocyte antigens. C4d staining or expression of validated transcripts/classifiers (criterion 2 earlier) may substitute for donor-specific antibodies.

Borderline or Suspicious

Foci of tubulitis (t1–3) with mild interstitial inflammation (i1) or mild tubulitis (t1) with moderate to severe interstitial inflammation (i1 or i2)

Chronic Active (All Three Criteria Must Be Met for Diagnosis)

1. Morphologic evidence of chronic tissue injury, including 1 or more of the following:
   - Transplant glomerulopathy (cg > 0)
   - Severe peritubular capillary basement membrane multilayering on electron microscopy
   - Arterial intimal fibrosis
2. Identical to criterion 2 for active antibody-mediated rejection, above
3. Identical to criterion 3 for active antibody-mediated rejection, above

Chronic Inactive (All Three Criteria Must Be Met for Diagnosis)

1. Transplant glomerulopathy (cg > 0) or severe ptc basement membrane multilayering
2. Absence of criterion 2 of current/recent antibody interaction with the endothelium
3. Prior documented diagnosis of active or chronic active antibody-mediated rejection and/or documented prior donor-specific antibodies

cg, Chronic glomerulopathy; g, glomerulitis; ptc, peritubular capillaritis; v, vasculitis.

Modified from Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T-cell- and antibody-mediated rejection. Am J Transplant. 2020;20:2318–2331.

distinguished from other nonimmunologic processes that may lead to vascular and interstitial fibrosis by the presence of persistent infiltrating cells within vessels. This is covered in greater detail in Chapter 107

Borderline Rejection

The finding of inflammation in 10% to 25% of the interstitium with tubulitis of less than four mononuclear cells per tubular cross-section is classified as borderline rejection, which remains a pathologic definition without clear clinical significance. When identified in the setting of graft dysfunction or with other findings such as glomerulitis, the risk for progression to clinical rejection on subsequent biopsies is increased and thus treatment may be considered.13

CLINICAL MANIFESTATIONS

The clinical presentation of acute rejection is common to both T-cell–mediated and antibody-mediated rejection. Patients typically present with a rapid rise in serum creatinine and in severe cases may have decreasing urine output, weight gain, fever, or graft tenderness. The clinical findings are commonly nonspecific, and other etiologies of graft dysfunction should be considered at the time of presentation (Box 109.3) together with the patient’s risk for acute rejection (Box 109.4). As a result of the increase in the number of patients who undergo transplantation despite a risk factor for humoral rejection (e.g., presensitization, known donorspecific antibody in desensitization protocols, and ABO-incompatible transplants), approximately 25% of acute rejection episodes now have a humoral component. In acute humoral rejection there may be features of thrombotic microangiopathy with anemia, evidence of hemolysis, and thrombocytopenia. If there is immediate cyanosis of the graft on revascularization (hyperacute rejection) or an abrupt decline in urine output and graft tenderness 3 to 14 days after transplant (delayed hyperacute or accelerated rejection), donor-specific antibody is implicated. Typically, there is type III ACR and interstitial hemorrhage on biopsy.

Acute

Grade IA: Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i > 2) and moderate tubulitis (t2, 4–10 mononuclear cells/tubular cross section)

Grade IB: Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i > 2) and severe tubulitis (t3, >10 mononuclear cells/tubular cross section)

Grade IIA: Mild to moderate intimal arteritis (v1, 0%–25% of luminal area), with or without interstitial inflammation and/or tubulitis

Grade IIB: Severe intimal arteritis (v2, >25% of luminal area), with or without interstitial inflammation and/or tubulitis

Grade III: Transmural arteritis and/or fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocyte inflammation (v3)

Chronic Active

Grade IA: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) and >25% of total cortical parenchyma (ti2 or ti3) with moderate tubulitis (t2 or t-IFTA2) involving one or more tubules

Grade IB: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) and >25% of total cortical parenchyma (ti2 or ti3) with severe tubulitis (t3 or t-IFTA3) involving one or more tubules

Grade II: Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)

i, Interstitial inflammation; i-IFTA, inflammatory interstitial fibrosis and tubular atrophy; t, tubulitis; t-IFTA, tubulitis in areas of tubular atrophy; v, vasculitis.

Modified from Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T-cell- and antibody-mediated rejection. Am J Transplant. 2020;20:2318–2331.

PROPHYLAXIS AND PREVENTION

Prophylaxis

The primary goal of transplant management is prevention of immunologic graft loss in the early period after transplant. Over time, the risk for acute rejection diminishes and the approach to immunosuppressive therapy shifts toward considerations of adverse effects of the

A
B

C

D

Fig. 109.3 Acute Antibody-Mediated Rejection. (A) Peritubular and glomerular capillaries contain numerous polymorphonuclear leukocytes and mononuclear cells. (B) Numerous polymorphonuclear leukocytes are observed in a peritubular capillary (arrows). Interstitial edema is noted. (PAS stain, ×200.) (C) Immunofluorescence staining of peritubular capillaries with C4d. (Fresh frozen tissue sample, ×250.) (D) Immunohistochemistry demonstrating peritubular capillary staining of C4d. (Paraffin-embedded tissue, ×480.) (From Moll S, Pascual M. Humoral rejection of organ allografts. Am J Transplant. 2005;5:2611–2618.)

Fig. 109.4 Transplant Glomerulopathy. Light microscopy showing typical membranoproliferative changes, including glomerular basement membrane duplication and thickening (arrows).

*

Fig. 109.5 Banff Class I Cellular Rejection. Mononuclear cell infiltrate of the tubules (arrow) and interstitium (asterisk) (Hematoxylin-eosin stain, ×200.) (Courtesy Dr. Maxwell Smith, University of Colorado, Denver.)

Fig. 109.8 Chronic T-Cell–Mediated Rejection. Chronic allograft arteriopathy with the formation of a fibrous neointima (between arrowheads) and embedded mononuclear cell infiltration (arrow). (Hematoxylin-eosin stain, ×200.) (Courtesy Dr. Maxwell Smith, University of Colorado, Denver.)

BOX 109.3 Differential Diagnosis of Kidney Allograft Dysfunction

Fig. 109.6 Banff Class II Cellular Rejection. Type II rejection, called acute vascular rejection, manifests with endothelialitis with mononuclear cell infiltration (arrows) beneath the arterial endothelium. (PAS stain, ×200.) (Courtesy Dr. Agnes Fogo, Vanderbilt University, Nashville, TN.)

Fig. 109.7 Banff Class III Cellular Rejection. Severe small-vessel vasculitis with transmural mononuclear cell infiltration, fibrinoid necrosis (arrows), and very swollen endothelial cells (asterisks). (PAS stain, ×400.) (From Racusen LC, Colvin RB, Solez K, et al. Antibody-mediated rejection criteria—an addition to the Banff 97 classification of renal allograft rejection. Am J Transplant. 2003;3:708–714.)

Week 1 Posttransplantation
- Acute tubular necrosis
- Hyperacute or accelerated rejection
- Urologic
- Obstruction
- Urine leak
- Vascular thrombosis
- Renal artery
- Renal vein
- Volume contraction

Less Than 12 Weeks Posttransplantation
- Acute rejection
- Calcineurin inhibitor toxicity
- Volume contraction
- Urologic
- Obstruction
- Infection
- Bacterial pyelonephritis
- Viral infections
- Interstitial nephritis
- Recurrent disease

Longer Than 12 Weeks Posttransplantation
- Acute rejection
- Volume contraction
- Calcineurin inhibitor toxicity
- Urologic
- Obstruction
- Infection
- Bacterial pyelonephritis
- Viral infections
- Chronic allograft nephropathy
- Recurrent disease

- Renal artery stenosis
- Posttransplantation lymphoproliferative disorder

BOX 109.4

Rejection

Risk Factors for Acute

High Risk
- Donor-specific HLA sensitization
- Positive cell-based crossmatch (flow cytometry or CDC)
- Donor-specific antibody on single-antigen bead analysis
- Delayed graft function
- Deceased donor source
- Increased donor age
- Prolonged ischemic time
- Donor brain death
- Donor acute kidney dysfunction
- HLA mismatching
- ABO incompatibility
- Corticosteroid minimization
- Infection
- Bacterial pyelonephritis
- Cytomegalovirus
- Adolescent recipient
- Previous rejection episode

Low Risk
- Zero HLA mismatch
- Elderly recipient of young donor kidney
- Preemptive transplantation
- Living donor source
- First transplant

CDC, Complement dependent cytotoxicity; HLA, human leukocyte antigen.

therapy and risks for other events such as cardiovascular (CV) disease and malignancy. Therefore, management includes intensive immunosuppression and monitoring in the first months after transplant with a reduction in the intensity of treatment thereafter.

Prevention of Acute T-Cell–Mediated Rejection:
Induction Therapy

A brief course of potent immunosuppression at the time of transplant (referred to as induction therapy) is commonly used to prevent acute rejection in transplant recipients, regardless of immunologic risk. According to the Scientific Registry of Transplant Recipients (SRTR), over 90% of US kidney transplant recipients received induction therapy in 2018. The assessment of immunologic risk at the time of transplant has historically considered factors such as overall level of anti-HLA sensitization (panel reactive antibody, or PRA), repeat transplant, African-American race, and recipient age. More recent data suggest pretransplant donor-specific antibodies (DSA) and HLA A/B/DR mismatch to be the main predictors of antibody-mediated rejection and T-cell–mediated rejection, respectively, while PRA and repeat transplantation had no predictive effect14 (Box 109.4). There continues to be significant variability among transplant centers in the assessment of immunologic risk and its influence on induction immunosuppression prescribing practice. Nevertheless, for higher immunologic risk patients, induction therapy is usually combined with standard doses of immunosuppression to prevent rejection. For those at lower immunologic risk, induction therapy is often employed to minimize exposure to maintenance immunosuppression.

Induction agents can be classified as T-cell depleting or nondepleting. Nondepleting agents include the monoclonal humanized interleukin-2 (IL-2) receptor antibody (IL-2ra) basiliximab. The IL-2 receptor was identified as a potential immunosuppressive target because it is present on T-cells and inhibition of IL-2/IL-2r signaling inhibits T-cell proliferation (see Chapter 106). Use of IL-2ra has led to lower rates of acute rejection with minimal side effects when combined with cyclosporine-based immunosuppression in the absence of mycophenolate.[15] Importantly, these agents have not been studied in a prospective randomized fashion in combination with a tacrolimus/mycophenolate-based maintenance regimen; thus questions remain regarding the relative benefits of the addition of IL-2ra with more potent, commonly used maintenance agents.[16]

Depleting agents include antithymocyte globulin and anti-CD52 monoclonal antibody (alemtuzumab). Unlike the IL-2ra agents, none of these agents have been compared with placebo for the prevention of rejection, and thus their use as induction agents is considered off-label in the United States. Antithymocyte globulin is a polyclonal preparation of antibodies directed at T-cells prepared by immunizing animals with human lymphoid cells derived from the thymus. Currently, the most common antilymphocyte preparation in use is rabbit antithymocyte globulin (rATG). Alemtuzumab binds to CD52, an antigen of unclear physiologic significance that is present on both B and T-cells, and results in depletion of both lymphoid cell lines. Its ability to induce prolonged, significant lymphopenia for up to 6 to 12 months after dosing led to its use in refractory chronic lymphocytic leukemia. Unlike other depleting agents, alemtuzumab is a humanized antibody, and therefore has fewer infusion-related side effects than rATG. Initial trials suggest equivalence to other depleting agents for preventing rejection, but the long-term impact of prolonged lymphopenia on the risk for infection or posttransplant lymphoproliferative disorder has yet to be determined, and comparative trials of induction agents are lacking (see later discussion). Alemtuzumab has been rebranded for use in multiple sclerosis in the United States and is often cost-prohibitive as transplant induction therapy; however, it is still in use in some US and European centers.

Although depleting agents are effective in inhibiting the T-cell response, there is concern about long-term safety. Registry analyses suggest there is an increased risk for future development of lymphoma with depleting agents compared with nondepleting agents or no induction therapy,[17,18] an association that appears to be dose dependent. Therefore, the potential for recovery or improvement of graft function as a result of repeated or prolonged courses of depleting antibody therapy must be balanced against the potential long-term risk for malignancy.

Three multicenter randomized trials have compared the efficacy of induction agents in the prevention of acute rejection. A multicenter trial in patients at high risk for acute rejection (defined as recipients with an elevated risk for delayed graft function, elevated PRAs, repeat transplants, or HLA mismatches) compared the IL-2ra basiliximab to rATG with maintenance immunosuppression of cyclosporine, mycophenolate mofetil (MMF), and prednisone.[19] At 12 months, the rate of acute rejection in the basiliximab cohort was 26% versus 16% in the rATG arm. A second trial in patients at high risk for acute rejection (defined by elevated PRAs, repeat transplants, or loss of a previous kidney transplant to acute rejection) compared the IL-2ra daclizumab to rATG, with a remarkable increase in the risk for rejection for patients randomized to daclizumab (27%) compared with rATG (15%) at 1 year.[20] Thus, for patients at increased risk for rejection, rATG provided greater prevention of acute rejection, supporting its use in higher risk populations. In contrast, the European multicenter randomized controlled HARMONY trial showed no difference in the proportion of low immunologic risk patients with acute rejection receiving either rATG followed by rapid steroid withdrawal or basiliximab with or without rapid steroid withdrawal.21 Finally, a clinical trial compared anti-CD52 to either rATG in high-risk patients (repeat transplant, elevated PRAs, or Black ethnicity) or to an IL-2ra in low-risk patients, followed by early corticosteroid withdrawal and maintenance tacrolimus and mycophenolate immunosuppression.22 Acute rejection rates over the first 12 months in the high-risk arms were 10% for anti-CD52 and 13% for rATG and in the low-risk arms were 20% for IL-2ra and 3% for anti-CD52. However, acute rejection rates in anti-CD52–treated patients were higher in both low- and high-risk arms, suggesting a delayed (>12 months) immunologic risk for immune reconstitution with anti-CD52 therapy. This may be problematic for transplant care providers who generally adhere to less rigorous late (>12 months) clinical monitoring protocols for otherwise stable transplant recipients. Therefore, we recommend adhering to a more frequent late (>1 year) clinical monitoring protocol for patients receiving induction with alemtuzumab.

In summary, it remains unclear whether induction therapy is required in low-risk patients pending further prospective head-tohead trials, whereas patients at higher immunologic risk appear to benefit from lymphocyte-depleting treatment. Based on SRTR data in 2018, approximately 75% of US transplant recipients received rATG induction and 20% received IL-2ra induction, with the remaining cohort receiving either no induction or other agents. Induction regimens are commonly protocolized at individual transplant centers by balancing immunologic protection against cost and the risk of adverse effects. Common dosing regimens of induction agents are listed in Table 109.1

Prevention of Acute Antibody-Mediated Rejection: Desensitization and Paired Exchange

Nearly all patients with high levels of donor-specific antibodies before transplant or who are blood type–incompatible to the donor before transplant will develop acute antibody-mediated rejection after transplant without pretransplant intervention such as desensitization protocols. Desensitization protocols typically involve removal of preformed antibody with plasma exchange and/or suppression of antibody production and action with intravenous immunoglobulin (IVIG) or B-cell inhibition with rituximab. Choice of desensitization strategy is influenced by factors such as type of transplant (living vs. deceased donor) and the degree of HLA-antibody reactivity one is attempting to overcome. In the case of living donation the crossmatch barriers are known in advance, so plasma exchange followed by low-dose (100–200 mg/kg) IVIG can be arranged followed by transplantation when the desired crossmatch results are obtained. Protocols consisting of monthly highdose IVIG (1–2 g/kg) infusions with or without rituximab23 have been used when pretransplant plasma exchange is not feasible, such as in sensitized patients without living donor options awaiting a deceased donor kidney, but the effectiveness of this strategy has been questioned.24 Published desensitization agents and protocols are listed in Table 109.2

TABLE 109.1

Desensitization strategies allow transplantation to proceed in many sensitized patients, but are associated with high rates of acute rejection, ranging from 20% to 70% (depending factors including specific protocol, induction immunosuppression, and immunologic risk), which are often humoral and frequently progress to chronic antibody-mediated injury.25 26

Kidney paired exchange programs increasingly have been used over the past 10 years in Europe and the United States and allow patients with existing HLA- or ABO-incompatible living donors to receive a compatible transplant while avoiding toxicities and long-term immunologic damage associated with desensitization protocols. Donorrecipient “chains” are usually initiated by a single nondirected live donor and can result in multiple patients with incompatible live donors receiving HLA- and ABO-compatible organs. According to the US

Agents Used for Induction and Treatment of T-Cell–Mediated Rejection

Agent	Target	Dose (Induction)	Dose (Rejection)
Methylprednisolone	B cells, T-cells, macrophages	250–500 mg IV with induction therapy, followed by taper over 1–5 days	3–5 mg/kg (250–500 mg) IV × 3–5 days
Basiliximab	IL-2 receptors on cells	20 mg IV × 2 on days 0 and 4	N/A
rATG	T-cell surface antigens	1–1.5 mg/kg IV × 4–14 days	1–1.5 mg/kg IV × 7–14 days
Alemtuzumab	CD52 on T and B cells	30–60 mg × 1 or 2 on days 0 and 2	Same as induction

IL-2, Interleukin-2; IV, intravenous; N/A, not applicable; rATG, rabbit antithymocyte globulin.

TABLE 109.2

Agents Used for Desensitization and Treatment of Antibody-Mediated Rejection

Treatment

Mechanism

Protocol (Desensitization)

Dose (Antibody-Mediated Rejection)

Plasma exchange[a]

Antibody removal

2–4 sessions or until XM acceptable, combined with IVIG

2–5 treatments, daily or every other day, combined with IVIG

IVIG[a]

Multiple, antibody inhibition(?)

100–200 mg/kg after plasma exchange until acceptable XM or 1–2 g/kg/mo until transplant

100–200 mg/kg after plasma exchange

Rituximab[a]

Anti-CD20 B-cell inhibition

375 mg/m2 (day 15) combined with IVIG 1–2 g/kg (days 1 and 30)

375 mg/m2 with plasma exchange and IVIG

Bortezomib

Plasma cell inhibition

Not established

1.3 mg/m2 × four doses over 1–2 wk, usually combined with plasma exchange and IVIG

Eculizumab

Terminal complement C5 inhibition

Not established

For prevention in + XM transplant: 600–1200 mg/wk × 4 then biweekly until successful antibody reduction

Splenectomy

B-cell removal

No longer used

N/A, for severe refractory cases only

[a] Commonly

used.
IVIG, Intravenous immunoglobulin; N/A, not applicable; XM, crossmatch.

Renal Data System, paired exchange accounted for 14% of living donor transplants in 2018, up from 5% in 2009. Recent data show no difference in graft or patient survival at 3, 5, and 7 years between patients receiving paired exchange transplants through the US National Kidney Registry versus those receiving direct living donor transplants in the United States, despite a higher burden of risk factors in the patients transplanted through paired exchange.27

Maintenance Therapy for Prevention of Acute Rejection

Current maintenance immunosuppression most commonly includes a CNI, an antiproliferative agent, and corticosteroids. This combination of agents forms the standard against which novel strategies are compared, such as corticosteroid withdrawal/avoidance and CNI withdrawal/avoidance. Cyclosporine has been replaced by tacrolimus as the preferred CNI in the United States and, together with the antiproliferative agent MMF, it forms the most common immunosuppressive regimen in current practice in most high-income countries (Table 109.3).

More affordable regimens that include cyclosporin A (CsA) and azathioprine (AZA) are commonly used in areas where resources are more limited, but appear to lead to higher rates of rejection.28

Calcineurin Inhibitors in the Prevention of Acute Rejection

Since the early 1980s, when the introduction of CsA led to reduced risk of acute rejection and to better graft survival,29 calcineurin inhibition has been a cornerstone of maintenance immunosuppression.

Tacrolimus, first introduced in 1990s and compared head-to-head with CsA in multiple trials, provides greater protection from acute rejection but with a different side effect profile. A recent meta-analysis of trials demonstrated that compared with CsA, tacrolimus reduced the risk of acute rejection by 31% but increased the risk of new diabetes by 86%. Tacrolimus was also associated with better death-censored graft survival (hazard ratio, 0.56), particularly at target trough doses less than 10 ng/mL, a finding that was not shown in individual studies.30

Antiproliferative Agents in the Prevention of Acute Rejection

AZA was the first antiproliferative agent used in kidney transplantation and was used initially in conjunction with corticosteroids and later with CsA. Although its development was critical in the advancement of allotransplantation, acute rejection was quite common, with acute rejection rates of 35% to 40% in a number of clinical trials using CsA/AZA/prednisone. Newer antiproliferative agents emerged in the 1990s with MMF and later with the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus, which significantly reduced the incidence of acute rejection.

TABLE 109.3 Immunosuppression Regimens in the United States, 2018

Regimen	Percent (Approximated)
Induction Regimens at Time of Transplant	
IL-2 receptor antibody	20
T-cell depleting	72
Maintenance Regimens at Time of Hospital Discharge	
TAC/MMF-MPA/Pred	65
TAC/MMF-MPA	
Other	

30
5

MMF, Mycophenolate mofetil; MPA, mycophenolate acid; Pred, prednisone; TAC, tacrolimus.
Modified from OPTN/SRTR Annual Report, 2020.

MMF is a purine antagonist that interferes with DNA synthesis in rapidly dividing cells such as activated lymphocytes, and it gained popularity after a number of multicenter prospective clinical trials demonstrated that it reduced the risk of acute rejection by approximately 50% compared with AZA.31 32 A recent meta-analysis of 23 studies showed MMF to be associated with significantly fewer cases of acute rejection and graft loss compared with AZA.28 Most studies in this analysis reported outcomes of MMF and AZA in combination with CsA and thus may not translate to regimens using tacrolimus. One drawback of MMF has been its poor gastrointestinal (GI) tolerability, which often results in reduction of therapy with attendant risks for acute rejection33 and graft loss.34 An MMF analog, enteric-coated mycophenolate acid (MPA), has been developed and appears to be “noninferior” in efficacy to MMF,35 with fewer GI side effects reported in one open-label study.36

Similar to MMF, the mTOR inhibitors sirolimus and everolimus were initially tested in clinical trials as a substitute for AZA and reduced the risk of acute rejection to a similar extent as MMF.37 mTOR inhibitors inhibit the progression from G1 to S phase of the cell cycle and appear to have additional antiproliferative effects on nonimmune cells that may increase the risk of side effects (impaired wound healing, lymphocele formation, proteinuria, and slower recovery from delayed graft function) but may reduce the incidence of viral infection and malignancy.38 39 mTOR inhibitors also augment the nephrotoxic effects of CNI, and therefore a reduced dose of CNI is advisable when used together with mTOR inhibitors. A recent large trial (TRANSFORM) randomized 2037 subjects to reduced-dose CNI, most commonly tacrolimus (tacrolimus C0 2–4 ng/mL) in combination with everolimus (everolimus C0 3–8 ng/mL), or standard CNI (e.g., tacrolimus C0 6–10 ng/mL) with mycophenolate.40 At 12 months posttransplant, noninferiority was demonstrated between treatment arms for the combined endpoint of treated biopsy-proven acute rejection or estimated glomerular filtration rate (eGFR) less than 50 mL/min/1.73 m2 (48.2% in everolimus arm vs. 45.1% in mycophenolate arm) with no difference in graft loss or death but less cytomegalovirus and BK virus infections in the everolimus arm.

Acute Rejection Rates in Calcineurin-Sparing and CorticosteroidSparing Immunosuppression Regimens

There has been increasing interest in how best to minimize side effects of immunosuppression. Avoidance of CNIs offers the hope of prolonged graft survival given the inherent nephrotoxicity of these medications, and avoidance of corticosteroids offers the hope of reducing a number of cosmetic, metabolic, and CV side effects attributable to prednisone.

In the United States approximately one-third of patients undergo early corticosteroid cessation (within 7 days after transplant).41 Generally, patients at lower immunologic risk (low PRAs, first transplants) are selected,42 43 and immunosuppression includes induction therapy, a CNI, and an antiproliferative agent. The proportion of patients with acute rejection in single-center studies ranges from 10% to 15%. In the largest prospective, double-blind multicenter study to date of corticosteroid cessation versus standard corticosteroid maintenance,44 a standard steroid taper or a rapid elimination of steroids at 7 days posttransplant was compared on the background of induction therapy plus a tacrolimus/MMF-based immunosuppression.

Patient survival, graft survival, and creatinine clearance were comparable at 5 years. CV risk factors and weight gain were not significantly different between groups, but corticosteroid withdrawal was associated with less bone disease, less insulin-requiring new-onset diabetes, and lower triglyceride levels. One cause for concern with corticosteroid withdrawal was that rejection rates were higher (18% vs. 11%, P = .04), and a post hoc analysis suggested a higher proportion of chronic allograft nephropathy in the corticosteroid withdrawal arm. In contrast, the aforementioned HARMONY study reported similar rejection rates and significant reductions in posttransplant diabetes in two rapid (8-day) steroid withdrawal arms (one using basiliximab and the other using rATG induction) compared with the control arm of basiliximab induction and maintenance steroids, with all patients receiving tacrolimus and MMF.21

Clinicians must weigh the possibility of higher rejection risk versus the potential benefits when counseling patients regarding corticosteroid withdrawal. Consideration of corticosteroid withdrawal is best supported for the patient with a lower risk of rejection (low immunologic risk, expected immediate graft function) or increased risk of corticosteroid-related complications such as bone disease and diabetes.

CNI avoidance has been studied with both dual therapy (MMF/prednisone) and triple therapy with two antiproliferative agents (sirolimus/MMF/prednisone) in combination with induction therapy. In general, MMF/prednisone maintenance immunosuppression does not appear to effectively prevent rejection (70% incidence in one pilot study45), and although single-center studies report acute rejection rates of 6% to 13% with sirolimus/MMF/prednisone therapy,46 47 a large multicenter trial using this combination and target trough concentrations of sirolimus 4 to 8 ng/mL also revealed an excessively high acute rejection rate (38%).48 CNI avoidance with the costimulation blocker belatacept also is associated with a higher proportion of early acute rejection than CNI-based regimens but still may better protect glomerular filtration rate (GFR) over the longer term. In the BENEFIT trial, which compared 2 dosing regimens of belatacept (low and moderate intensity) to CsA with IL-2ra induction and MPA/prednisone maintenance,49 higher 1-year acute rejection rates were noted in the belatacept arms (22% and 17% for higher and lower intensity, respectively, vs. 7% for CsA) but graft survival was comparable and measured GFR was significantly higher for those receiving belatacept (65 and 63 mL/min for high- and low-intensity belatacept vs. 50 mL/min for CsA). With follow-up to 7 years, the belatacept arms demonstrated a 43% reduced risk for a composite endpoint of death or graft loss compared with CsA.50 Importantly, patients with low immunologic risk were selected for study, and excluded those who were Epstein-Barr virus (EBV)-seronegative given higher rates of posttransplant lymphoproliferative disorder associated with belatacept use in previous reports.51

A post hoc analysis of patients included in both the BENEFIT and BENEFIT-EXT studies (the latter including patients receiving extended-criteria donor kidneys) showed significantly lower blood pressure, serum lipids, and incidence of new-onset diabetes in those randomized to belatacept regimens compared with CsA.52 We suggest that EBV-seronegative patients at low immunologic risk, in particular those with pretransplant metabolic profiles at risk for posttransplant metabolic complications, may benefit from belatacept-based CNI-free immunosuppression.

In contrast to their use in strategies, that avoid CNI, mTOR inhibitors have achieved relative success when used in CNI withdrawal53 54 and conversion protocols. In one study, patients receiving a CNI, MMF, and prednisone were randomized to continue this regimen or undergo CNI conversion to sirolimus at 1 to 6 months after transplant with statistically similar rates of acute rejection and comparable kidney function at 2 years.55 Another study, employing a similar approach of CNI conversion to everolimus at 4 to 5 months posttransplant, demonstrated equivalent rates of acute rejection (15% in both groups) and significantly better eGFR at 12 months in the conversion group (72 mL/min vs. 62 mL/min in the CNI continuation arm).56 A recent meta-analysis that included 23 studies comparing CNI conversion to mTOR inhibitors found a modest improvement in GFR with no difference in rates of rejection or graft loss.57 Widespread acceptance of CNI to mTOR inhibitor conversion strategies has been hindered because of mTOR inhibitor–related side effects and reluctance to alter immunosuppression in stable transplant recipients.

Ideally, a strategy of combined CNI and steroid avoidance would eliminate the chronic accumulation of side effects and toxicities caused by these agents. A recent trial using depleting antibody induction (alemtuzumab or rATG) and belatacept/MMF-based immunosuppression combined with early corticosteroid withdrawal demonstrated comparable kidney function and patient and graft survival compared with rATG, tacrolimus/MMF-based immunosuppression with early corticosteroid withdrawal.58 However, 1-year acute rejection rates were still higher in the belatacept cohorts (15.9% with alemtuzumab, 22.1% with rATG) compared with the tacrolimus cohort (4.8%, P = .024 and < .001, respectively). Thus, there is still room for improvement and additional immunosuppression strategies are needed to minimize side effects while preventing alloimmunity. Acute rejection rates by treatment regimen reported in recent multicenter clinical trials are shown in Table 109.4.

TREATMENT

Acute T-Cell–Mediated Rejection

Treatment of T-cell–mediated acute rejection is often directed by the findings on biopsy and the clinical response to pulse corticosteroids. For the patient with graft dysfunction and biopsy-proven rejection, treatment with intravenous methylprednisolone 3 to 5 mg/kg (250–500 mg/day) for 3 to 5 days is often effective if the histologic injury is tubulointerstitial (Banff class IA or IB). Remarkably few studies of the clinical response to corticosteroids in the treatment of acute rejection have been performed under modern immunosuppression, but prior data suggest that 60% to 70% of patients will respond with improved urine output and decreasing serum creatinine within 5 days. If there is inadequate response after corticosteroid pulse therapy or if there is vascular involvement (Banff class IIA, IIB), corticosteroids often must be supplemented with T-cell–depleting antibody therapies in a similar dosing strategy but longer treatment course compared with their use for induction (see Table 109.1). The duration of treatment has typically been 7 to 14 days, with no clinical trials investigating the efficacy of shorter courses versus longer courses. For patients who are on a maintenance regimen that is not tacrolimus based, tacrolimus conversion may be considered in the setting of rejection with an inadequate response to corticosteroids,59 whereas for patients on a corticosteroid-free regimen, reinstitution of maintenance prednisone may be warranted.60 For patients who do not respond adequately to corticosteroids, T-cell–depleting agents are required. A typical course of rATG for T-cell–mediated rejection is 1.5 mg/kg for 4 to 14 days dictated by clinical response and absolute lymphocyte counts, again with no controlled study comparing one treatment regimen versus another.

Acute Antibody-Mediated Rejection

Treatment of acute humoral rejection is indicated when the triad of graft injury, evidence of antibody/endothelium interaction, and circulating donor-specific antibody is present, but should also be considered in high-risk circumstances (prior desensitization or known donor-specific antibody) even if all three criteria are not met. Highquality randomized trials investigating treatment options for acute humoral rejection are lacking,61 and strategies are generally dictated by center experience. Traditionally, treatment has entailed plasma exchange (to remove the pathogenic immunoglobulin[s]) and IVIG (to inhibit/suppress antibody production). In general, at least 5 plasma exchange treatments should be administered with 1 to 2 g/kg total dose

TABLE 109.4 Maintenance Immunosuppression and Reported Rejection Rates in Randomized
Multicenter Trials
Regimen

Induction

Low Immunologic Risk
CsA/AZA/Pred
CsA/AZA/Pred

IL-2ra

CsA/MMF/Pred

CNI Dose or Trough Level
Goal (ng/mL)

Antiproliferative Dose or
Trough Level Goal

Acute Rejection at 6
Months (%)

4 mg/kg/d

1.5–2 mg/kg/day

36

Not stated

Not stated

22

150–300 × 3 mo, 100–200

1 g bid

24

CsA/MMF/Pred

IL-2ra

125–400 × 3 mo, 100–300

1 g bid

12

TAC/AZA/Pred

OKT3 or Atgam

5–14

1.5 mg/kg/day

32

TAC/MMF/Pred

OKT3 or Atgam

5–14

1 g bid

7

TAC/MMF/Pred

IL-2ra

7–16 × 3 mo, 5–15

1 g bid

4

CsA/SRL/Pred

200–350 × 1 mo, 200–300 × 1 mo,
150–250

2 mg/day

17

TAC/SRL/Pred

8–16 × 3 mo, 5–15

4–12 ng/mL

13

High Immunologic Risk
CsA/SRL/Pred
IL-2ra or rATG

200–300 0–14 days 150–200

10–15 ng/mL

14a

TAC/SRL/Pred

10–15 0–14 days 5–10

10–15 ng/mL

17

IL-2ra or rATG

Drug Minimization or Avoidance
CsA (low)/MMF/Pred
IL-2ra

50–100

1 g bid

23

TAC (low)/MMF/Pred

IL-2ra

3–7

1 g bid

1248

TAC/MMF

IL-2ra or rATG

10–20 × 3 mo, 5–15

1.5 g bid × 14 days 1 g bid

944

SRL/MMF/Pred

IL-2ra

N/A

SRL 4–8 ng/mL MMF 1 g bid

38

Bela/MMF/Pred

IL-2ra

N/A

1 g bid

22 (MI) 17 (LI)a,49,50

CNI → SRL/MMF/Pred

IL-2ra or rATG or
OKT3

N/A

SRL 5–10 ng/mL MMF 1–1.5 g bid

7.4a

CsA → EVL/MMF/Pred

IL-2ra

N/A

EVL 6–10 ng/mL MMF 1 g bid

15a

TAC (low)/EVL/Pred

IL-2ra or rATG

Month 0–2; 3–6; >6:
TAC 4–7; 2–5; 2–4

EVL 3–8 ng/mL

10a

Bela/MMF

Anti-CD52 or rATG

N/A

MMF 1 g bid

16a (anti-CD52); 22a (rATG)

Bold denotes suggested regimens by the authors based on available data.
aAcute rejection rate at 12 months.
AZA, azathioprine; Bela, belatacept; bid, twice daily; CNI, calcineurin inhibitor; CsA, cyclosporine A; EVL, everolimus; IL-2ra, interleukin-2 receptor antibody; LI, less intensive; MI, more intensive; MMF, mycophenolate mofetil; N/A, not applicable; Pred, prednisone; rATG, rabbit antithymocyte globulin; SRL, sirolimus; TAC, tacrolimus.

IVIG. IVIG is removed by plasma exchange, so a common strategy is to administer IVIG 100 to 200 mg/kg after each exchange. For refractory acute humoral rejection, rituximab may be considered despite targeting B-cells at an earlier phase of maturation than the antibodyproducing plasma cell line.62 The largest randomized clinical trial of rituximab treatment for antibody-mediated rejection to date found no difference between the treatment group and placebo when added to plasma exchange and IVIG for a composite endpoint of early improvement in kidney function at 12 days after treatment and graft loss at 1 year. However, the study was limited by a small sample size (n = 38) and significant crossover between groups with 42% of subjects in the placebo arm receiving rescue doses of rituximab.63 In contrast, the proteosome inhibitor bortezomib directly inhibits antibody-producing plasma cells and has been reported in single-center case series as a potential treatment for refractory antibody-mediated rejection, usually in combination with other modalities such as plasma exchange and IVIG.64 Eculizumab is a humanized monoclonal antibody that blocks terminal complement activation and has been shown to significantly reduce the risk for acute humoral rejection, as well as subsequent transplant glomerulopathy in patients who have undergone positive

crossmatch kidney transplant65; however, feasibility of this approach is limited by high cost. Targeting the initiation of the classical complement cascade with C1 inhibition has also gained recent interest; pilot studies suggest that C1 inhibition may be associated with improved eGFR and a reduced risk of development of transplant glomerulopathy.66 67 Finally, there are case reports of splenectomy for refractory acute humoral rejection.68 These therapies are typically coupled with targeted T-cell therapy such as high-dose steroids and/or depleting antibody therapy, because histologic evidence of mixed T-cell rejection is often present and helper T-cell function may contribute to an enhanced B-cell response. Agents used for treatment of acute humoral rejection are summarized in Table 109.2

Chronic Rejection (T-Cell–Mediated and/or Antibody Mediated)

T-cell–mediated or antibody-mediated injury in a graft without features of acute tissue injury remains a therapeutic dilemma. No intervention has been proven effective in reversing the chronic tissue injury; transitioning to tacrolimus/MMF therapy or increasing the dose of these agents should be considered if CNI nephrotoxicity is not identified.69 Any intervention should be weighed against the potential for risk for enhanced immunosuppression and the lack of long-term data. This topic is discussed in greater detail in Chapter 112

PROGNOSIS

Acute rejection may predispose to chronic graft dysfunction, with increased histologic findings of chronic rejection and/or interstitial fibrosis and tubular atrophy and clinical findings of reduced graft survival. The clinical response to antirejection therapy appears to be critical in this regard because the change in kidney function from 6 and 12 months posttransplant is more predictive of long-term graft survival than the occurrence of prior episodes of acute rejection.70 Two analyses (one examining the US experience71 and another examining the Australia/New Zealand experience72) have shed light on risk factors for graft loss after episodes of acute rejection. In general, acute T-cell–mediated rejection that responds to therapy with return to near baseline kidney function does not portend worse graft survival. However, vascular rejection, late rejection (after 3 months), and rejection that does not respond to within 75% of baseline serum creatinine is associated with worse graft outcomes. Although the risk for acute rejection has fallen significantly over the past decade, the likelihood of graft survival has not improved in parallel, possibly because contemporary rejection is less responsive to therapy, with fewer cases achieving near-baseline serum creatinine levels. The long-term prognosis after episodes of acute antibody-mediated rejection has not been fully defined in prospective analyses. However, it appears that episodes of acute humoral rejection likely affect longterm graft survival. For example, a retrospective analysis of 302 patients with biopsy-proven acute rejection (192 with T-cell–mediated rejection and 110 with antibody-mediated rejection) found a threefold to ninefold increased risk for graft loss at 5 years associated with antibody-mediated rejection compared with T-cell–mediated rejection.10 Similarly, the emergence of de novo HLA antibodies at any time after transplant is associated with a 5% worse graft survival per year compared with those who do not form anti-HLA antibodies.73 For this reason, patients who have had episodes of acute rejection must be rigorously monitored with optimization of baseline maintenance immunosuppression. Remaining questions include the value of escalated immunosuppression, such as longer-term scheduled antibody therapy and additional IVIG treatment for those without adequate clinical response or with persistently elevated titers of HLA antibodies.

SUMMARY AND RECOMMENDATIONS

The incidence of acute rejection has decreased over time, but it remains an important cause of graft dysfunction and progressive graft loss, particularly when antibody-mediated forms of injury are identified. Higher-risk patients benefit from induction therapy with lymphocytedepleting agents for the prevention of rejection. Although many maintenance immunosuppressive regimens have been used to minimize the incidence of rejection and side effects, the most effective maintenance immunosuppressive regimen for the prevention of rejection is a threedrug regimen consisting of tacrolimus, mycophenolate, and prednisone. Alternative immunosuppressive strategies may be considered for side effects or toxicities related to immunosuppressive agents, which in clinical practice has led to a myriad of treatment combinations (see Table 109.4). Steroid minimization and belatacept-based CNI-free immunosuppression have been associated with adequate short- and intermediate-term outcomes but should be limited to those patients at lower immunologic risk for acute rejection. Until it is possible to determine an individual patient's degree of immune function, suppression, or graft-specific immunity, the clinician must determine the best treatment regimen based on potency (potential to minimize rejection) and tolerability.

SELF-ASSESSMENT QUESTIONS

1. According to the Banff Working Classification of Renal Allograft Pathology, which one of the following patterns would be recognized as acute antibody-mediated rejection?
A. Circulating donor-specific antibodies, severe tubulitis, interstitial inflammation
B. Peritubular capillaritis (ptc1), interstitial inflammation, moderate transplant glomerulopathy (cg2)
C. Circulating donor-specific antibodies, mild to moderate largevessel intimal arteritis, moderate interstitial fibrosis
D. Peritubular capillary C4d deposition, circulating donor-specific antibodies, peritubular capillaritis (ptc2)

2. Which one of the following statements is true regarding induction immunosuppression for the prevention of acute rejection?
A. rATG is a monoclonal antibody directed against the CD3 subunit of the T-cell receptor associated with a significant innate immune response resulting in a cytokine release syndrome.
B. Lymphocyte-depleting agents are more effective in preventing acute rejection compared with IL-2 receptor antibodies in patients at high immunologic risk.
C. The risk for posttransplant lymphoproliferative disorders is higher in patients treated with IL-2 receptor antibodies than in those treated with lymphocyte-depleting agents.
D. Patients at low immunologic risk experience higher early (<12 months) rates of acute rejection when treated with anti-CD52

therapy (Campath) compared with IL-2 receptor antibody therapy.

3. Which one of the following is the most effective maintenance immunosuppressive regimen for the prevention of rejection?
A. Sirolimus, MMF, prednisone
B. Tacrolimus, MMF, prednisone
C. Belatacept, MMF, prednisone
D. Tacrolimus, MMF, prednisone withdrawal at 7 days posttransplant

4. A 47-year-old man treated with tacrolimus, MMF, and 5 mg of prednisone after undergoing deceased-donor kidney transplant 5 months prior presents with an elevated serum creatinine of 5.2 mg/dL (recent baseline 1.3 mg/dL) and mild graft tenderness. Kidney ultrasound is nondiagnostic, a workup for infectious causes is negative, and an assay for donor-specific antibody is negative. Allograft biopsy is performed and reveals severe tubulitis with vascular intimal arteritis without evidence of peritubular capillary C4d deposition. Which of the following is the most appropriate initial therapy?
A. Increasing the dose of maintenance prednisone to 60 mg/day for 7 days followed by a dose taper back to 5 mg
B. 3 to 5 days of intravenous methylprednisolone at 500 mg/day
C. rATG 1.5 mg/kg IV for 7 to 14 days
D. Plasmapheresis followed by 100 to 200 mg/kg immune immunoglobulin for a total of 5 sessions

REFERENCES

1. Hamburger J, Vaysse J, Crosnier J, et al. Renal homotransplantation in man after radiation of the recipient. Experience with six patients since 1959. Am J Med. 1962;32:854–871.
2. Cooper JE. Evaluation and treatment of acute rejection in kidney allografts. Clin J Am Soc Nephrol. 2020;15(3):430–438.
3. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int. 1999;55(2):713–723.
4. Solez K, Colvin RB, Racusen LC, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant. 2007;7(3):518–526.
5. Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol. 2007;18(4). 1096–1056.
6. Loupy A, Haas M, Roufosse C, et al. The Banff 2019 kidney meeting report (I): updates on and clarification of criteria for T-cell- and antibodymediated rejection. Am J Transplant. 2020;20:2318–2331.
7. Einecke G, Sis B, Reeve J, et al. Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009;9(11):2520–2531.
8. Sis B, Jhangri GS, Bunnag S, et al. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. Am J Transplant. 2009;9(10):2312–2323.
9. Loupy A, Hill GS, Suberbielle C, et al. Significance of C4d Banff scores in early protocol biopsies of kidney transplant recipients with preformed donor-specific antibodies (DSA). Am J Transplant. 2011;11(1):56–65.
10. Lefaucheur C, Loupy A, Vernerey D, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. Lancet. 2013;381(9863):313–319.
11. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. Am J Transplant. 2009;9(3):527–535.
12. Cosio FG, Gloor JM, Sethi S, Stegall MD. Transplant glomerulopathy. Am J Transplant. 2008;8(3):492–496.
13. Wehmeier C, Honger G, Cun H, et al. Donor specificity but not broadness of sensitization is associated with antibody-mediated rejection and graft loss in renal allograft recipients. Am J Transplant. 2017;17(8):2092–2102.
14. Meehan SM, Siegel CT, Aronson AJ, et al. The relationship of untreated borderline infiltrates by the Banff criteria to acute rejection in renal allograft biopsies. J Am Soc Nephrol. 1999;10(8):1806–1814.
15. Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med. 1998;338(3):161–165.
16. Gralla J, Wiseman AC. The impact of IL2ra induction therapy in kidney transplantation using tacrolimus- and mycophenolate-based immunosuppression. Transplantation. 2010;90(6):639–644.
17. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005;80(9):1233–1243.
18. Kirk AD, Cherikh WS, Ring M, et al. Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant. 2007;7(11):2619–2625.
19. Brennan DC, Daller JA, Lake KD, et al. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355(19):1967–1977.
20. Noel C, Abramowicz D, Durand D, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. J Am Soc Nephrol. 2009;20(6):1385–1392.
21. Thomusch O, Wiesener M, Opgenoorth M, et al. gRabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet. 2016;388:3006–3016.
22. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. Alemtuzumab induction in

renal transplantation. N Engl J Med. 2011;364(20):1909–1919.

23. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242–251.
24. Marfo K, Ling M, Bao Y, et al. Lack of effect in desensitization with intravenous immunoglobulin and rituximab in highly sensitized patients. Transplantation. 2012;94(4):345–351.
25. Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. Clin J Am Soc Nephrol. 2011;6(4):922–936.
26. Gloor JM, Cosio FG, Rea DJ, et al. Histologic findings one year after positive crossmatch or ABO blood group incompatible living donor kidney transplantation. Am J Transplant. 2006;6(8):1841–1847.
27. Leeser DB, Thomas AG, Shaffer AA, et al. Patient and kidney allograft survival with national kidney paired donation. Clin J A Soc Nephrol. 2020;15(2):228–237.
28. Wagner M, Earley AK, Webster AC, et al. Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev. 2015;12:CD007746.
29. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000;342(9):605–612.
30. Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ. 2005;331(7520):810.
31. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. Transplantation. 1995;60(3):225–232.
32. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation. 1996;61(7):1029–1037.
33. Knoll GA, MacDonald I, Khan A, Van Walraven C. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. J Am Soc Nephrol. 2003;14(9):2381–2386.
34. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. Transplantation. 2006;82(1):102–107.
35. Salvadori M, Holzer H, de Mattos A, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant. 2004;4(2):231–236.
36. Bolin P, Tanriover B, Zibari GB, et al. Improvement in 3-month patientreported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. Transplantation. 2007;84(11):1443–1451.
37. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicenter study. The Rapamune US Study Group. Lancet. 2000;356(9225):194–202.
38. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol. 2006;17(2):581–589.
39. Brennan DC, Legendre C, Patel D, et al. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: pooled analysis of three clinical trials. Am J Transplant. 2011;11(11):2453–2462.
40. Pascual J, Berger SP, Witzke O, et al. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol. 2018;29(7):1979–1991.
41. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 annual data report: kidney. Am J Transplant. 2020;20(suppl s1):20–130.
42. Matas AJ, Kandaswamy R, Gillingham KJ, et al. Prednisone-free

maintenance immunosuppression-a 5-year experience. Am J Transplant. 2005;5(10):2473–2478.
43. Kaufman DB, Leventhal JR, Axelrod D, et al. Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation:

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58.

comparison with basiliximab induction—long-term results. Am J Transplant. 2005;5(10):2539–2548.
Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248(4):564–577.
Asberg A, Midtvedt K, Line PD, et al. Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. Transplantation. 2006;82(1):62–68.
Larson TS, Dean PG, Stegall MD, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. Am J Transplant. 2006;6(3):514–522.
Flechner SM, Goldfarb D, Modlin C, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation. 2002;74(8):1070–1076.
Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357(25):2562–2575.
Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10(3):535–546.
Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med. 2016;374(4):333–343.
Grinyo J, Charpentier B, Pestana JM, et al. An integrated safety profile analysis of belatacept in kidney transplant recipients. Transplantation. 2010;90(12):1521–1527.
Vanrenterghem Y, Bresnahan B, Campistol J, et al. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). Transplantation. 2011;91(9):976–

983.
Mota A, Arias M, Taskinen EI, et al. Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. Am J Transplant. 2004;4(6):953–961.
Mulay AV, Hussain N, Fergusson D, Knoll GA. Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials. Am J Transplant. 2005;5(7):1748–1756.
Weir MR, Mulgaonkar S, Chan L, et al. Mycophenolate mofetilbased immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. Kidney Int. 2011;79(8):897–907.
Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurininhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet. 2011;377(9768):837–847.
Sawinski D, Trofe-Clark J, Leas B, et al. Calcineurin inhibitor minimization, conversion, withdrawal, and avoidance strategies in renal transplantation: a systematic review and meta-analysis. Am J Transplant. 2016;16(7):2117–2138.
Woodle SE, Kaufman DB, Shields AR, et al. Belatacept-based immunosuppression with simultaneous calcineurin inhibitor avoidance

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and early corticosteroid withdrawal: a prospective, randomized multicenter trial. Am J Transplant. 2020;20(4):1039–1055.
Jordan ML, Shapiro R, Vivas CA, et al. FK506 “rescue” for resistant rejection of renal allografts under primary cyclosporine immunosuppression. Transplantation. 1994;57(6):860–865.
Humar A, Gillingham K, Kandaswamy R, et al. Steroid avoidance regimens: a comparison of outcomes with maintenance steroids versus continued steroid avoidance in recipients having an acute rejection episode. Am J Transplant. 2007;7(8):1948–1953.
Wan SW, Ying TD, Wyburn K, et al. The treatment of antibody-mediated rejection in kidney transplantation: an updated systematic review and meta-analysis. Transplantation. 2018;102(4):557–568.

Faguer S, Kamar N, Guilbeaud-Frugier C, et al. Rituximab therapy for acute humoral rejection after kidney transplantation. Transplantation. 2007;83(9):1277–1280.

Sautenet B, Blancho G, Buchler M, et al. One-year results of the effects of rituximab on acute antibody-mediated rejection in renal transplantation: RITUX ERAH, a multicenter double-blind randomized placebocontrolled trial. Transplantation. 2016;100(2):391–399.

Walsh RC, Alloway RR, Girnita AL, Woodle ES. Proteasome inhibitor-based therapy for antibody-mediated rejection. Kidney Int. 2012;81(11):1067–1074.

Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011;11(11):2405–2413.

Viglietti D, Gosset C, Loupy A, et al. C1 inhibitor in acute antibodymediated rejection nonresponsive to conventional therapy in kidney transplant recipients: a pilot study. Am J Transplant. 2016;16:1596–1603.

Montgomery RA, Orandi BJ, Racusen L, et al. Plasma-derived C1 esterase inhibitor for acute antibody-mediated rejection following kidney transplantation: results of a randomized double-blind placebo-controlled pilot study. Am J Transplant. 2016;16:3468–3478.

Locke JE, Zachary AA, Haas M, et al. The utility of splenectomy as rescue treatment for severe acute antibody mediated rejection. Am J Transplant. 2007;7(4):842–846.

Theruvath TP, Saidman SL, Mauiyyedi S, et al. Control of antidonor antibody production with tacrolimus and mycophenolate mofetil in renal allograft recipients with chronic rejection. Transplantation. 2001;72(1):77–83.

Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int. 2002;62(1):311–318.

Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. Am J Transplant. 2004;4(3):378–383.

McDonald S, Russ G, Campbell S, Chadban S. Kidney transplant rejection in Australia and New Zealand: relationships between rejection and graft outcome. Am J Transplant. 2007;7(5):1201–1208.

Terasaki PI, Ozawa M, Castro R. Four-year follow-up of a prospective trial of HLA and MICA antibodies on kidney graft survival. Am J Transplant. 2007;7(2):408–415.

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Infections and Malignancies in the Kidney Transplant Recipient

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INFECTIOUS DISEASES

Infection follows cardiovascular (CV) disease as the second most common cause of death with a functioning graft in kidney transplant recipients. Infection and malignancy are more commonly the cause of death among those without diabetes. Predisposing risk factors for infectious complications include immunosuppression, increased recipient age, indwelling Foley or vascular catheters, surgical drains, drug-induced leukopenia, and metabolic derangement. Epidemiologic exposures, shifts in nosocomial flora associated with repeated antimicrobial exposures (antimicrobial resistance), and improvement in molecular diagnostic assays also contribute to the emergence of novel infections and changes in the epidemiology of infections.1

Immunizations Before and After Transplantation

All kidney transplant candidates should receive immunization for hepatitis B, pneumococcus, and other standard immunizations appropriate for age and the presence of end-stage kidney disease. Inactivated vaccine should be completed by 2 weeks prior to transplantation to optimize immune response to vaccination, and a minimum of 4 weeks should elapse between live attenuated virus vaccine administration and transplantation to minimize the possibility of live vaccine–derived infection in the posttransplantation period.2 Live virus or live organism vaccines should be avoided after transplantation. Immunizations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients. Most centers restart vaccinations 3 to 6 months after transplantation. Vaccination during the first 3 months after transplantation may result in suboptimal response and protection because of increased levels of immunosuppression early posttransplant, especially in patients who receive lymphocyte-depleting agents as part of induction. Ensuring adequate response to hepatitis B vaccination is important to prevent transmission of donor-derived infection. Seasonal influenza vaccine is safe and effective, and no conclusive evidence exists for a link between vaccination and allograft dysfunction. Household members, close contacts, and health care workers should also be fully immunized. In addition, they should receive annual influenza vaccine, preferably with inactivated influenza vaccine. If live attenuated vaccine is used, frequent handwashing for a 2-week period after vaccination is recommended. With the exception of smallpox and oral polio vaccines, there is little to no risk to the transplant recipient if family members or close contacts receive live vaccines. Pets should also be fully immunized. Immunization of pets with live vaccines (e.g., canine Bordetella bronchiseptica intranasal vaccine) poses little to no risk of transmission.2 Recommended immunizations before and after transplantation are listed in Table 110.1. For vaccination of transplant recipients who travel to countries where endemic infections such as malaria are present, see Buchan et al.3 All solid organ transplant recipients should be seen by a travel medicine specialist prior to traveling to destinations with higher rates of infection.3

Infectious Causes

The type and occurrence of infections in the immunocompromised transplant recipient follow a predictable pattern based on time since transplantation (Table 110.2). Timing of infections may be altered by the intensity of immune suppression, use of target antibiotic prophylaxis, and patient exposures.

Risk Factors for Posttransplant Infectious Complications

Risk factors for posttransplant infectious complications include active or latent infections in the donors, net state of immunosuppression, surgical instrumentation, wound-healing issues, abdominal fluid collections, reactivation of latent infections, epidemiologic exposure, metabolic conditions (e.g., diabetes, uremia), infections with immunomodulating viruses, and hypogammaglobulinemia, among others.

Severe hypogammaglobulinemia (immunoglobulin [Ig] G < 400 mg/dL) during the first year posttransplantation is associated with a significant increase in the risk for cytomegalovirus (CMV) infection, fungal and respiratory infections, and 1-year all-cause mortality among recipients of solid organ transplantation.[4] Although controlled trials are lacking, posttransplant monitoring of IgG levels and Ig replacement therapy to keep IgG level above 700 to 800 mg/dL may reduce infection rates in patients with hypogammaglobulinemia.

Donor-Derived Infections

Donor-derived infections include bacterial, fungal (Candida spp.), viral (human immunodeficiency virus [HIV], hepatitis B and C [HBV and HCV], cytomegalovirus [CMV]), and parasitic infections (malaria, Babesia and Balamuthia infections, amebic meningitis). Allografttransmitted infections with unusual viruses include lymphocytic choriomeningitis virus, West Nile virus, and rabies. Despite routine surgical prophylaxis, transmission of resistant organisms, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycinresistant enterococci (VRE), and azole-resistant Candida spp. may still occur. Donor-derived carbapenem-resistant Enterobacteriaceae (CRE) infections are associated with high morbidity and mortality. Donation of organs that are directly involved in CRE infection should be evaluated on a case-by-case basis with input from an infectious disease consultation given the high risk of donor-derived infection (e.g., kidneys from donors with CRE urinary tract infection [UTI], donors with CRE bacteremia). Systematic review and meta-analyses revealed that donor derived viral infections were most prevalent (56.0%), followed by bacterial (15.5%), fungal (15.5%), and parasitic (13.0%) infections. Among viral donor derived transmissions, HIV and human T cell lymphotrophic virus (HTLV) were the most frequently observed infections (9.7%), followed by West Nile virus (6.3%). Most commonly reported donor-transmitted bacterial infections were Mycobacterium tuberculosis (4.8%) and Pseudomonas aeruginosa (4.3%); Candida spp.

TABLE 110.1

Recommended Immunizations Before and After Transplantation

Vaccine

Inactivated (I)
Virus or Live
Attenuated
(LA) Virus

Before
Transplant

After Transplant
(>3–6 Mo
Posttransplant)

MMR

LA

Yes

Contraindicated

DPT
Herpes zoster (Shingrix)
Poliovirus
Haemophilus influenza
type b
Influenza A and Ba

I
I
I
I

Yes
Yes
Yes
Yes

See comments
Yes
Yes
Yes

I

Yes

Yes

Hepatitis A

I

Yes

Yes

Hepatitis B (Heplisav,
Engerix)

I

Yes

Yes

PCV20 (Prevnar)
PPSV23 (Pneumovax)

I
I

Yes
Yes

Yes
Yes

HPV
Neisseria meningitidis
(both quadrivalent and
group B vaccines)

I
I

Yes
Yes

Yes
Yes

COVID-19

Vaccine typec:
mRNA
Replication
defective
adenovirus
vectord

Yes

Yes

Comments
Presence of measles antibody can be assessed to determine need for vaccination or revaccination prior to transplantation
Diphtheria and tetanus: booster every 10 yr
Indicated for age ≥ 50 yr
For travelers to endemic areas (e.g., some parts of Asia, Africa)
Indicated for patients with sickle cell disease, complement deficiency, or those who had a splenectomy
Annuallyb
All patients who are >3 mo posttransplant should receive influenza vaccine
May be administered in the immediate posttransplant period during an outbreak
Recommended posttransplant if not administered pretransplant

For travelers to endemic areas
Recommended posttransplant if not administered pretransplant
Monitor titers for response
Repeat series if needed
If possible, PCV13 should be administered before PPSV23For adults who have not previously received PPSV23, administer PCV13, followed by PPSV23 at least 8 wk later
For adults who just received PPSV23 but have not received PCVI3, wait 12 mo before administering PCV13
Adults <65 years who are high risk should receive 2 doses of PPSV23 5 yr apart (but no sooner than 8 wk after PCV13), with a third dose after they turn age 65 yr
Nonpregnant female candidates ages 11–26 yr, males ages 11–21 yr
Recommended for patients with properdin terminal component deficiencies or receiving eculizumab therapy, or those with functional or anatomic asplenia
Others: military members travelers to high-risk areas, college freshmen living on campus
Preexposure prophylaxis with tixagevimab plus cilgavimab is recommended for all immunosuppressed kidney transplant recipients unless contraindicated (must complete primary vaccine series)
Monovalent vaccines protect against the original SARS-CoV-2 whereas bivalent vaccines protect against both the original and the Omicron variants BA.4 and BA.5 (should be administered at least 2 months after completion of the primary series)

aLive

attenuated nasal influenza vaccine has been removed from the US market.
possible, patients being treated for or recently treated for allograft rejection should avoid vaccinations until 3 months after treatment to ensure optimal immune response. However, vaccination should not be delayed if such delay represents more of a risk than the risk of impaired response.
All transplant recipients over age 65 years should receive the high-dose vaccine where available.
cVaccines available in the United States: mRNA (Pfizer-BioNTech, Moderna), protein-based (Novavax), replication defective adenovirus vector (Johnson & Johnson’s Janssen).
dThe US Centers for Disease Control and Prevention recommend that the Janssen vaccine only be considered in certain situations due to safety concerns (last updated August 2022).
AST, American Society of Transplantation; DPT, diphtheria, pertussis, tetanus; HPV, human papillomavirus; MMR, measles, mumps, rubella; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
bIf

(3.9%) and Toxoplasma gondii (3.4%) were the most common donorderived fungal and parasitic infections, respectively.5 Nucleic acid testing (NAT) for HIV and hepatitis infections should be performed on all donors, and all recipients should undergo posttransplant infection surveillance. If a donor is at increased risk for HIV, HBV, or HCV

transmission, potential recipients of such kidneys should undergo additional counseling prior to organ acceptance (Box 110.1). Currently all deceased and living organ donors and potential recipients are tested for the novel COVID-19 by polymerase chain reaction (PCR) prior to organ procurement or transplantation. One fatal case of transmission

TABLE 110.2

Timetable of Infections

Timetable of Infections

Comments

First Month After Transplant

Bacterial (Sites and Sources)

- Urinary tract
- Respiratory system
- Bacteremia
- Surgical wound or intraabdominal sources (lymphoceles, hematoma, urine leak)
- Vascular access or instrumentations (catheters, drains, urinary stents)
- Anatomic or functional genitourinary tract abnormalities (ureteral stricture, vesicoureteric reflux, neurogenic bladder)
- Clostridioides difficile or center-specific multidrug-resistant species

Viral

- Uncommon except HSV

Fungal

- Candida spp. predominate (recipient pretransplant colonization or donor derived)

- Common nosocomial bacterial pathogens and Candida spp. predominate
- Risk can be mitigated by appropriate prophylaxis
- Minimize or avoid environmental exposure at all times after transplant (primarily avoiding pigeons and areas of active building construction)

Organisms Transmitted With Donor Organs

Months 1–6

Viral

- CMV, HSV, VZV, EBV, HBV, HCV, BK virus (exogenous infection or reactivation of latent disease as a result of immunosuppression)
- Others: HHV-6, HHV-7, influenza, parainfluenza, RSV, adenovirus

Fungal

- Aspergillus spp., Cryptococcus, agents of mucormycosis

Bacterial

- Recurrent urinary tract infections or pyelonephritis, Nocardia, Listeria, Mycobacterium spp. (tuberculous and nontuberculous), Legionella

Parasitic

- Pneumocystis jirovecii, Toxoplasma and Strongyloides spp., leishmaniasis, Trypanosoma cruzi

After 6 Months

Stable Patients on Low-Dose Immunosuppressants

- Community-acquired respiratory and GI viral pathogens

History of Multiple Rejection Episodes Requiring Intensification of Immunosuppression

- Viral infections (invasive CMV such as CMV colitis or pneumonitis, VZV, parvovirus B19), late opportunistic infections (Pneumocystis, Cryptococcus, Listeria, nocardiosis), tuberculosis

Persistent Infections

- HBV, HCV, papillomavirus, BK virus

Geographically Restricted Infections

- Examples: coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis

Deep-Seated Infections
🐧•🐧 Examples: osteomyelitis, paravertebral abscess
🐧•🐧 Predisposing risk factors: chronic skin infections, long-standing poorly controlled diabetes, peripheral vascular disease
Associated With Malignancies
🐧•🐧 EBV (PTLD), papilloma virus (squamous cell carcinoma), HSV (cervical cancer), HHV-8 (Kaposi sarcoma)
aAll

🐧•🐧 Unconventional or opportunistic infections secondary to immunosuppression
🐧•🐧 Measures to reduce HBV and HCV infection and/or reactivation
🐧 •🐧 Universal immunization for HBV
🐧 •🐧 All patients with HBV infection (HBsAg or HBeAg positive) should receive lifelong antiviral prophylaxisa
🐧 •🐧 HCV patients should be referred to a hepatologist for consideration of DAA therapyb
🐧•🐧 Minimize or avoid environmental exposure at all times after transplant

🐧•🐧 Infection risks associated with duration and intensity of immunosuppression and epidemiologic exposures
🐧•🐧 Excellent sustained virologic response achieved with direct-acting antiviral agents may lower the long-term incidence of chronic liver disease and cirrhosis in HCV patients
🐧•🐧 Minimize or avoid environmental exposure at all times after transplant

patients should receive antiviral therapy after transplantation. Transplant candidates with active HBV replication (i.e., detectable HBV DNA) should start therapy pretransplant.
bIn patients with HBV and HCV coinfection, HBV antiviral prophylaxis should be considered prior to DAA therapy because HBV reactivation can occur as a consequence of DAA therapy. Patients with evidence of resolved infection (hepatitis B core antibody positive) should be monitored for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy.
CMV, Cytomegalovirus; DAA, direct-acting antiviral agent; EBV, Epstein-Barr virus; GI, gastrointestinal; HBeAG, hepatitis B e-antigen; HBsAG, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HSV, herpes simplex virus; PTLD, posttransplant lymphoproliferative disease; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

United Network for Organ Sharing Protocol Surveillance for All Transplant Recipients

BOX 110.1

Pretransplant

At baseline:

- Any CDC-approved HIV testing modality
- HBsAg
- HCV quantitative PCR

Posttransplant

At 4–8 wk posttransplant:

- HIV RNA quantitative PCR
- HBV DNA quantitative PCR
- HCV RNA quantitative PCR

At 12 mo posttransplant (for liver transplant recipients only)

- HBsAg or HBV NAT, anti-HBsAb, and anti-HBcAb

CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NAT, nucleic acid testing; PCR, polymerase chain reaction.

of COVID-19 from lung donor to recipient has been reported despite a negative nasopharyngeal swab.6 Hence, for thoracic organ transplantation, COVID-19 testing of the donor lower respiratory tract is recommended (if safe and feasible). Limited data suggest that transplantation of nonlung organs from COVID-19 infected donors can be safely performed. Assessing viral load using cycle threshold might be helpful in clinical decision-making (opinion based).

Month 1 After Transplantation

In the first month after transplantation, donor- and recipient-derived infections with common nosocomial bacterial microorganisms and Candida spp. predominate. Infections caused by multidrug-resistant bacteria are center specific. Despite the advent of potent broadspectrum antimicrobial agents, infections caused by multidrugresistant bacteria, including gram-positive bacteria (MRSA, VRE), extended-spectrum β-lactamases, and gram-negative bacilli and multidrug-resistant nonfermenting gram-negative bacilli, including CRE, continue to be important causes of morbidity and mortality.

Most bacterial infections during this period involve wounds, catheters, and drainage sites. Aspiration pneumonia and UTIs are common. Most UTIs are caused by gram-negative bacteria with Escherichia coli being the predominant causative organism. Enterococcus species account for the majority of gram-positive pathogens. Preventive measures for UTIs include early urethral catheter removal and antibiotic prophylaxis. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis during the first 3 to 6 months after transplantation may reduce the risk for UTIs and eliminate urosepsis unless anatomic or functional derangement of the urinary tract is present. Strict aseptic surgical techniques and perioperative use of first-generation cephalosporins reduce the incidence of wound infections. Except for herpes simplex virus (HSV), viral infections are uncommon during this period.

Months 1 to 6

During months 1 to 6, unconventional or opportunistic infections secondary to immunosuppression are most common. Viral infections such as CMV, HSV, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), HBV, and HCV may occur from exogenous infection or reactivation of latent disease. Historically, reactivation of de novo

HCV infection was an important cause of morbidity and mortality after transplantation. The advent of fixed-dose direct-acting antiviral agent (DAA) combination therapy has improved outcomes in hepatitis C–positive transplant recipients. Repeated courses of antibiotics and corticosteroids increase the risk for fungal infections, whereas viral infections not only may result from immunosuppression but may further impair immunity and increase the risk for additional opportunistic infections. TMP-SMX prophylaxis eliminates or reduces the incidence of Pneumocystis, Listeria monocytogenes, Nocardia spp., and Toxoplasma gondii infection Reactivation of latent infection such as from Mycobacterium tuberculosis, Trypanosoma cruzi, Leishmania spp., Strongyloides stercoralis, Cryptococcus neoformans, Histoplasma capsulatum, and Coccidioides and Paracoccidioides spp. may be observed.

Community-acquired respiratory viruses are a common hazard in these vulnerable immunocompromised patients during this period, whereas BK polyomavirus infection is an important cause of allograft loss (discussed later).

After 6 Months

After 6 months, the infection risk is largely a function of chronic maintenance immunosuppression, exposure to T-cell–depleting agents, graft function, and epidemiologic exposures. Patients can be divided into three categories of infection risk.

The first category consists of most transplant recipients (70%–80%), who have satisfactory or good allograft function, relatively low doses of immunosuppressants, and no history of chronic viral infection. The risk for infection approaches that of the general population, with community-acquired respiratory viruses constituting the major infective agents. Opportunistic infections are unusual unless environmental exposure has occurred.

The second group (~10% of patients) consists of those with chronic viral infection that may include HBV, HCV, CMV, EBV, BK polyomavirus (BKPyV), or papillomavirus. In the setting of immunosuppression, such viral infections may lead to the development of BKPyV-associated nephropathy (BKVAN), posttransplantation lymphoproliferative disorder (PTLD), squamous cell carcinoma (papillomavirus), or progressive liver disease or cirrhosis (HBV, HCV).

The sustained virologic response achieved with DAAs in both the dialysis and kidney transplant populations with chronic hepatitis C may lower the long-term incidence of chronic liver disease and cirrhosis in these populations. The advent of pangenotypic (genotypes 1–6) DAAs along with universal immunization for HBV can potentially eradicate HBV and HCV infection after transplant.7 8 New infections occurring after the first 6 months posttransplantation often reflect new exposures (e.g., L. monocytogenes [dietary ingestion], Lyme disease [tick exposure], and malaria [travelers to endemic areas]).1 Alemtuzumab (a humanized monoclonal antibody directed against CD52 found on T and B cells) is associated with increased risk for late invasive viral and fungal infections because of its profound and prolonged effect on pan–T-cell depletion.

The third group (~10% of patients) consists of those who experience multiple rejection episodes requiring repeated exposure to heavy immunosuppression. These patients are the most likely to develop chronic viral infections and superinfection with opportunistic infections. Causative opportunistic pathogens include Pneumocystis, Listeria, Nocardia, Cryptococcus, and geographically restricted mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis). Risk factors include intensive immunosuppression for graft rejection, CMV infection, higher-dose corticosteroid therapy (defined as >20 mg of prednisone daily for at least 2 weeks), prolonged neutropenia, or flare of autoimmune disease. The widespread use of prophylactic therapy has resulted in a decrease in the incidence of Pneumocystis infection in solid organ transplant recipients with an estimated incidence of

0.3% to 1.5% compared with 3% to 5% historically.9

TABLE 110.3

Posttransplantation Antimicrobial Prophylaxis

Prophylaxis

Regimen

Comments

Pneumocystis
jirovecii

First line: TMP-SMX × 6–12 mo[a] (lifelong in some, especially thoracic organs)
Second line (sulfa allergies)[b]: dapsone, atovaquone, or aerosolized pentamidine[c]
Nystatin S&S or fluconazole[c]

TMP-SMX also reduces the incidence of Toxoplasma gondii, Listeria monocytogenes, and Nocardia asteroides and reduces the incidence of UTI in kidney transplant recipients
Check G6PD before initiation of dapsone
Fluconazole recommended in high-risk recipients (e.g., simultaneous pancreas-kidney or liver-kidney transplant recipients, history of coccidioidomycosis, or patients who live in endemic areas)
Acyclovir (or famciclovir or valacyclovir) for HSV and VZV prophylaxis for patients not on CMV prophylaxis

Fungal

CMV

Acyclovir, valganciclovir, ganciclovir (for CMV prophylaxis protocol, see Box 110.2)

[a]Duration

of therapy may vary among centers. Restart TMP-SMX prophylaxis for 3–6 months after any corticosteroid pulse or antibody treatment.
in order of preference. Dapsone is preferred over atovaquone for patients without anemia or G6PD deficiency. Consider adding fluoroquinolones or cephalexin (or other agents) for antibacterial activity for higher risk patients.
[c]We advocate lifelong therapy in patients with history of coccidioidomycosis or in those who live in endemic areas.
CMV, Cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; HSV, herpes simplex virus; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VZV, varicella zoster virus.
[b]Listed

MANAGEMENT AND PROPHYLACTIC THERAPY FOR SELECTED INFECTIONS

Suggested prophylactic therapy in kidney transplant recipients is shown in Table 110.3

Cytomegalovirus Infection

CMV infection may cause primary infection in a seronegative recipient (donor seropositive, recipient seronegative), reactivation of endogenous latent virus (donor seropositive or seronegative, recipient seropositive) or superinfection with a new virus in a seropositive recipient (donor seropositive, recipient seropositive). Primary CMV infection is usually more severe than reactivated infection or superinfection.

Clinical Manifestations

CMV infection may be asymptomatic, manifesting as a mononucleosislike syndrome, an influenza-like illness with fever and leukopenia or thrombocytopenia, or a severe systemic or tissue-invasive CMV disease. Gastroenteritis is the most common tissue-invasive CMV disease observed in solid organ transplantation but any organ system may be affected. Patients may present with esophagitis, gastroenteritis, hepatitis, pneumonitis, carditis, encephalitis, chorioretinitis, and even otitis. The spectrum of CMV-induced kidney injury includes tubulointerstitial nephritis, CMV glomerulopathy, and rarely CMV-induced thrombotic microangiopathy. CMV often invades the transplanted allograft due to aberrant immune response within the allograft. Without prevention strategies (discussed in a later section), CMV infection typically occurs during the first 3 months after transplant. Delayed-onset CMV infection refers to the occurrence of CMV infection 3 to 6 months after completion of antiviral prophylaxis, whereas late-onset CMV infection refers to the development of CMV infection 1 year after transplantation. Suggested risk factors for delayed-onset CMV infection include D+/R− serostatus, allograft rejection, overimmunosuppression, severe lymphopenia, and lack of CMV-specific immunity.

the development of posttransplantation diabetes mellitus (also known as new-onset diabetes after transplantation; see Chapter 111). A Swiss transplant cohort study involving heart, kidney, liver, and lung transplant recipients demonstrated significantly increased risk of graft rejection within 4 weeks after detection of CMV replication with the highest risk seen in lung transplants and the lowest risk in kidney grafts. There was no significant difference in rejection risk among patients with asymptomatic untreated, asymptomatic treated, and symptomatic CMV replication.10 In recipients of liver and lung transplants, donor or recipient CMV seropositivity was associated with increased incidence of rejection even in the absence of detectable CMV DNA or disease. Although the cause-and-effect relationship of CMV infection and allograft rejection remains hypothetical, the common mediator may be the release of inflammatory cytokines. It also remains possible that immunosuppression reduction in the context of CMV DNAemia may increase the risk of acute rejection, whereas intensification of immunosuppression to treat rejection may trigger CMV reactivation.

Risk Factors for Cytomegalovirus Infection

High-risk donor and recipient serostatus (donor CMV seropositive, recipient CMV seronegative) and the use of blood products from CMV-seropositive donors are well-established risk factors for CMV infection. Other risk factors include antilymphocyte antibodies, prolonged or repeated courses of antilymphocyte preparations, high doses of maintenance immunosuppression, acute rejection episodes, comorbid illnesses, concomitant HHV-6 and HHV-7 viral infections, neutropenia, hypogammaglobulinemia, and lack of CMV-specific CD4+ and CD8+ T cells. Belatacept-based maintenance immunosuppression is associated with an increased risk of CMV primary infection and a prolonged course of viral replication in CMV high-risk patients.11 CMV infection is lower among kidney transplant recipients receiving mTOR inhibitor-based compared with calcineurin inhibitor (CNI)based regimens.12

Immunomodulating Effects of Cytomegalovirus Infection

CMV Screening and Prevention

CMV infection is associated with immune modulation and dysregulation of helper and suppressor T cells. It may be a risk factor for acute and chronic allograft rejection, secondary infection with opportunistic agents (e.g., Pneumocystis, Candida, Aspergillus), and reactivation of human herpesvirus 6 (HHV-6) and HHV-7 and may favor development of PTLD. CMV infection may also accelerate HCV infection and

Surveillance for CMV is best performed using PCR-based methods for CMV DNA. Whole blood may result in higher CMV DNA results than plasma, hence it is best to use one specimen type for comparison. CMV DNA assay is highly specific and sensitive for the detection of CMV DNAemia. Antigen-based methods (e.g., testing for pp65) have largely been replaced by CMV DNA testing, and the former may also be falsely negative in the setting of leukopenia. Quantitative CMV assays in patients with invasive colitis and gastritis or neurologic disease, including chorioretinitis, are often negative and diagnosis may require invasive testing and biopsies. CMV DNAemia is rarely useful as a predictor of CMV retinitis and diagnosis is generally based on ophthalmologic examination. The detection of CMV DNA in vitreous fluid may be helpful in guiding the diagnosis of CMV retinitis.13

CMV prevention can be achieved by prophylaxis or preemptive therapy. Prophylaxis involves antiviral therapy beginning in the immediate postoperative period and continuing for 3 to 6 months. Preemptive therapy entails close CMV surveillance after transplant and initiation of treatment in patients who are found to reach a certain threshold of positive CMV DNA by PCR (threshold to treat may differ among centers). Oral acyclovir (or famciclovir or valacyclovir) is necessary for HSV and VZV prophylaxis in patients not receiving anti-CMV prophylaxis. A preemptive approach (with once weekly surveillance for 3–4 months) and universal prophylaxis appear to be comparably effective for preventing CMV disease among D+/R− and/or R+ kidney transplant recipients, and both are recommended in the 2018 International Consensus Guidelines. However, prophylaxis may be preferred in donor and/or recipient seropositive patients whose risk for CMV may be increased, and a longer duration of prophylaxis (i.e., 6 months) may also be more effective.13 CMV surveillance weekly for 8 to 12 weeks after the end of prophylaxis may be considered in patients at increased risk for postprophylaxis CMV disease. Retrospective studies demonstrated that secondary prophylaxis after successful treatment completion is not protective against CMV relapse.13 14 Suggested CMV prophylaxis protocol is shown in Box 110.2

Treatment

The Third International Consensus Guidelines and the AST Infectious Diseases Community of Practice Guidelines on the Management of CMV in Solid-Organ Transplantation are summarized in Box 110.3. Mutation in the viral kinase UL97 gene that prevents phosphorylation of ganciclovir to its active form confers ganciclovir resistance. Cidofovir and foscarnet should be reserved for those with ganciclovir-resistant strains because of their associated nephrotoxicity and potential synergistic nephrotoxicity with CNIs. Mutation in the UL54 gene, which encodes for CMV DNA polymerase (a target for all currently available systemic anti-CMV drugs) could lead to cidofovir or foscarnet resistance or cross-resistance among ganciclovir, foscarnet, and cidofovir. Concomitant UL97 and UL54 mutations often confer high-level ganciclovir resistance. Letermovir is a novel anti-CMV agent with a mechanism of action distinct from that of the CMV DNA polymerase inhibitors. Letermovir inhibits CMV viral terminase complex (encoded by UL56, UL51, and UL89 genes) and is used in CMV prophylaxis in allogeneic hematopoietic stem cell transplant recipients.15 However, letermovir has no activity against other herpesviruses, and its use for CMV prophylaxis should be complemented by acyclovir (or famciclovir or valacyclovir) for the prevention of HSV and VZV. Unlike cidofovir and foscarnet, it does not share cross-resistance with ganciclovir. Whether letermovir is effective in treating refractory or resistant CMV infection remains to be determined,16 and whether it is superior to valganciclovir in preventing CMV disease in high-risk (CMV D+/R−) adult kidney transplant recipients is being evaluated in a phase III clinical trial (study results not yet available). Maribavir is another new antiviral medication with a novel mechanism of action that has proven activity against resistant and refractory disease.17

Candida Infections

Candida infections are common in transplant recipients; Candida albicans and Candida tropicalis account for 90% of the infections. Risk factors include diabetes, high-dose corticosteroids, broad-spectrum antibacterial therapy, indwelling urinary tract device, and, rarely,

BOX 110.2 Suggested CMV Prophylaxis and Preemptive Protocol a

2018 International Consensus Guidelines

D+/R−

- Antibody induction with lymphocyte depleting agents: valganciclovir 900 mg PO once a day × 6 mo
- If no antibody induction: valganciclovir 900 mg PO once a day × 3 mob
- After the end of prophylaxis, consider CMV DNA weekly × 3 moc

R+ (D− or D+)

- Valganciclovir 900 mg PO once a day × 3–6 mo
- Lung transplantation, composite tissue: valganciclovir 900 mg PO once a day × 6 mo

D−/R−

- Acyclovird 400 mg twice a day (for herpes prophylaxis) × 3 mo
- CMV DNA screening when clinically indicated (or if exposure to high volume of blood products)

2019 AST Infectious Diseases Community of Practice Guidelines

D+/R−

- Prophylaxis: valganciclovir (preferred), IV ganciclovir,a or valacyclovira × 6 mo
- Preemptive therapye: weekly CMV DNA (or pp65 antigenemia) for 12 weeks after transplant. If a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg orally twice a day (preferred) or (b) ganciclovir 5 mg/kg IV q12h until negative test

R+ (D− or D+)

- Prophylaxis: valganciclovir (preferred), IV ganciclovir, or valacyclovir × 3 mo
- Preemptive therapye: weekly CMV DNA (or pp65 antigenemia) for 12 weeks after transplant. If a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg PO twice a day (preferred) or (b) ganciclovir 5 mg/kg IV q12h until negative test

aValganciclovir, ganciclovir, acyclovir, valacyclovir, famciclovir: dose adjustment for renal function necessary.

bAt the authors’ institution, 6 months of valganciclovir prophylaxis is recommended for high risk (D+/R–) transplant recipients regardless of induction therapy.

cAt the authors’ institution, because of the increased incidence of delayed CMV DNAemia in high-risk (D+/R−) transplant recipients, preemptive CMV surveillance is routinely performed after completion of prophylaxis therapy as follows: following discontinuation of CMV prophylaxis, CMV DNA is monitored biweekly for 2 months. If after 2 months postmedication discontinuation, the patient is found to be CMV negative, CMV DNA testing is performed monthly until 1 year posttransplant.

dMay use acyclovir, famciclovir, or valacyclovir (center dependent).

eIf logistic support is available.

CMV, Cytomegalovirus; D+, donor CMV seropositive; D−, donor CMV seronegative; IV, intravenous; PO, orally; R+, recipient CMV seropositive; R−, recipient CMV seronegative.

donor-derived candidiasis. Fluconazole is commonly considered the drug of choice for the prevention or treatment of donor-derived candidiasis. Other azoles (such as voriconazole or itraconazole) and the echinocandins do not effectively enter the urine as active drugs and should not be used.

Superficial candidal infections involving the mouth or intertriginous areas can be treated with nystatin and topical clotrimazole, whereas candidal UTIs require systemic antifungal therapy (see Chapter 55). Whenever possible, bladder catheters, surgical drains, and urinary stents should be removed. Systemic antifungal therapy is

BOX 110.3

CMV Treatment Protocol

CMV Treatment

First-Line Treatment

- Mild to moderate disease: valganciclovir 900 mg PO twice daily (adjusted for GFR)
- Severe or life-threatening disease or GI malabsorption: ganciclovir 5 mg/kg IV q12h (adjusted for GFR)

Second-Line Treatment (for Patients Resistant to Valganciclovir or Ganciclovir)

- Foscarnet

Comments

Monitoring During Treatment

- Weekly plasma CMV DNA.
- Due to individual variation in virologic response, change in antiviral agent is not recommended in clinically improving patients with unchanged or rising DNAemia during the first few weeks of therapy (strong, moderate).
- Antiviral drug doses should be reduced only for worsening estimated GFR because suboptimal dosing may increase risk of clinical failure and/or resistance.
- In the setting of leukopenia, treatment with GCSF and/or withholding of myelosuppressive agents should be considered before changing valganciclovir or ganciclovir to another agent (strong, low).

Treatment Duration

- Treatment should be continued for a minimum of 2 weeks, until clinical resolution of disease and eradication of CMV DNAemia below a specific threshold (e.g., LLOQ < 200 U/mL) on 1 or 2 consecutive weekly samples.

Other

- In patients without concomitant rejection immunosuppression, reduction may be considered in the settings of severe CMV disease, inadequate clinical response, high viral loads, and cytopenia.
- Adjunctive immunoglobulin therapy is not routinely recommended.
- Secondary prophylaxis is not routinely recommended.
- In patients with prior cumulative exposure to valganciclovir or ganciclovir that exceeds 6 weeks, drug resistance should be suspected in the setting of clinical treatment failure despite 2 weeks of antiviral treatment or development of DNAemia during prophylaxis.

CMV, Cytomegalovirus; GCSF, granulocyte colony-stimulating factor; GFR, glomerular filtration rate; GI, gastrointestinal; IV, intravenously; LLOQ, lower limits of quantification; PO, orally.

indicated in the presence of any blood culture positive for Candida spp. (see Chapter 55).

BK Polyomavirus Infection

The clinical spectrum of BKPyV infections includes BK viruria, BK DNAemia (formerly known as BK viremia), BKVAN, and, less commonly, ureteral stenosis. The highest prevalence of BK viruria and BK DNAemia occurs at 2 to 3 months, and 3 to 6 months, respectively. BKPyV is an important cause of allograft dysfunction and graft loss and commonly manifests with an asymptomatic rise in serum creatinine during the first posttransplantation year. However, BKVAN may occur as early as the first week and as late as 6 years after transplantation. Urinalysis is usually unremarkable but may reveal pyuria, hematuria, and/or cellular casts consisting of kidney tubular cells and inflammatory cells. The American Society of Transplantation Infectious Diseases Community of Practice expert panel defines sustained BK DNAemia as more than 1000 copies/mL in two measurements within 3 weeks, or increasing to more than 10,000 copies/mL in at least 1 of 2 measurements as probable and presumptive BK nephropathy (BKN), respectively. Since PCR assays are not standardized, the sensitivity and specificity of the assays vary. A definitive diagnosis of BKVAN requires an allograft biopsy demonstrating BK viral inclusions in kidney tubular cell nuclei and occasionally in glomerular parietal epithelium (Fig. 110.1). However, a false negative BKVAN biopsy rate of 10% to 30% can occur if the biopsy sample lacks tissue from the kidney medulla where a significant reservoir of BKPyV can be found. Interstitial mononuclear inflammation, often with many plasma cells, degenerative changes in tubules, and focal tubulitis, may mimic acute rejection.

BKPyV infection and acute rejection may occur simultaneously, and distinguishing between BKVAN and acute rejection or the presence of both can be a diagnostic challenge. The 2017 Banff Working Group on BKN proposed using interstitial fibrosis and intrarenal BK load levels to diagnose “definitive BKN.” BKVAN can be further categorized into 3 classes based on the percentage of tubules/ducts with evidence of viral replication, as well as Banff scores of interstitial inflammation and tubulitis. Class 1 denotes early stage BKN with favorable outcome. Class 2 and class 3 have a more pronounced negative effect on graft function, with graft failure rate reaching 50% in class 3.

Treatment strategies for BK DNAemia with or without BKVAN vary, but immunologic containment of BKV replication is universally accepted as the mainstay of therapy.[18] Optimal reduction of immunosuppressive therapy may allow sufficient reconstitution of BKPyV-specific T cells to control BKPyV replication while maintaining adequate immunosuppression to prevent allograft rejection. The 2019 AST-IDCOP guidelines recommend testing all kidney transplant recipients for BK-DNAemia monthly until month 9, and then every 3 months until 2 years posttransplant. Extended surveillance after 2 years may be considered in pediatric kidney transplant recipients. Stepwise immunosuppression reduction is recommended for patients with plasma BK DNAemia more than 1000 copies/mL sustained for 3 weeks or increasing to more than 10,000 copies/mL, or in those with biopsy-proven BK-associated nephropathy.

Allograft biopsy is not required for treating BK DNAemic patients whose GFR is at or close to their baseline.[19]

Experimental studies demonstrated that sirolimus impairs BKPyV replication in kidney tubular epithelial cells during viral early gene expression but not during viral late gene expression by interfering with mammalian target of rapamycin (mTOR)-SP6-kinase activation. Cyclosporine was similarly shown to inhibit BKPyV replication, whereas tacrolimus activates BKPyV replication and reverses sirolimus inhibition, leading to increased BKPyV replication.[20] In a small trial of 40 kidney transplant recipients, mycophenolate mofetil (MMF) to everolimus conversion versus 50% MMF dose reduction showed a nonsignificant trend toward improved viral clearance with everolimus conversion at 3 months follow-up.[21] There have been no trials evaluating the safety and efficacy of leflunomide or cidofovir in BK DNAemia or BKVAN. A systematic review of 40 studies showed no graft survival benefit of adding cidofovir or leflunomide to immunosuppressive reduction for the management of BKN.[22] Despite virological rationales, no trial data support switching from tacrolimus to cyclosporine-A, from mycophenolate to mTOR inhibitors or leflunomide or adding adjuncts such as intravenous immunoglobulins, cidofovir, or leflunomide (AST-IDOCP guidelines).[19] Although quinolones have been shown to inhibit DNA topoisomerase and SV40 larger tumor antigen helicase, a prospective, double-blind, randomized, placebocontrolled trial of ciprofloxacin versus placebo for the prevention of BK viremia in kidney transplant recipients demonstrated no benefit of ciprofloxacin at preventing BK viremia.[23] Fluoroquinolones are not recommended for prophylaxis or therapy. BK virus–specific T-cell adoptive transfer therapy is a subject of ongoing clinical research.

Reduction in immunosuppression is not universally effective. Nonetheless, routine BK screening and early reduction in

A

B

C

Fig. 110.1 BK Virus Nephropathy. (A) Prominent intranuclear viral inclusions are present within tubular epithelial cells (arrows). (H&E stain; original magnification ×400.) (B) Tubulointerstitial nephritis with diffuse intranuclear polyomavirus inclusions (arrows). (H&E stain, original magnification ×200.) (C) Immunohistochemistry staining highlights in trinuclear polyomavirus inclusions. (SV40 immunoperoxidase stain; original magnification ×200.) (Courtesy Charles Lassman and William Dean Wallace, David Geffen School of Medicine at UCLA.)

immunosuppression if positive may prevent the development of BKVAN. Monitoring plasma BK alone (vs. urine BK alone or simultaneous urine and plasma BK) appears to be cost-effective because BKVAN is unusual in the absence of BK viremia. Suggested guidelines for posttransplant screening and monitoring for BKPyV replication are shown in Fig. 110.2. Although immunosuppression reduction may improve BK DNAemia and subsequent development of BKN, it may increase the risk of de novo donor specific antibody (DSA) development, underscoring the need for routine DSA surveillance. Treatment should be individualized based on each patient’s immunologic risk. Although evidence is lacking, mycophenolic acid (MPA) to mTOR inhibitor switch may be considered in patients with steadily rising BK DNAemia despite MPA dose reduction or withdrawal or in those with impaired graft function to avoid the long-term nephrotoxic effect of CNI toxicity. One large international multicenter, open-label clinical trial of kidney transplant recipients randomized to receive everolimus with reduced-exposure CNI (everolimus arm) or MPA with standard-exposure CNI (MPA arm), reported less BKPyV infection (in the everolimus compared with the MPA-treated arm. Histologic evidence of organ involvement occurred in 1.2% and 2.1% of patients, respectively.[24]

There is no consensus on the management of biopsy-proven acute rejection and concomitant BKVAN. We treat acute rejection with antirejection therapy with subsequent reduction in maintenance immunosuppression. Intravenous immunoglobulin (IVIG) therapy may be considered in patients with persistent BK DNAemia and DSAs (which may be seen arising in association with BK viremia), in those with BKVAN and histopathologic changes that are indistinguishable from those of rejection, and in those with hypogammaglobulinemia. IVIG may be beneficial due to its direct BKPyV neutralizing activity and immunomodulatory effects. Retransplantation after allograft loss due to BKPy nephropathy can be successful if BK DNAemia is definitively cleared, independent of failed allograft nephrectomy.[19]

Tuberculosis

Tuberculosis (TB) is an important cause of morbidity and mortality in solid organ transplantation, with an estimated mortality rate of 20% to 30%. Over two-thirds of reported cases of active TB in solid organ transplant recipients occur in the first posttransplant year (median, 6–11 months). Although TB commonly results from inhalation of airborne bacilli, it more commonly emerges from the reactivation of dormant lesions due to immunosuppressive therapy. Hence, all potential kidney transplant candidates should undergo a purified protein derivative (PPD) skin test or preferably the interferon-γ (IFN-γ) release assays before transplantation to diagnose latent

Management of BK Viral Infection in the Kidney Transplant Recipient
- Quantitative plasma BK DNA by PCR monthly × 9, then every 3 months until 2 years posttransplant, then annually up to
5 years posttransplant, and
- At the discretion of the clinician: (1) When allograft dysfunction occurs or (2) When allograft biopsy is performed or (3)
After treatment of acute rejection

BK not detecteda

BK ≤ 1000 copies/mLa

BK > 1000 copies/mLa

Spontaneous resolution

Repeat BK DNA in 2–3 weeks

Rising BK DNAemia

Reduction in immunosuppressionb
Consider monitoring DSA, particularly in high immunologic risk patients

Resolution of BK DNAemia

Repeat in 2–4 weeks until undetectable

Improving BK DNAemia

Rising BK DNAemia

1. Consider biopsy if increase SCr and/or BK DNA > 10 4 copies/mL
2. Consider further immunosuppression reduction based on viral load and immunologic risk
3. Consider IVIG in patients with persistent BK DNAemia and de novo DSA or hypogammaglobulinemia
4. Consider mycophenolic acid derivatives to mTOR inhibitor switch (see text)

Acute rejectionc

BKVANc

Acute rejection + BKVANc

Treat rejection

Consider (2) and/or (3) above if not already done
Consider IVIGd or CNI to mTOR inhibitor switche

Treat rejection with subsequent reduction
in maintenance immunosuppression
Consider IVIG if DSA is present

Fig. 110.2 Management of BK Viral Infection in the Kidney Transplant Recipient. aNo standardized PCR
assays for BK virus are currently available. Cutoff levels for viral detection should be based on PCR assays
used at individual institutions. Viral load of 500 copies/mL is the lowest detection level at the author’s institution. bCommon practice: (1) Decrease or hold MFA derivatives (or antimetabolite). (2) Decrease (MFA +

CNI by 25% to 50%. (3) Decrease CNI. Less common practice: (1) Decrease prednisone with or without a decrease in CNI. (2) CNI to mTOR inhibitor switch with or without a decrease in MFA. (3) Tacrolimus to cyclosporine switch. cBiopsy proven. dIf DSA is present or histopathologic findings are indistinguishable from those of rejection. eMay avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as >500 mg/24 h or at the discretion of the clinician).
BKVAN, BKPyV-associated nephropathy; DSA, donor specific antibody; IVIG, intravenous immunoglobulin; MFA, mycophenolic acid; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; SCr, serum creatinine.

TB. A positive skin test or IFN-γ release assay result or a history of TB mandates ruling out active disease. Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation. Isoniazid (INH) prophylactic therapy should be considered in the following situations:

- Transplant candidates with a history of positive tuberculin skin test or IFN-γ release assay result
- Patients with evidence of old granulomatous disease on chest radiograph or computed tomographic imaging and epidemiologic risk factors for TB
- Those with known prolonged exposure to a person with active TB
- Kidney transplant recipients in endemic areas

- Donor with positive tuberculin skin test or IFN-γ release assay result, or history of untreated TB
- In highly endemic areas where TB transmission is common, universal INH prophylaxis for the first year posttransplant during the period of maximum immunosuppression is recommended. In countries where there is an increased prevalence of INH-resistance strain, such as India, close monitoring and treatment of active infection is recommended over initiation of INH prophylaxis.
- In patients with a known history of adequately treated TB infection, we suggest secondary INH prophylaxis for the first 9 months after transplantation in patients with a history of extensive disease such as positive blood cultures, visceral involvement, or recent treatment

history (arbitrarily defined as <10 years before transplant). Others, however, have suggested that INH prophylaxis is not indicated for patients whose TB had been properly treated.

Strongyloides

Strongyloides is a rare but important cause of infection in transplant patients, particularly those from endemic areas such as Southeast Asia. In the presence of immunosuppression, a hyperinfection syndrome may be observed with parasitic pneumonia and gastrointestinal (GI) involvement.

EMERGING INFECTIOUS DISEASE

COVID-19

The coronavirus disease 2019 (COVID-19) pandemic caused by SARSCoV-2 has severely impacted both immunocompetent and immunocompromised populations worldwide. Solid organ transplant (SOT) recipients, including kidney transplant recipients, are at increased risk because of their immunocompromised state.25 Similar to the general population, the clinical spectrum of COVID-19 in SOT recipients spans from asymptomatic/pauci-symptomatic to acute respiratory distress syndrome with multiorgan failure and death. Common presenting symptoms include fever, dry cough, dyspnea, and fatigue. Others include diarrhea, anorexia, nausea, headache, myalgias, and anosmia. Limited retrospective studies suggest that the Omicron variant causes less severe illness compared with ancestral SARS-CoV-2 in both the general population and in SOT recipients. In addition, although vaccination response as measured by humoral or T-cell response is impaired in SOT recipients compared with those on dialysis or healthy controls,26 one large singlecenter registry study (n = 2151 SOT recipients) demonstrated decreased hospitalization and mortality rates among vaccinated compared with unvaccinated SOT recipients with COVID-19 infection.27

Management of Immunosuppression During COVID-19 Infection

The optimal approach to the management of immunosuppression in kidney transplant recipients infected by COVID-19 has not been well defined. Nonetheless, many transplant centers favor reduction or discontinuation of antimetabolites in symptomatic patients, particularly those with lymphopenia. Additionally, the use of lymphocytedepleting agents such as antithymocyte globulin is generally avoided.

Lymphopenia at the time of admission correlates with worse outcomes, including increased mortality and intensive care unit admission.28 Rituximab causes B-cell depletion and has been shown to compromise antiviral immunity and impair COVID-19 vaccine efficacy.

A meta-analysis of randomized controlled trials conducted in the general population demonstrated that in critically ill COVID-19 patients, administration of systemic corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone) was associated with lower 28-day all-cause mortality, compared with standard care or placebo.29 The beneficial effect of high-dose corticosteroids may be due to their immunomodulatory and antiinflammatory effects. The Centers for Disease Control and Prevention guidelines recommend that hospitalized patients, including kidney transplant recipients requiring supplemental oxygen, receive a short course of dexamethasone (6 mg daily for 5 to 10 days) (https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-hospitalized-adults/). Low-dose chronic maintenance prednisone therapy is withheld until after completion of dexamethasone.

Interleukin-6 (IL-6), which stimulates the inflammatory pathways in response to infection, is commonly found to be elevated in subjects with severe COVID-19 infection,30 suggesting that IL-6 could be a potential therapeutic target for patients presenting with severe cytokine storm syndrome. Calcineurin inhibitors (CNIs) inhibit IL-6 and IL-1 pathways, and their use may confer theoretical benefits in the settings of COVID-19 infection. Hence CNIs can generally be continued without dose reduction.

Large randomized controlled trials demonstrated that adding an immunomodulator such as an IL-6 inhibitor (e.g., tocilizumab or sarilumab) or Janus kinase inhibitor (e.g. baricitinib, tofacitinib) to dexamethasone improved survival in symptomatic hospitalized patients with evidence of systemic inflammation. A phase III randomized, double-blind, parallel-group, placebo-controlled trial demonstrated that baricitinib reduced 28-day and 60-day all-cause mortality when used in conjunction with standard care, including systemic corticosteroid (e.g., dexamethasone), antiviral (remdesivir), or both (hazard ratio [HR], 0.57; 95% CI, 0.410.78; nominal P = .0018; and HR, 0.62; 95% CI, 0.470.83; P = .0050, respectively). There was a nonsignificant reduction in the frequency of disease progression (defined as progression to high-flow oxygen, noninvasive ventilation, mechanical ventilation, or death by day 28).31 Safety profile was similar among baricitinib-treated and standard of care alonetreated patients. Nonetheless, immunosuppressed organ transplant recipients must be closely monitored for secondary infections.

The beneficial effect of tocilizumab has not been consistently demonstrated in randomized controlled trials conducted earlier in the pandemic. However, a subsequent international, multifactorial, adaptive platform trial consisting of critically ill patients (defined as those requiring intensive care unit admission and receiving respiratory or cardiovascular organ support) demonstrated that both IL-6 receptor antagonists tocilizumab (n = 353) and sarilumab (n = 48) confer a survival benefit compared with controls (n = 402). The in-hospital mortality in the pooled IL-6 receptor antagonist groups was 27% vs. 36% in the control group.32

Antiviral Therapy

Remdesivir is the first FDA-approved COVID-19 specific antiviral agent. It binds to the SARS-CoV-2 RNA-dependent RNA polymerase and inhibits viral replication via premature termination of RNA transcription. In vitro studies showed that remdesivir retains antiviral activity against the Omicron variant and subvariants. Potential adverse effects include increased serum transaminase levels and accumulation of the potentially nephrotoxic drug vehicle cyclodextrin in patients with kidney dysfunction. Remdesivir is indicated for both nonhospitalized and hospitalized patients who require no to minimal supplemental oxygen therapy (https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-nonhospitalizedadults/). Dexamethasone and remdesivir combination therapy should be considered in those requiring supplemental oxygen. Other FDAapproved antiviral agents include molnupiravir and ritonavir-boosted nirmatrelvir (Paxlovid). The latter should be avoided in tacrolimus or cyclosporine-treated patients due to significant drug-drug interactions. Ritonavir is a strong CYP3A4 inhibitor that is used as a druglevel boosting agent for nirmatrelvir to achieve its target therapeutic range. Similarly, concomitant use of ritonavir and drugs that are metabolized primarily by the CYP3A4 system, such as cyclosporine and tacrolimus, can result in significantly elevated CNI drug level and CNI toxicity.

At the time of this writing, there is insufficient data to recommend or refute the use of molnupiravir in kidney transplant recipients. In one single-center prospective cohort study (n = 16 with SARS-CoV-2 [Omicron variant] and mild symptoms), one of nine patients treated with molnupiravir developed pneumonia requiring hospital admission, whereas none of seven patients treated with remdesivir progressed in disease severity. No drug-drug interaction with tacrolimus or adverse effect related to molnupiravir were observed.33 3031

Management of COVID-19 in Kidney Transplant Recipients

COVID-19 detected by PCR

Asymptomatic

Symptomatic

Self-isolation for 20 days[a]

Reduce or hold mycophenolate acid derivatives or antimetabolite[b]

Mild to moderate symptoms and within 7 days of symptom onset
Outpatient monoclonal antibody,[c] remdesivir, or molnupiravir[d]

Moderate to severe symptoms requiring hospitalization[c]

Minimal supplemental oxygen requirement

- Remdesivir
- Consider convalescent plasma
- Add dexamethasone if increasing oxygen requirement

High-flow oxygen or noninvasive ventilation

- Remdesivir plus dexamethasone
- Consider convalescent plasma
- Add immunomodulatory drug in patients with rapid respiratory decompensation and systemic inflammation (e.g., baricitinib or tocilizumab)[f]

Mechanical ventilation

Remdesivir plus dexamethasone plus immunomodulatory drug (e.g., baricitnib or tocilizumab)[f]

Fig. 110.3 Management of COVID-19 in Kidney Transplant Recipients. [a]Self-isolation period may vary among geographical locations and countries. [b]Consider resuming mycophenolic acid derivatives or antimetabolites when patients are asymptomatic for 5 to 7 days (opinion based). [c]Bebtelovimab retains its activity against the Omicron variant and its subvariants. [d]Consider molnupiravir for those unable to receive monoclonal antibody or remdesivir. [e]Monitor inflammatory markers at

the discretion of the clinician: CBC with differentials, ferritin, D-dimer, CRP, LDH. fMonitor closely for secondary infections. Obtain baseline Strongyloides antibody, and interferon release assay (quantiferon test). Recommended prophylactic therapy: TMP-SMX daily for 3 months and valacyclovir 500 mg twice daily for 3 months. Monitor cytomegalovirus DNA at the discretion of the clinician. Low threshold for initiation of antifungal prophylaxis or treatment with prolonged steroid use. CBC, Complete blood cell count; CRP, C-reactive protein; LDH, lactate dehydrogenase; MPA, mycophenolic acid; PCR, polymerase chain reaction.

Monoclonal Antibody Therapy

Anti-SARS-CoV-2 monoclonal antibodies target against the SARSCoV-2 spike protein, thereby blocking the attachment and entry of the virus into host cells. Bebtelovimab is recommended for nonhospitalized patients with mild to moderate symptoms who are at high risk of progressing to severe disease (https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-nonhospitalized-adults/). The United States CDC expert panel recommends against the use of bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab because of their markedly reduced in vitro susceptibility to the Omicron variant and its subvariants. Such variants have become the dominant SARS-CoV-2 variant in the United States. Monoclonal antibody therapy is still considered first-line therapy for high-risk outpatients with contraindication to ritonavir-boosted nirmatrelvir (Paxlovid) use due to drug-drug interactions such as the typical SOT recipient.

suppress viral replication. There is currently insufficient evidence to recommend for or against the use of convalescent plasma in kidney transplant recipients. However, given the low side effect profile of this treatment and immunologic rationale for antibody administration in immunocompromised patients, it is reasonable to consider convalescent plasma therapy in kidney transplant recipients requiring hospitalization (https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/covid-19-convalescentplasma/). With the emergence of the Omicron variant, only high-titer products collected after the surge of the Omicron variant should be used. Furthermore, studies suggest that they should be given early in the course of illness for best efficacy.34 A suggested algorithm for the management of COVID-19 in kidney transplant recipients is shown in Fig. 110.3 (authors’ institution protocol).

Anti-SARS-CoV-2 Convalescent Plasma

GASTROINTESTINAL DISEASE

Plasma from donors who have recovered from COVID-19 may contain antibodies against the SARS-CoV-2 that could potentially

Posttransplantation GI complications are common. Selected complications are discussed.

Drug-Related Gastrointestinal Complications

MMF and to a lesser extent, enteric-coated mycophenolate sodium (EC-MPS) cause GI side effects, including nausea, vomiting, dyspepsia, anorexia, flatulence, and diarrhea. Dose reduction, temporary drug discontinuation, or administration of the drug in 3 or 4 divided doses often ameliorate the symptoms. Switching from MMF to EC-MPS can increase the maximum tolerated dose of MFA and reduce GI symptoms. MMF- and MPA-induced diarrhea may be due to direct enterocyte damage35; although uncommon, Crohn's disease-like changes in the colon, erosive enterocolitis, and graft-versus-host disease–like colonic changes associated with the use of MMF have also been reported.36 Proton pump inhibitor (PPI) use can reduce the dissolution of MMF by increasing gastric pH. In contrast to MMF, EC-MPS is not absorbed in the stomach, and its bioavailability is not affected by PPIs. Sirolimus, everolimus, tacrolimus, and cyclosporine may cause diarrhea in some patients. Diarrhea associated with tacrolimus use is thought to be due to increased GI motility. Sirolimus may cause oral mucocutaneous lesions that may resemble HSV or CMV infection but are culture negative. Drug-related oral ulcers usually resolve after discontinuation of the offending agent.

Infections

Posttransplantation infections of the GI tract may have a viral, fungal, or bacterial cause. Viral infections are most commonly caused by CMV and HSV; C. albicans and C. tropicalis are common opportunistic fungal infections. Leukoplakia and posttransplant lymphoproliferative disorders (PTLDs) may develop in patients with EBV infection (PTLD is discussed in a later section). Commonly encountered bacterial pathogens include Clostridium difficile and Helicobacter pylori.

Fig. 110.4 Tissue Obtained From Patient's Vomitus. Histologic examination of the necrotic tissue showed numerous fungal organisms (consistent with Candida spp.), and degenerated squamous epithelium with detached columnar (gastric foveolar type) epithelium. Occasional cells demonstrated enlarged nuclei and intracytoplasmic granular eosinophilic inclusions, consistent with cytomegalovirus viral inclusions.

the first month after transplantation is recommended. Fluconazole prophylaxis is warranted in high-risk candidates, including liver or pancreas transplant recipients.

Cytomegalovirus Infection

Helicobacter Infection

CMV can affect any segment of the GI tract. Patients may present with dysphagia, odynophagia, nausea, vomiting, gastroparesis, abdominal pain, diarrhea, or GI bleeding. Leukopenia and elevated transaminases are common. Persistent or unexplained symptoms of nausea, vomiting, or diarrhea, particularly in the early posttransplantation period or during intensification of immunosuppression, warrant further investigation with upper and lower endoscopies and biopsies. At our institution, severe CMV and candidial gastritis/esophagitis were found in a patient who was heavily immunosuppressed with antithymocyte globulin and presented with intractable vomiting 4 months after transplantation. Histologic examination of the tissue obtained from the vomitus was compatible with foveolar gastric lining detachment (Fig. 110.4).

H. pylori infection is associated with a wide range of GI complications including chronic gastritis, duodenal and gastric ulcers, mucosaassociated lymphatic tissue (MALT) lymphoma, and gastric carcinoma, both in the general population and in solid organ transplant recipients. Unexplained dyspeptic or reflux symptoms should be investigated further with endoscopy and biopsy to exclude malignancy. H. pylori–associated MALT lymphoma in kidney transplant recipients may be less aggressive than other lymphomas, and the disorder may be cured by eradication of H. pylori.

Herpes Simplex Virus Infection

HSV infection results primarily from reactivation of endogenous latent virus, causing clinical infection within the first 1 to 2 months after transplantation. Patients commonly present with oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia. HSV esophagitis has been noted to occur in patients receiving high-dose corticosteroids and antilymphocyte preparations for acute rejection. Limited oral mucocutaneous lesions are treated with oral acyclovir; extensive infections require intravenous acyclovir or ganciclovir. For patients not receiving anti-CMV prophylaxis, acyclovir prophylaxis in the early posttransplantation period is recommended (see Box 110.2).

Fungal Infections

Candida stomatitis and esophagitis are common during the first 6 months after transplantation and are increased in patients with leukopenia, severe immunosuppression, diabetes, or concomitant infections. The use of prophylactic oral nystatin “swish and swallow” during

Diarrhea and Colon Disorders

Diarrhea is common after solid organ transplantation because of adverse drug effects (discussed in an earlier section) and infectious pathogens. Clostridiodes difficile (formerly known as Clostridium difficile) is the most commonly encountered bacterial pathogen, and CMV and norovirus are the most commonly encountered viral pathogens. Suggested treatment regimen for C. difficile diarrhea is shown in Table 110.4. Although norovirus often causes acute self-limited illness in immunocompetent individuals, solid organ transplant recipients can experience prolonged or intermittent diarrhea associated with chronic viral shedding. A median viral shedding period of 289 days (97–898 days) has been reported. Molecular analysis of viral strains in kidney transplant recipients with chronic intermittent diarrhea suggests that continuous genetic mutation and viral evolution may promote viral persistence.37 Other less common infectious causes of posttransplantation diarrhea are shown in Table 110.4 35 36 38

Diverticulitis and colonic perforations may be life-threatening and difficult to diagnose after transplantation because symptoms may be masked by immunosuppressive therapy, particularly in the early postoperative period. Diverticulitis complicated by perforation, abscess formation, phlegmon, or fistula has been reported in 1% of kidney

TABLE 110.4 Causes of Diarrhea After Solid Organ Transplantation

Pathogens
Bacterial
Clostridioides difficile
Campylobacter spp.
Salmonella spp.
Shigella spp.
Aeromonas spp.
Escherichia coli
Others: Vibrio cholera, Yersinia enterocolitica, bacterial overgrowth, chlamydia, Helicobacter pylori

Viral
CMV
Norovirus
Sapovirus
Others: rotavirus, adenovirus, enterovirus, herpes simplex virus, SARS-CoV-2
Parasitic
Giardia, Cryptosporidium, Cyclospora, Microsporidia, Strongyloides, Entamoeba, Isospora

Suggested Therapies/Comments

Meta-Analysis Standardized Incidence Ratios (SIRs) for Cancers Related to Infections in Transplant Recipients

TABLE 110.5

Cancers
C. difficilea
- First episode: Oral vancomycin 125 mg 4 times daily for 10–14 days or fidaxomicin 200 mg twice daily for 10 days
- First relapse: treatment same as first episode
- Second relapse: oral vancomycin or fidaxomicin
- Third or more relapses: prolonged oral vancomycin taper (125 mg 4 times a day for 10–14 days, twice times a day for a week, once a day for a week, and then every 2 or 3 days for 2–8 weeks). May consider fecal microbiota transplantation or bezlotoxumab (monoclonal antibody).

E. coli
- Enteropathogenic: fluoroquinolone, cephalosporin
- Enterohemorrhagic: avoid antimotility agents, role of antibacterials unclear and should be avoided

CMV (see text)
Norovirus
- Diagnostic testing: norovirus PCR

• Treatment: supportive (volume repletion, antimotility agents), reduction of immunosuppression (inconclusive evidence), nitazoxanide (anecdotal case reports)

[a] Metronidazole is no longer considered first-line treatment because of the risk of recurrence after treatment.
CMV, Cytomegalovirus; PCR, polymerase chain reaction.

transplant recipients, and its incidence may be increased in patients with autosomal dominant polycystic kidney disease (ADPKD).39 Early posttransplantation colonic perforations are largely caused by high-dose corticosteroids, diverticulitis, CMV colitis, and intestinal ischemia; perforations occurring late or years after transplantation are commonly caused by diverticulosis or malignant disease.

TRANSPLANT-ASSOCIATED MALIGNANCY

The incidence of de novo malignancies is twofold to fourfold greater in solid organ transplant recipients compared with the general population.40 Among long-term survivors after kidney transplantation (>20 years), cancer was the most common cause of death with a functioning graft followed by CV disease.41 The intensity and duration of immunosuppression, as well as the ability of these agents to promote replication of various oncogenic viruses, are important risk factors. Table 110.5 provides a summary of the incidence of cancers related to infections in solid organ transplant recipients.42 The Transplant Center March Study database demonstrated a strong association of lip cancer with

	Meta-Analysis SIRs
EBV-Related Cancers	
Hodgkin lymphoma	3.89 (2.42–6.26)
Non-Hodgkin lymphoma	8.07 (6.40–10.2)
HHV-8–Related Cancer	
Kaposi sarcoma	208.0 (114–369)
HBV- and HCV-Related Cancer	
Liver	2.13 (1.16–3.91)
HPV-Related Cancers	
Cervix uteri	2.13 (1.37–3.30)
Vulva and vagina	22.8 (15.8–32.7)
Penis	5.8 (5.79–34.4)
Anus	4.85 (1.36–173)
Oral cavity and pharynx	3.23 (2.40–4.35)
Nonmelanocytic-related skin	28.6 (9.39–87.2)

EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpes virus; HPV, human papilloma virus; SIR, standardized incidence ratio.
Modified from McCaughan JA, Courtney AE. The clinical course of kidney transplant recipients after 20 years of graft function. Am J

Transplant. 2015;15(3):734–740.

White ethnicity and prior history of skin cancer, suggesting that ultraviolet (UV) radiation exposure is an important risk factor. A higher incidence of lip cancer was also found among transplant recipients receiving cyclosporine and azathioprine (AZA) compared with tacrolimus/MMF maintenance immunosuppression. The contributory role of cyclosporine and AZA was thought to be due to their photosensitizing or DNA damaging effects.43 Other suggested risk factors for posttransplantation malignancies include older age, male sex, White ethnicity, pretransplant dialysis duration, smoking history, deceased donor organ, cumulative exposure to radiation from repeated medical imaging studies, and prior use of immunosuppressive agents.

Skin cancers are the most common de novo posttransplant tumors in the adult transplant population and occur with increasing frequency with time. Among nonskin malignant neoplasms, PTLDs are the most common type of posttransplantation malignancy. The mean time to diagnosis of different neoplasms varies with the type of organ involved. Kaposi sarcoma, PTLD, testicular cancer, cancer of the small intestine, and thyroid cancer occur early (<800 days) after transplantation. In the AZA era, nearly 50% of adult transplant recipients have one or more skin cancers by 20 years after kidney transplant. The use of MPAcontaining regimen has been reported to be associated with a lower incidence of posttransplantation nonmelanoma skin cancers compared with AZA. (The effects of various immunosuppressive agents on cancer risk are discussed later.40) Renal cell carcinoma (RCC) occurs mainly in native kidneys and is associated with acquired cystic kidney disease and dialysis duration. A bimodal distribution is observed with the highest incidence occurring in the first year and a second peak 4 to 15 years after transplant.44 RCC occurring early after transplant is thought to reflect undetected or malignant transformation of preexisting cysts that developed during the course of end-stage kidney disease. Common cancers in the general population, including cancers of the breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some but not all studies. The Kidney Disease Outcomes Quality Initiative guidelines suggest an individualized plan for each kidney transplant recipient, considering the patient’s medical and family history, tobacco use, and competing risk for death. We evaluate hepatitis B–positive transplant candidates and recipients for hepatocellular carcinoma with abdominal ultrasound and α-fetoprotein level every 6 months. Although practice differs among centers, screening should be considered in high-risk patients, such as those with high HBV viral load, hepatitis B e antigen–positive, hepatitis B surface antigen–positive, and Asian or African ethnicity. Screening for cervical, breast, prostate, and colon cancer should follow local guidelines for the general population. In recipients with a history of preexisting malignant neoplasms, close monitoring for recurrences is mandatory. Suggested guidelines for tumor-free waiting periods for common pretransplant malignant neoplasms are shown in Table 110.6.45

Posttransplantation Lymphoproliferative Disorder

PTLD encompasses a wide spectrum of lymphoid proliferations ranging from reactive polyclonal lesions to frank malignant monoclonal lymphomas and can be divided into four subtypes based on morphology, clonality, and molecular criteria (Table 110.7).45,46 Most PTLDs are non-Hodgkin lymphoma of B-cell origin, 80% to 90% of which are linked to EBV infection. However, the incidence of EBV-negative PTLD has increasingly been reported. PTLD commonly occurs in the first year after transplant, although the cumulative incidence increases with time after transplantation. Registry studies demonstrate that PTLD occurs at a median of 18 to 18.5 months after transplantation. Notably, EBV-negative PTLD generally manifests later after transplant (>5 years) and has been suggested to account for the bimodal distribution pattern of PTLD occurrence, with early cases being predominantly EBV positive and late cases being EBV negative.40 Another registry study suggests that late-occurring PTLD (8–10 years) is less likely to be due to EBV lymphoproliferation and more likely to be a consequence of aging and duration of immunosuppression exposure.47 The incidence of EBV-associated PTLD by PTLD subtypes and time of onset after transplant is shown in Table 110.8.45 Mortality is greater with PTLD than with lymphomas in the general population.

EBV-Positive Versus EBV-Negative PTLD

Immunosuppression-related decrease in T-cell immune surveillance may play a major contributory role in EBV-positive PTLD. In immunocompetent hosts, EBV-specific CD8+ effector and memory T cells are responsible for controlling EBV-infected B cells from uncontrolled proliferation and transformation. The pathogenesis of EBV-negative PTLD remains speculative. Proposed hypotheses include hit-and-run EBV infection (disappearance of EBV following an initial infection that leads to PTLD), viral infection other than EBV (e.g., cytomegalovirus), persistent antigen stimulation by the graft, and long-term immunosuppression. Molecular-genomic studies revealed that EBV-negative PTLD shares many genomic and transcriptomic features with diffuse large B-cell lymphoma in immunocompetent patients, whereas EBVpositive PTLD has fewer genomic abnormalities. Although the molecular genetic separation between EBV-positive and EBV-negative PTLD is well-defined, EBV status is not prognostic or predictive with respect to treatment response. In a subset of patients, reduction in immunosuppression alone is effective regardless of EBV status.

Risk Factors

Risk factors for PTLD can be classified into those associated with EBV or other infectious agents, the type of organ transplant, recipient age, the type and intensity of immunosuppression, and human leukocyte antigen (HLA) mismatch among others (Table 110.9). Selected risk factors are discussed.

Epstein-Barr virus infection. During primary infection, EBV is incorporated into B lymphocytes and establishes lifelong latency.

Immunocompetent hosts mount an antibody response and, more importantly, an EBV-specific cytotoxic T-cell immune response. EBVnaive transplant recipients lack both virus-specific antibodies and EBV-specific T cells; therefore an EBV-negative recipient of an EBVpositive donor is at greatest risk for developing PTLD.

Type of immunosuppression

Calcineurin inhibitors. Cyclosporine and tacrolimus may enhance the development of EBV-associated PTLD by directly promoting survival of EBV-infected B cells, presumably via the inhibition of EBV-transformed cells from apoptosis. Although singlecenter retrospective studies demonstrated that tacrolimus increased the risk for PTLD twofold to fivefold compared with cyclosporine, tacrolimus use has not been consistently shown to be associated with increased PTLD risk compared with cyclosporine.48

mTOR inhibitors. Sirolimus has a strong antiproliferative effect on PTLD-derived B-cell lines. Although there are theoretical reasons to suspect that mTOR inhibitors might decrease the risk of PTLD, one retrospective study demonstrated that sirolimus-containing regimens are associated with a 1.2-fold higher incidence of PTLD compared with no sirolimus.49 The UNOS/OPTN database similarly demonstrated that in EBV-negative kidney transplant recipients, mTOR inhibitor + tacrolimus (Tac) combination therapy was associated with a nearly twofold increased PTLD risk compared with MMF/MPS + Tac combination therapy, whereas MMF/MPS + cyclosporine A (CsA) immunosuppression was associated with lower PTLD risk.50 In contrast, a favorable effect of mTOR inhibitor on PTLD has also been reported. In a case series of 13 kidney transplant recipients with PTLD, immunosuppression reduction (MMF or AZA dose reduction along with discontinuation of Tac or CsA) in conjunction with initiation of sirolimus alone was effective in induction of remission in 4 patients with diffuse large B-cell PTLD after a median time of 12 weeks.51 The potential beneficial effect of sirolimus on PTLD risk reduction was also shown in a retrospective study of 523 heart transplant recipients. Of these, 307 underwent CNI to sirolimus conversion therapy with complete withdrawal of CNI at a median of 1.1 years after heart transplant. Over median follow-up of 10 years posttransplantation, 0.65% of patients (2/307) in the sirolimus conversion group developed PTLD compared with 10.18% of patients (22/216) in the CNI group (adjusted HR, 0.13; P = .009). Of note, however, 7.9% of patients in the CNI maintenance group were recipients of combined heart-lung transplantation, whereas only 0.65% of patients in the sirolimus group received combined heart-lung transplant. Whether the overall degree of immunosuppression accounted for the higher incidence of PTLD in the CNI-maintenance group could not be determined from the study.52

Antimetabolites. The use of antimetabolites such as AZA and MMF has not been consistently shown to be associated with an increased risk for PTLD.

Induction agents. Whereas induction therapy with muromonab CD3/OKT3 (removed from the US market in 2010) or antithymocyte globulin may increase PTLD risk, the use of IL-2 receptor inhibitors (basiliximab and daclizumab [removed from the market in 2018]) or anti-CD52 antibody (alemtuzumab) induction has not been reported to increase PTLD risk. Analysis of the UNOS/OPTN database demonstrated that thymoglobulin was associated with significantly increased PTLD risk, whereas alemtuzumab, basiliximab, and daclizumab were associated with a borderline protective effect (P = .06). In this study maintenance therapy with an mTOR inhibitor was strongly associated with PTLD, in contrast to earlier reports suggesting its beneficial effect on PTLD because of its antiproliferative and antiangiogenic effects. Although both alemtuzumab and thymoglobulin are T-cell–depletional agents, the former has been shown to have a more

TABLE 110.6

Tumor-Free Waiting Period for Common Pretransplantation Malignancies [a,b]

No Waiting Time

Long-standing history of MGUS; hematology-oncology consult is advisable in patients with newly diagnosed monoclonal gammopathy

No Waiting Time if Cure at the Time of Transplantation

Incidental renal cell carcinoma, in situ carcinoma of bladder, in situ carcinoma of cervix, basal cell carcinoma

Waiting Time Varies With Staging, Tumor Size

Breast cancer

2–5 years

2-year waiting time for ductal carcinoma in situ

Patients with stage III or IV breast cancer should be advised against transplantation

Prostate cancer

Old paradigm: 2-year tumor-free waiting time

Current trend[b]: shorter waiting time is acceptable for patients with grade group 1 or 2 prostate cancer (Gleason score ≤ 6 or Gleason 3 + 4, respectively)

Renal cell carcinoma

2 years if <5 cm

5 years if >5 cm or <5 cm with invasion

Old paradigm: 0- to 2-year waiting time

Skin SCC[b c]

New paradigm[d]: low-risk SCC: surgical excision with clear margins or Mohs surgery and no waiting time

High-risk SCC with no perineural invasion: surgical excision with clear margins or Mohs surgery and 2-year waiting time

High-risk SCC with perineural invasion: surgical excision with clear margins or Mohs surgery ± adjuvant radiation therapy and waiting time of 5 years

High-risk SCC with local nodal disease: surgical excision, lymph node dissection, adjuvant radiation therapy, and 5-year waiting time

Old paradigm: 5-year waiting time

Melanoma[b c]

New paradigm[d]: in situ: wide excision and no waiting time

Stage Ia: wide local excision and 2-year waiting time

Stage Ib/IIa: wide local excision and ± sentinel lymph node biopsy and 2- to 5-year waiting time

Stage IIb/IIc: wide local excision and ± sentinel lymph node biopsy and 5-year waiting time

Stage III or IV: not a transplant candidate

PTLD (retransplantation)

At least 1–2 years[b]

Waiting Time 2–5 Years[b]

2-year waiting time: invasive bladder, uterine body, Wilms tumor

2- to 5-year waiting time: lymphoma, invasive cervical carcinoma, colorectal carcinoma (at least 5 years for Dukes Bl or higher)

[a] Certain cancers may recur despite a tumor-free waiting period.

evaluation or consultation with the Israel Penn International Transplant Tumor Registry at https://ipittr.uc.edu may be invaluable.

[c] Dermatology consultation is recommended.

[d] Mittal A, Colegio OR. Skin cancers in organ transplant recipients. Am J Transplant. 2017;17(10):2509–2530.

MGUS, Monoclonal gammopathy of undetermined significance; PTLD, posttransplantation lymphoproliferative disorder; SCC, squamous cell carcinoma.

TABLE 110.7

WHO Classification of Posttransplant Lymphoproliferative Disorder

Categories

Histopathology

EBV Association/Comments

Early lesions

- Plasmacytic hyperplasia: many polyclonal plasma cells with occasional immunoblasts and lymphocytes
- Infectious mononucleosis–like: many immunoblasts, with T lymphocytes and plasma cells
- Florid follicular hyperplasia (included in the 2016 WHO classification of lymphoid neoplasms)
- Lymphocytes, plasma cells, immunoblasts, may be Reed-Sternberg–like cells
- Often monoclonal, may have necrosis
- Fulfills WHO criteria for non-Hodgkin lymphoma or plasma cell neoplasm
  - B cell (most common)
  - Diffuse large B-cell lymphoma, not otherwise specified
  - Burkitt lymphoma
  - Plasmacytoma-like lesions and plasmacytoma
  - Other
- T cell/NK cell: EBV negative
  - Peripheral T-cell lymphoma, not otherwise specified
  - Hepatosplenic lymphoma
  - T-cell/NK-cell lymphoma
  - Other
- Rare, usually mixed cellularity type

- Usually EBV positive
- No or very focal clonality, no atypical morphology

Polymorphic PTLD
Monomorphic PTLD

Hodgkin lymphoma–like PTLD

•
•
•
•

Often EBV positive
Cellular atypia, gene rearrangements may occur
EBV less often positive
Uniform population of neoplastic cells with clonality and gene rearrangements

- EBV positive

EBV, Epstein-Barr virus; NK, natural killer; PTLD, posttransplantation lymphoproliferative disorder; WHO, World Health Organization.

pronounced B-cell–depleting effect. We speculate that depletional induction is not an independent risk factor for PTLD, but rather that maintenance drug selection and the balance between B-cell and T-cell depletion may determine the risk of PTLD. Nonetheless, aggressive PTLD attributed to alemtuzumab induction has been reported. It is speculated that the overall intensity of immunosuppression increases PTLD risk by decreasing host cytotoxic T cells directed against grafted EBV-infected B lymphocytes.

Belatacept. Belatacept is a nonantigen-specific biologic agent that blocks T-cell costimulatory signals, hence preventing T-cell activation. Phase III clinical trials suggest that its use in transplant recipients with pretransplant EBV seronegativity is associated with an increased risk for PTLD. However, a systematic review suggested that belatacept use at different dosages and in patients who were EBV seronegative or seropositive before transplant confers no additional risk compared with CNI immunosuppression.53 Nonetheless, the black box warning for belatacept use in EBV-seronegative transplant candidates remains, and its use should be avoided in transplant recipients with pretransplant EBV-seronegative or unknown EBV status.

Incidence of EBV-Associated PTLD by Subtypes and Time of Onset After Transplant

TABLE 110.8

PTLD Subtypes	EBV Association	Onset After Transplant
Early lesions	Almost 100% EBV positive	Most early PTLD
Polymorphic PTLD	>90% EBV positive	Variable
Monomorphic PTLD	Both EBV positive and EBV negative	• EBV positive: most occur within the first 3 years after transplant • EBV negative: late occurring PTLD (>5 years after transplant)
Hodgkin lymphoma–like PTLD	>90%	

EBV, Epstein-Barr virus; PTLD, posttransplantation lymphoproliferative disorder.

TABLE 110.9

Donor-recipient HLA mismatch and HLA type. Retrospective analysis of more than 172,000 kidney, heart, pancreas, and lung recipients transplanted in the United States demonstrated that compared with recipients who had 2 HLA-donor-recipient (DR) mismatches, those with zero or 1 mismatch had reduced diffuse large B-cell lymphoma (DLBCL) risk (0 DR mismatch: incidence rate ratio [IRR], 0.76; 95% confidence interval [CI], 0.61–0.95; P = .0149; 1 DR mismatch: IRR, 0.83; 95% CI, 0.69–1.00). Analysis of individual HLA type showed that recipient HLA-B38 was associated with a 1.48-fold increased DLBCL risk, whereas recipient HLA-B58 and HLA-DR13 were associated with reduced DLBCL risk.54

Clinical Manifestations

PTLD may manifest with constitutional symptoms such as fevers, night sweats, malaise, and weight loss or with localized symptoms of the respiratory tract (infection or mass, including tonsillar or even gingival involvement), GI tract (diarrhea, pain, perforation, bleeding, mass), or central nervous system (CNS; headache, seizure, confusion). Other clinical manifestations may include lymphadenopathy or symptoms related to allograft dysfunction or compression of surrounding structures. Extranodal involvement occurs in more than two-thirds of patients. GI tract involvement occurs in 20% to 30% of cases, and solid graft organs in 10% to 15%. In contrast to lymphomas in the general population, the CNS is frequently involved in PTLD, occurring in up to 25% to 30% of patients, and can be the only site of disease. Early diagnosis requires a high index of suspicion and radiologic findings. Although computed tomography and magnetic resonance imaging are the most commonly used imaging modalities in PTLD, positron emission tomography-computerized tomography (PET-CT) has emerged as a potentially useful adjunct test for the diagnosis, staging, and

Risk Factors for PTLD

Risk Factors

Comments

- Pretransplant EBV seronegative and primary EBV infection
- Young recipient age (children compared with adults)

- Well-established risk factor
- Higher incidence of PTLD in children compared with adults has been attributed to pretransplant EBV-naive status in pediatric population
- More intensive immunosuppression and the amount of donor-derived lymphoid tissue transferred at organ transplantation may account for a high incidence of PTLD in multiorgan and bowel transplantation

PTLD incidence by type of organ transplant:
- Small bowel and multiviscera (up to 33%)
- Lung, heart, and heart-lung (2%–10%)
- Pancreas or simultaneous kidney-pancreas (2%–3%)
- Liver (1%–4%)
- Kidney (1%–2%)

Type of immunosuppression:
- Belatacept (increased risk in pretransplant EBV seronegative recipients)
- Lymphocyte-depleting agents (antithymocyte globulin > alemtuzumab)
- CNIs
- mTOR inhibitors (inconclusive or contradictory data)
- Antimetabolites (inconsistent data)
- Others (less well-established or controversial): HLA matching/HLA type, Black ethnicity, male sex, CMV infection/disease, HCV, pretransplant malignancy, HHV-8 and simian virus 40 infections, preexisting chronic immune stimulation, recipient MGUS

- Belatacept use is contraindicated in patients with pretransplant

EBVseronegative or unknown EBV status

- Overall intensity of induction and maintenance therapy may play a more important role than any single agent
- Duration of immunosuppression
- 2 DR mismatches compared with 0–1 DR mismatch

CMV, Cytomegalovirus; CNI, calcineurin inhibitor; EBV, Epstein-Barr virus; DR, donor-recipient; HCV, hepatitis C virus; HHV, human herpesvirus; HLA, human leukocyte antigen; MGUS, monoclonal gammopathy of undetermined significance; mTOR, mammalian target of rapamycin; PTLD, posttransplantation lymphoproliferative disorder.

assessment of PTLD treatment response.55 Tissue sampling is necessary for a definitive diagnosis and subcategorization of PTLD.

Treatment

Immunosuppression reduction is the first-line of treatment. Although their use has not been consistently demonstrated to increase PTLD risk, azathioprine and MPA derivatives are generally discontinued because of the theoretical net protumor effect of overimmunosuppression. CNI dose (or target level) can be reduced by 50% to 75% at the discretion of the clinician. Low-dose prednisone 5 mg daily can be continued to prevent allograft rejection. The 2019 AST-IDCOP do not recommend for or against switching to an mTOR inhibitor because of insufficient data.55 Although a direct antitumor effect of sirolimus cannot be excluded, it is speculated that the beneficial effect of conversion to sirolimus monotherapy (or sirolimus and prednisone dual therapy) may be due to a reduction in overall immunosuppression. Restaging should be performed 2 to 4 weeks after immunosuppression reduction. For critically ill patients and those with monoclonal tumors or extensive disease, immunosuppression should be drastically reduced or discontinued. Currently reducing immunosuppression and risk-stratified sequential treatment with rituximab followed by cyclophosphamide, hydroxydaunorubicin or doxorubicin, oncovin or vincristine, prednisone (R-CHOP) is considered standard of care for polymorphic and monomorphic diffuse large B-cell lymphoma-like PTLD irrespective of EBV status (rituximab at 375 mg/m2 weekly for 4 weeks, followed by CHOP every 3 weeks with granulocyte-stimulating factor support). Surgical resection with or without adjunctive local radiation can be used for localized disease. Local radiation has been advocated to treat PTLD involving the CNS, but chemotherapy is still recommended by some experts in the field. Poor prognostic factors include multiple-site versus single-site involvement, tumor monoclonality, graft organ involvement, advanced age, CD20-negative large cell lymphomas, and recipient EBVnegative serostatus. Other poor prognostic factors include World Health Organization performance status score of 3 or 4 (a score of 3 is defined as confined to bed or a chair for more than 50% of waking hours, and a score of 4 as completely disabled), late onset of disease (>1 year after transplant), elevated lactate dehydrogenase (LDH), CNS disease, severe organ dysfunction, acute kidney injury at diagnosis, impaired kidney function, and T-cell disease.45 Suggested treatment modalities for PTLD are shown in Table 110.10. Acyclovir and ganciclovir are of unproven benefit. A systematic review of 31 studies showed no beneficial effect of antiviral prophylaxis on the incidence of PTLD in high-risk EBV-naive transplant recipients. The findings were consistent across all types of solid organ transplants, age groups, prophylactic or preemptive therapy, duration of antiviral prophylaxis, or different antiviral agents (acyclovir, valacyclovir, ganciclovir, valganciclovir).56 Although arginine butyrate (a thymidine kinase–inducing agent) and ganciclovir combination therapy appears to have a promising role in EBV-associated PTLD, clinical trials evaluating its safety and efficacy have not been done.

EBV Monitoring and Preemptive Treatment Strategies

Most patients with EBV+ PTLD were shown to have a significantly higher viral load than those without PTLD. Posttransplantation EBV surveillance and preemptive treatment strategies including

TABLE 110.10

PTLD Treatment Modalities

Treatment

Indications

Comments

IS reduction

• Mainstay of therapy in all PTLD subtypes

• Factors predictive of a poor response to IS
reduction alone: elevated LDH, organ dysfunction
at diagnosis, multiple organ involvement, bulky
disease (tumor deposit > 7 cm), advanced stage
(Ann Arbor stage III or IV), age > 50 years

Rituximab
Chemotherapy

• First-line treatment for CD20+ PTLD not responsive to IS reduction alone
• For those who do not achieve complete remission despite IS reduction and
rituximab therapy
Currently, IS reduction and risk-stratified sequential treatment with rituximab
followed by CHOP (aka R-CHOP) are considered standard of care for
polymorphic and monomorphic diffuse large B-cell lymphoma
• Other indications: aggressive disease at presentation, lesions not amenable
to
surgery among others
• For localized disease in conjunction with IS reduction
• Palliative care (symptomatic relief)
• For localized disease in conjunction with surgery and IS reduction
• Palliative care (symptomatic relief)
• Acyclovir and ganciclovir are of unproven benefit because their activity is
dependent on intracellular phosphorylation by virally coded thymidine kinase
• EBV-driven lymphomas do not express thymidine kinase

Surgery
Radiation therapy
Antiviral therapy

mTOR inhibitors
Adoptive immunotherapy
(adoptive transfer of
EBV-specific cytotoxic
T cells)
Retransplantation

• Insufficient data to recommend or refute its use in the treatment of PTLD
• Relapsed or refractory PTLD

• CHOP-based therapy is the most widely used
regimen
• Increased infectious risk
• G-CSF use may decrease morbidity and
mortality

• Some centers continue to use antiviral therapy
based on limited studies suggesting that lytic
viral DNA (not just latent viral DNA) is also
present in established PTLD
• EBV-positive PTLD only
• Expensive, not readily available, time
consuming

• Should be disease-free for at least 1–2 years prior to retransplantation

🐧•🐧 Consultation with hematology-oncology recommended

CHOP, Cyclophosphamide, hydroxydaunorubicin or doxorubicin, oncovin or vincristine, prednisone; EBV, Epstein-Barr virus; G-CSF, granulocytecolony stimulating factor; IS, immunosuppression; LDH, lactate dehydrogenase; PTLD, posttransplantation lymphoproliferative disorder.

immunosuppression reduction, rituximab therapy, and/or adoptive transfer of EBV-specific T cells may have a beneficial effect on the incidence of PTLD. Rituximab-mediated elimination of B cells may prevent transmission of EBV to the recipient, because EBV persistence requires a latent infection in recipient B cells. Single-center retrospective study in pediatric kidney transplant recipients demonstrated that a highPCR EBV viral load (maximum peak EBV viral load above 59,909.5 copies/mL) was a significant and independent predictor of PTLD. Ten of 103 patients developed nonearly lesions PTLD, and 5 of 103 patients developed early lesions PTLD. In all cases EBV viral load was detected prior to the clinical diagnosis of PTLD.57 Of 5 patients who received rituximab, none developed PTLD in follow-up (range, 3–60 months). However, given the small number of patients in this group, no conclusions on the effect of rituximab could be drawn. In a multicenter observational study of 4765 solid organ transplant recipients, antiviral prophylaxis was found to have no beneficial effect on early or late EBV+ PTLD occurrence. However, of the 191 patients who received rituximab-containing induction regimen, none developed PTLD. In contrast, 1.2% of patients (57/4574) who did not receive rituximab induction developed PTLD.58 The 2019 AST-IDCOP guidelines recommend monitoring EBV viral load and preemptive interventions in patients who are EBV-seronegative pretransplant (weak/low).55 Currently, EBV surveillance and preemptive therapy cannot be routinely recommended because of the lack of standardized time points for monitoring, cutoff values, and sources of samples (e.g., whole blood, plasma, serum, peripheral blood mononuclear cells, or isolated B cells) and the unclear risks and benefits of immunosuppression reduction. Nonetheless, this approach warrants further exploration.

Skin Cancer

Skin cancers are the most common de novo posttransplant tumors in the adult transplant population. Risk factors include light skin color, total sun burden and recreational sun exposure, genetic factors, history or present use of AZA, increasing number of immunosuppressants used, pretransplant history of squamous cell carcinoma (SCC), older age at transplant (>50 years), male sex, and duration of follow-up after transplantation. Cumulative UV radiation exposure has been suggested to be the primary carcinogen. Daily high-SPF sunscreen use is associated with a decrease in the incidence of actinic keratosis, SCC, and basal cell carcinoma (BCC) in solid organ transplant recipients. Potential pathogenic mechanisms of photocarcinogenesis include direct DNA damage, UV effects on host immunity, and synergistic effect with immunosuppressive drugs (particularly CNIs and AZA).59 Limited studies suggest that AZA can also directly cause UVA-mediated DNA mutagenesis. Nonmelanoma skin cancer risk appears to be lower with MMF than with AZA use. In contrast, sirolimus or mTOR inhibitors may delay the onset or reduce the incidence of posttransplant skin and nonskin malignant neoplasms (discussed further later). Voriconazole (a previously commonly used antifungal agent to treat invasive fungal infection in organ transplantation) has been reported to be associated with a 73% increased risk of developing SCC. The newer antifungal agents posaconazole and isavuconazole have not been shown to increase skin cancer risk to date. Whereas BCC is the most common type of skin cancer in the general population, SCC has been reported to be 2 to 5 times more common than BCC in recipients of solid organ transplantation. In addition, immunosuppression in combination with enhanced sunlight exposure may induce malignant changes in papilloma-induced warts.

Immunosuppressive Therapy in Posttransplantation Malignancy

In principle, immunosuppression dose reduction improves immune surveillance against malignant cells. However, no systematic studies have been performed to determine whether immunosuppression reduction or withdrawal benefits the natural history of established posttransplantation malignancy. In our opinion, a switch from CNI to sirolimus or CNI minimization in conjunction with sirolimus may be a viable therapeutic option in selected posttransplant malignancies (the antitumoral effect of sirolimus is discussed later). In patients with metastatic cancer, manipulation of immunosuppression is probably futile, and the risk for rejection and graft loss likely outweighs the benefit.

Immunosuppressive agents appear to have different effects on cancer risk after transplantation. The carcinogenic effects of antithymocyte globulin, cyclosporine, tacrolimus, and AZA have been well documented. In contrast to AZA, MFA derivatives have been shown to have an antiproliferative effect and have been suggested to be protective of posttransplantation malignancy. Analysis of more than 17,000 adult patients with preexisting diabetes indicated a significantly higher incidence of malignancy in AZA-treated than in MMF-treated patients (3.7% vs. 2.2%). In a nested case-control study to evaluate the association between immunosuppressive medications and squamous cell skin cancer risk among cardiac (n = 35) and kidney transplant recipients (kidney alone, n = 124; simultaneous kidney-pancreas, n = 11), an inverse association between MFA derivatives and squamous cell skin cancer was observed independent of tacrolimus use. MFA use was associated with a 57% squamous cell skin cancer risk reduction compared with no MFA derivative use. In contrast, AZA use was associated with a greater than twofold increase in squamous cell skin cancer risk compared with no AZA use.[60] In a study of 544 lung transplant recipients with a median survival of 11 years, the sequential use of AZA and MMF, each for at least 1 year, was similarly found to be associated with a lower risk of developing a cutaneous SCC compared with AZA use only (hazard ratio [HR], 0.24; 95% CI, 0.10–0.56).[61] Limited studies suggest that AZA to MMF conversion therapy reduces skin photosensitivity to UVA and attenuates UVA-induced skin DNA damage. Nonetheless, one single-center study consisting of 930 heart transplant recipients demonstrated a lower incidence of skin cancer among patients receiving CsA/AZA combination therapy compared with those receiving CsA/MMF or Tac/MMF combination therapy.[62] Whether MMF is protective of posttransplant malignancies remains unclear. Nonetheless, it is common practice to reduce or discontinue MMF in the presence of malignancies because of the theoretical risk for net protumor effect of overimmunosuppression.

Both sirolimus and everolimus have antiproliferative and antitumoral effects. mTOR inhibitor-containing regimens are associated with decreased nonmelanoma skin cancer risks, and their use is effective in both primary and secondary skin cancer prevention. The earlier the conversion after an initial diagnosis of cutaneous SCC, the greater the efficacy. The protective effect of mTOR inhibitors against skin cancer may be a result of its inhibition of several UV-induced mechanisms involved in skin carcinogenesis. The mTOR inhibitors are also effective in inducing remission of Kaposi sarcoma in organ transplant recipients.[44]

Although sirolimus appears to have a beneficial effect for preventing primary and secondary skin cancer, its use in the management of other malignancies after solid organ transplantation remains to be defined. A systematic review of 20 RCTs and two observational studies demonstrated that sirolimus use was associated with lower overall cancer incidence, driven by a reduction in nonmelanoma skin cancer incidence. The protective effect of sirolimus on nonmelanoma skin cancer (NMSC) risk was most notable in studies comparing sirolimus against cyclosporine. After excluding NMSCs, there was no overall association between sirolimus and incidence of other cancers. Further analysis demonstrated that sirolimus use was associated with lower kidney cancer incidence (IRR = 0.40; 95% CI, 0.20–0.81), and higher prostate incidence (IRR = 1.85; 95% CI, 1.17–2.91). The lower incidence of NMSC among sirolimus users was thought to be due in part to cyclosporine withdrawal. Overall, these findings suggested that sirolimus may reduce kidney cancer risk but is not protective for other cancers (including non-Hodgkin lymphoma, Kaposi sarcoma, and lung cancers) and may increase prostate cancer risk.63 Notably, controlled trials demonstrated that although sirolimus was associated with a reduction in the risk of malignancy and nonmelanoma skin cancer in kidney transplant recipients, its use was associated with increased mortality risk compared with controls. This led some investigators to argue against mTOR inhibitor use in all patients with posttransplant malignancies.48

We start patients with newly diagnosed skin cancer, renal cell carcinoma, or Kaposi sarcoma on an mTOR inhibitor in conjunction with discontinuation of antimetabolites and reduction of CNI therapy tailored to each individual patient. In those with a history of these malignancies prior to transplant, mTOR inhibitor therapy is generally not introduced until after the first 3 posttransplant months. There are insufficient data to recommend or refute its use in PTLD. Available data do not support the routine use of mTOR inhibitors in the management of other cancer types. Of interest, however, experimental mouse models demonstrated that everolimus significantly inhibits breast cancer cell growth, migration, and invasion.64 The use of mTOR inhibitor in human breast cancer in the settings of transplantation warrants further studies.

SELF-ASSESSMENT QUESTIONS

1. Which one of the following statements regarding immunization before and after transplantation is correct?
A. Seasonal influenza vaccine is contraindicated in the early posttransplant period because it is associated with allograft dysfunction and acute rejection.
B. COVID-19 vaccine is contraindicated in kidney transplant recipients with prior COVID-19 infection.
C. Live virus vaccination should be administered at least 2 weeks before transplantation to minimize the possibility of live vaccine-derived infection in the posttransplantation period.
D. Immunization of pets with live vaccines (such as canine Bordetella bronchiseptica intranasal vaccine) poses little to no risk of transmission.
2. Clinical manifestations and management of CMV infections include all of the following except:
A. The absence of CMV DNAemia rules out invasive CMV disease.
B. Primary CMV infection is usually more severe than reactivated infection or superinfection.
C. Plasma CMV DNA should be monitored weekly during treatment.
D. The Third International Consensus guidelines on the management of CMV advocate foscarnet as the second-line agent for the treatment of ganciclovir-resistant CMV infection.
3. Which of the following statements regarding posttransplantation lymphoproliferative disorder (PTLD) is correct?
A. Antiviral therapy with acyclovir or ganciclovir should be considered in Epstein-Barr virus–positive PTLD refractory to immunosuppression reduction alone.
B. Substitution of calcineurin inhibitor (cyclosporine or tacrolimus) for an mTOR inhibitor (sirolimus or everolimus) is considered standard of care.
C. Rituximab is considered as first-line treatment for CD20positive PTLD that fails to respond to manipulation of immunosuppression alone.
D. PTLD is the most common type of posttransplantation malignancy in adult

kidney transplant recipients.
E. A and C.

REFERENCES

1. Fishman JA. Infections in immunocompromised hosts in organ transplant recipients: Essentials. Liver Transpl. 2011;17:S534–S537.
2. Danziger-Isakov L, Kumar D, AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13563.
3. Buchan CA, Kotton CN, AST Infectious Diseases Community of Practice. Travel medicine, transplant tourism, and the solid organ transplant recipient-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13529.
4. Florescu DF, Kalil AC, Qiu F, et al. What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant. 2013;13(10):2601–2610.
5. Shingde R, Habachou LI, Calisa V, et al. Unexpected donor-derived infectious transmissions by kidney transplantation: a systematic review. Transpl Infect Dis. 2018;20(2):e12851.
6. Kaul DR, Valesano AL, Petrie JG, et al. Donor to recipient transmission of SARS-Co-V2 by lung transplantation despite negative donor upper respiratory. Am J Transplant. 2021;21:2885–2889.
7. Corson M, Ashley Moch A, Saab S. Hepatitis C virus treatment in patients with chronic kidney disease and in kidney transplant recipients. Gastroenterol Hepatol. 2018;14(5):280–285.
8. Awan AA, Jadoul M, Martin P, et al. Hepatitis C in chronic kidney disease: an overview of the KDIGO guideline. Clin Gastroenterol Hepatol. 2020;18(10):2158–2167.
9. Fishman JA, Gans H, AST Infectious Diseases Community of Practice. Pneumocystis jiroveci in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13587.
10. Stern M, Hirsch H, Cusini A, Members of Swiss Transplant Cohort Study. Cytomegalovirus serology and replication remain associated with solid organ graft rejection and graft loss in the era of prophylactic treatment. Transplantation. 2014;98(9):1013–1018.
11. Karadkhele G, Hogan J, Magua W, et al. CMV high-risk status and posttransplant outcomes in kidney transplant recipients treated with belatacept. Am J Transplant. 2021;21(1):208–221.
12. Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV infections in renal transplant recipients receiving an mTOR inhibitor-based regimen versus a CNI-based regimen: a systematic review and meta-analysis of randomized, controlled trials. Clin J Am Soc Nephrol. 2017;12(8):1321–1336.
13. Kotton CN, Kumar D, Caliendo AM, et al. On behalf of the transplantation society international CMV consensus group. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2018;102(6):900–931.
14. Gardiner BJ, Chow JK, Lori Lyn Price LL, et al. Role of secondary prophylaxis with valganciclovir in the prevention of recurrent cytomegalovirus disease in solid organ transplant recipients. Clin Infect Dis. 2017;65(12):2000–2007.
15. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377(25):2433–2444.
16. Phoompoung P, Ferreira VH, et al. Letermovir as salvage therapy for CMV infection in transplant recipients. Transplantation. 2020;104(2):404–409.
17. Avery RK, Alain S, Alexander BD, et al. SOLSTICE Trial Investigators. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. Clin Infect Dis. 2022;75(4):690–701.
18. Pham PT, Schaenman J, Pham PC. BK virus infection following kidney transplantation: an overview of risk factors, screening strategies, and therapeutic interventions. Curr Opin Organ Transplant. 2014;19(4):401–412.
19. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of

Practice. BK polyomavirus in solid organ transplantation-guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13528.

20. Hirsch HH, Yakhontova K, Lu M, Manzetti J. BK polyomavirus replication in renal tubular epithelial cells is inhibited by sirolimus, but activated by tacrolimus through a pathway involving FKBP-12. Am J Transplant. 2016;16(3):821–832.
21. Wojciechowski D, Chandran S, Webber. A mycophenolate mofetil withdrawal with conversion to everolimus to treat BK virus infection in kidney transplant recipients. Transplant Proc. 2017;49(8):1773–1778.
22. Johnston O, Jaswal D, Gill JS, et al. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation. 2010;89:1057–1070.
23. Patel SJ, Knight RJ, Kuten SA, et al. Ciprofloxacin for BK viremia prophylaxis in kidney transplant recipients: results of a prospective, double-blind, randomized, placebo-controlled trial. Am J Transplant. 2019;19(6):1831–1837.
24. Pascual J, Berger SP, Witzke O, et al. Everolimus with Reduced calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol. 2018;29(7):1979–1991.
25. Schaenman J, Byford H, Grogan T, et al. Impact of solid organ transplant status on outcomes of hospitalized patients with COVID-19 infection. Transpl Infect Dis. 2022;24(4):e13853.
26. Galmiche S, Luong Nguyen LB, Tartour E, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. Clin Microbiol Infect. 2022;28(2):163–177.
27. Aslam S, Adler E, Mekeel K, Little SJ. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. Transpl Infect Dis. 2021;23(5):e13705.
28. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care. 2020;8:36.
29. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330–1341.
30. Chen X, Zhao B, Yueming Qu Y, et al. Detectable serum severe acute respiratory syndrome Coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated Interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(8):1937–1942.
31. Marconi VC, Ramanan AV, de Bono S, et al. COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9(12):1407–1418.
32. The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. New Engl J Med. 2021;384(16):1491–1502.
33. Villamarín M, Márquez-Algaba E, Esperalba J, et al. Preliminary clinical experience of molnupiravir to prevent progression of COVID-19 in kidney transplant recipients. Transplantation. 2022;106(11):2200–2204.
34. Libster R, Marc GP, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med. 2021. NEJMoa2033700.
35. Angarone M, Snydman DR, AST ID Community of Practice. Diagnosis and management of diarrhea in solid-organ transplant recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13550.
36. A I Al-Absi AI, Cooke CR, Wall BM, et al. Patterns of injury in mycophenolate mofetil-related colitis. Transplant Proc. 2010;42(9): 3591–3593.

37. Schorn R, Höhne M, Meerbach A, et al. Chronic norovirus infection after kidney transplantation: molecular evidence for immune-driven viral evolution. Clin Infect Dis. 2010;51(3):307–314.
38. Ghusson N, Vasquez G. Successfully treated norovirus- and sapovirusassociated diarrhea in three renal transplant patients. Case Rep Infect Dis.
2018;2018:6846873.
39. Scotti A, Santangelo M, Federico S, et al. Complicated diverticulitis in kidney transplanted patients: analysis of 717 cases. Transplant Proc. 2014;46(7):2247–2250.

40. Doycheva I, Amer S, Watt KD. De novo malignancies after transplantation: risk and surveillance strategies. Med Clin North Am. 2016;100(3):551–567.
41. McCaughan JA, Courtney AE. The clinical course of kidney transplant recipients after 20 years of graft function. Am J Transplant. 2015;15(3):734–740.
42. Grulich AE, van Leeuwen MT, Falster MO. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370:59–67.
43. Laprise C, Cahoon EK, Charles F, Lynch CF, et al. Risk of lip cancer after solid organ transplantation in the United States. Am J Transplant. 2019;19(1):227–237.
44. Engels EA, Pfeiffer RM, Fraumeni Jr JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–1901.
45. Miller JM, Abdalla B, Pham PT. Posttransplantation malignancies. In: Pham PT, Pham PC, eds. Quick Guide to Kidney Transplantation: From Initial Evaluation to Long-Term Post-Transplant Care. Lippincott Williams & Wilkins; 2019:206–216.
46. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–2390.
47. Caillard S, Lamy FX, Quelen C, et al. French Transplant Centers. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant. 2012;12(3):682–693.
48. Sprangers B, Nair V, Launay-Vacher V, et al. Risk factors associated with post-kidney transplant malignancies: an article from the Cancer-Kidney International Network. Clin Kidney J. 2018;11(3):315–329.
49. Nee R, Hurst FP, Dhamidharka VR. Racial variation in the development of posttransplant lymphoproliferative disorders after renal transplantation. Transplantation. 2011;92:190–195.
50. Sampaio MS, Cho YW, Shah T, et al. Association of immunosuppressive maintenance regimens with posttransplant lymphoproliferative disorder in kidney transplant recipients. Transplantation. 2012;93:73–81.
51. Ashrafi F, Shahidi S, Zeinab E, et al. Outcome of rapamycin therapy for post-transplant-lymphoproliferative disorder after kidney transplantation: case series. Int J Hematol Oncol Stem Cell Res. 2015;9(1):26–32.
52. Asleh R, Alfredo L, Clavell AL, Pereira NL. Incidence of malignancies in patients treated with sirolimus following heart transplantation. J Am Coll Cardiol. 2019;73(21):2676–2688.

53. Masson P, Henderson L, Chapman JR, et al. Belatacept for kidney transplant recipients. Cochrane Database Syst Rev. 2014;11:CD010699.
54. Hussain SK, Makgoeng SB, Everly MJ, et al. HLA and risk of diffuse large B cell lymphoma after solid organ transplantation. Transplantation. 2016;100(11):2453–2460.
55. Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, epstein-barr virus infection, and disease in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13652.
56. AlDabbagh MA, Gitman MR, Kumar D, et al. The role of antiviral prophylaxis for the prevention of Epstein-Barr virus-associated posttransplant lymphoproliferative disease in solid organ transplant recipients: a systematic review. Am J Transplant. 2017;17(3):770–781.
57. Colombini E, Isabella Guzzo I, Federica Morolli F, et al. Viral load of EBV DNAemia is a predictor of EBV-related post-transplant lymphoproliferative disorders in pediatric renal transplant recipients. Pediatr Nephrol. 2017;32(8):1433–1442.

58. Walti LN, Mugglin C, Sidler D, et al. Association of antiviral prophylaxis and rituximab use with post-transplant lymphoproliferative disorders (PTLD): a nationwide cohort study. Am J Transplant. 2021;21(7):2532–2542.
59. Howard MD, Su JC, Chong AH. Skin cancer following solid organ transplantation: a review of risk factors and models of care. Am J Clin Dermatol. 2018;19(4):585–597.
60. Coghill AE, Johnson LG, Berg D, et al. Immunosuppressive medications and squamous cell skin carcinoma: nested case-control study within the Skin Cancer after Organ Transplant (SCOT) Cohort. Am J Transplant. 2016;16(2):565–573.
61. Vos M, Plasmeijer EI, Bemmel BC, et al. Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. J Heart Lung Transplant. 2018;37(7):853–859.
62. Piponniau L, Kittleson M, Patel J, et al. Mycophenolate not azathioprine is associated with increased risk for skin cancer after heart transplant. J Heart Lung Transpl. 2013;32(4):S199.
63. Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med. 2015;4(9):1448–1459.
64. Du L, Li X, Zhen L, et al. Everolimus inhibits breast cancer cell growth through PI3K/AKT/mTOR signaling pathway. Mol Med Rep. 2018;17(5):7163–7169.

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Cardiovascular Disease and Metabolic Abnormalities in the Kidney Transplant Recipient

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CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the most frequent cause of death with a functioning kidney allograft. The US Renal Data System (USRDS) 2014 annual data report revealed that mortality from CVD among kidney transplant recipients (kidney alone or combined organ transplant) is nearly twice that observed for infection or malignancy. Cardiovascular (CV) risk factors in kidney transplant recipients encompass both conventional and unconventional risk factors. Although transplantation ameliorates some CV risks by restoring kidney function, it introduces new CV risks, including impaired glucose tolerance or diabetes mellitus (DM), hypertension, and dyslipidemia, which are derived in part from immunosuppressive medications. Box 111.1 summarizes suggested CV risk factors in transplant recipients. Selected risk factors are also discussed.

CONVENTIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Postttransplantation Hypertension

Hypertension is present in more than 50% of kidney transplant recipients, and the true proportion may be much higher. In one single-center study, ambulatory blood pressure (BP) measurements demonstrated that only 5% of kidney transplant recipients were normotensive (defined as BP < 130/80 mm Hg).1 Another study suggests that clinic BP measurements (vs. ambulatory BP monitoring) may underestimate the prevalence of hypertension in kidney transplant recipients; of 76 patients studied, 22.4% had masked hypertension (defined as BP > 130/80 mm Hg).2

Hypertension is a risk factor for both CVD and kidney graft failure. A retrospective cohort study revealed a graded risk for graft failure and death with increasing levels of systolic BP (each 10 mm Hg of systolic BP increase was associated with an increased relative risk for graft failure [risk ratio (RR), 1.12; P < .000], death-censored graft failure [RR, 1.17; P < .0001], and death [RR, 1.18; P < .0001]).3 Post hoc analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study showed that each 20 mm Hg increase in baseline systolic BP was associated with a 32% increase in CVD risk and a 13% increase in mortality risk. However, for every 10 mm Hg decrease in diastolic BP below 70 mm Hg, a 31% increase in CVD and mortality risk was observed. For diastolic BP levels greater than 70 mm Hg, no significant association between diastolic BP and outcomes was observed.4

Risk factors for posttransplantation hypertension include preexisting hypertension, cyclosporine (and, to a lesser degree, tacrolimus), corticosteroids, various donor-related factors (e.g., donor age, donor

hypertension, donor family history of hypertension), delayed graft function, chronic allograft injury, high body mass index or excess weight gain, acute rejection episodes, recurrent or de novo glomerulonephritis, and transplant renal artery stenosis. Sodium intake after transplantation and excess renin output from the native kidneys also may contribute in some patients. In kidney transplant recipients with severe hypertension refractory to medical therapy, bilateral native nephrectomy may ameliorate BP control. In a retrospective study of kidney transplant recipients with autosomal dominant polycystic kidney disease, ipsilateral native nephrectomy at the time of allograft transplant was associated with a significant decrease in the use of antihypertensive drugs needed for hypertension control compared with kidney transplantation alone at 12-, 24-, and 36-month follow-up. Subsequent contralateral native nephrectomy further improved BP control.5

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on BP management advocate liberalizing the BP target to less than 160/90 mm Hg in the early posttransplantation period to maintain organ perfusion and avoid hypotension to reduce the risk of graft thrombosis. Beyond the first posttransplantation month, more stringent BP control to less than 130/80 is recommended to prevent end-organ damage.6 The Kidney Disease: Improving Global Outcome (KDIGO) guidelines suggest a BP goal of less than 130/80 mm Hg for kidney transplant recipients irrespective of the level of albuminuria. However, such recommendations are based solely on epidemiologic data because no randomized trials demonstrate the optimal BP target in kidney transplant recipients. A BP goal of less than 125/75 mm Hg for patients with proteinuria is of uncertain benefit.

Management of posttransplantation hypertension should include identification and treatment of the underlying cause, lifestyle modifications (see Chapter 36), and treatment of associated CV risk factors.

We recommend perioperative β-blockers in transplant candidates with a history of coronary artery disease because they reduce coronary artery disease (CAD) events. Diuretics are frequently used in the early posttransplantation period in patients who are volume expanded. Most transplant centers use calcium channel blockers for initial therapy because of their added benefit of antagonizing calcineurin inhibitor (CNI)-induced afferent arteriolar vasoconstriction, and their demonstrated efficacy in the general population irrespective of age, sex, and salt intake.7 The nondihydropyridine calcium channel blockers diltiazem and verapamil are cytochrome CYP3A4 inhibitors, and their use also permits CNI or mammalian target of rapamycin (mTOR) inhibitor dose reductions. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can cause acute changes in renal function and hyperkalemia and hence are usually not started until allograft function is stable. Transplant renal artery

CHAPTER 111 Cardiovascular Disease and Metabolic Abnormalities in the Kidney Transplant Recipient

Cardiovascular Risk Factors in Kidney Transplant Recipients

BOX 111.1

Conventional
Modifiable
Hypertension
Dyslipidemia
Obesity or metabolic syndrome
Smoking
Nonmodifiable
Age
Family history
Male sex
History of pretransplant and posttransplant cardiovascular disease
Race/ethnicity (White ethnicity)
Unconventional
Modifiable or Potentially Modifiable
Proteinuria
Posttransplantation diabetes mellitus
Left ventricular hypertrophy
Inflammatory markers (e.g., inflammatory cytokines, C-reactive protein)
Anemia
Hyperuricemia
Cytomegalovirus infection
Delayed graft function
Hyperhomocysteinemia
Time on dialysis
Chronic kidney disease (posttransplant)
Low albumin
Obstructive sleep apnea
Prothrombotic state
Low physical activity
Nonmodifiable

Recipient Factors
Prior acute rejection episodes
Preexisting coronary calcification
Cardiac troponin T
Donor Factors (Donor Quality)
Donor age
Donor hypertension
Donor recipient size mismatch
Donor APOL1 gene polymorphism (may be associated with early graft dysfunction)

stenosis should be considered when serum creatinine rises to over 30% above baseline (see Chapter 43). Limited studies in kidney transplant recipients suggest that renin-angiotensin-aldosterone system (RAAS) blockade reduces CV events and ameliorates CNI-induced interstitial fibrosis and tubular atrophy. However, the beneficial effect of ACE inhibitors or ARBs on patient or graft survival has not been consistently demonstrated.8 A meta-analysis of eight randomized trials demonstrated that RAAS inhibitors did not significantly alter all-cause mortality (RR, 0.96; 95% confidence interval [CI], 0.62–1.51), graft failure (RR, 0.76; 95% CI, 0.49–1.18), or doubling of serum creatinine (RR, 0.84; 95% CI, 0.51–1.39) compared with placebo (with similar BP control) or standard of care.9 Because of the lack of conclusive evidence that one class of antihypertensive agent is superior to another in transplant recipients, treatment should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions with immunosuppressive agents. Potential advantages and disadvantages of different classes of antihypertensive agents in kidney transplant recipients are shown in Table 111.1

Posttransplantation Dyslipidemia

Dyslipidemia is common after transplantation, in part because of the hyperlipemic effect of corticosteroids, cyclosporine, tacrolimus, and the mTOR inhibitors sirolimus and everolimus. Sirolimus and everolimus are associated with the worst lipid profiles, followed by cyclosporine, and to a lesser extent tacrolimus. One single-center study demonstrated that the mean values of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TGs) and the incidence of CAD were higher among patients receiving mTOR inhibitors compared with those receiving CNI-based immunosuppression (controls). However, the risk for CV events is not significantly higher among patients receiving mTOR inhibitors compared with controls.10 11 A substudy of the MECANO trial also found no difference in CV outcomes among kidney transplant recipients randomized to early cyclosporine (CSA) to everolimus conversion therapy (n = 96) compared with those remaining on CSA-based immunosuppression (n = 89) over a 7-year follow-up period.12 Studies in heart transplant recipients suggest that CNI to sirolimus conversion therapy may attenuate cardiac allograft vasculopathy (CAV) progression and CAV-related events compared with CNI continuation independent of LDL levels.13 The antiproliferative and cardioprotective effects of mTOR inhibitors and the reduction in CNI-related risk factors may offset the adverse effects of mTOR inhibitor–associated hyperlipidemia.

Other etiologic factors for posttransplant dyslipidemia include age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, genetic predisposition, and the use of diuretics and β-blockers (nonselective > selective β1-blockers).

Management of Hyperlipidemia

Lifestyle changes (diet and exercise) and statins remain the cornerstone of therapy. In addition to their lipid-lowering effect, statins may protect against CVD via their antiproliferative and anti-inflammatory properties and ability to reduce circulating endothelin-1, C-reactive protein levels, systolic and diastolic BP, and pulse pressure. The benefits of statins in the general population have been demonstrated in several large randomized controlled trials (RCTs). The ALERT trial, the only prospective RCT in transplant recipients comparing statins (fluvastatin) with placebo, found a beneficial effect of early initiation of fluvastatin on posttransplant CV outcome. Patients who received statin therapy within the first 4 years after transplantation had a risk reduction of 64% compared with 19% for those who received therapy after 10 years.14

Box 111.2 summarizes different guidelines for the management of posttransplantation dyslipidemia.15 16 The different classes of lipid lowering-agents are discussed in the following sections.

Statin Therapy

Kidney transplantation is considered a risk factor for CAD similar to other conventional cardiac risk factors. Despite the lack of evidencebased recommendations, most transplant centers treat dyslipidemias aggressively with statin therapy along with lifestyle modification. The concomitant use of statins and cyclosporine often results in a severalfold increase in statin blood level because CSA inhibits CYP450 3A4 enzyme, of which statins are major substrates. In addition, CSA inhibits

OATP1B1/SLCO1B1-mediated hepatic uptake of statins, resulting in significant medication interaction. Therefore, in CSA-treated
patients, all statins should be introduced at low doses and uptitrated

Potential Advantages and Disadvantages of Different Classes of Antihypertensive Agents

TABLE 111.1
Classes of Drugs

Advantages/Beneficial Effects

Disadvantages/Adverse Effects

ACE inhibitors, ARBs

•
•
•
•
•
•

Beneficial in patients with proteinuria,[a] DM, LVH
Potential renoprotective and cardioprotective effects
Beneficial in posttransplantation erythrocytosis
Losartan may lower serum uric acid levels[b]
Improve outcome in patients with HFrEF
May improve blood pressure control in difficult-to-treat hypertension
• Beneficial in patients with benign prostatic hypertrophy or neurogenic bladder
• Beneficial in patients with CAD or ischemic heart disease

• Potential worsening anemia
• GFR decline, hyperkalemia

Mineralocorticoid receptor antagonists
(e.g., spironolactone, eplerenone)
α-Blockers (e.g., prazosin)
β-Blockers (e.g., carvedilol, metoprolol, bisoprolol)
Calcium channel blockers: nondihydroperidine (diltiazem, verapamil) and dihydroperidine (amlodipine, nifedipine)
Central α-agonists (e.g., clonidine, methyldopa)
Diuretics (loop and thiazide)

Direct vasodilators (e.g., hydralazine, minoxidil)

•
•
•
•
•
•

Ameliorate CNI-induced vasoconstriction
Diltiazem may permit CNI dose reduction by up to 40%
Verapamil by 30%–50%
Beneficial in patients with diabetic autonomic dysfunction
Beneficial in patients who are volume expanded
Thiazide may improve hyperkalemia commonly seen in CNItreated patients. Its use

may also increase BMD decrease fracture risk (beneficial in osteoporosis).

🐧•🐧 Minoxidil: may be beneficial in difficult-to-treat hypertension

🐧•🐧 Hydralazine/nitrate combination therapy is recommended as add-on therapy in African Americans with refractory HFrEF and NYHA class III-IV heart failure despite standard of care therapy

🐧•🐧 Severe hyperkalemia when used in combination with ACE inhibitor or ARB, particularly in patients with poor kidney function

🐧•🐧 Orthostatic hypotension

🐧•🐧 Blunting of hyperglycemic unawareness, erectile dysfunction, hyperlipidemia, hyperkalemia (nonselective > selective β1- blockers), bronchospasm

[a]The

2009 KDIGO clinical practice guidelines recommend an ACE inhibitor or ARB as first-line therapy for patients with hypertension and proteinuria of 1 g/day or greater.

[b]May be beneficial in patients with gout.

ACE, Angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CAD, Coronary artery disease; CNI, calcineurin inhibitor; DM, diabetes mellitus; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

at the discretion of the clinicians. Maximal doses should be avoided because CSA-induced increase in statin bioavailability can result in an increased risk for myopathy and rhabdomyolysis. In contrast, tacrolimus does not inhibit CYP3A4 to a significant extent and has no effect on OATP1B1/SLCO1B1 and thus drug-drug interaction with statins is not observed. However, rhabdomyolysis associated with tacrolimus and statin use may be seen in patients on concomitant diltiazem therapy because the latter is a moderate CYPA3A4 inhibitor.

Non-Statin Drug Therapy

Ezetimibe. Ezetimibe and statin combination therapy may improve cholesterol control because of their complementary mechanisms of action. Ezetimibe blocks intestinal absorption of dietary cholesterol, whereas statin inhibits hepatic cholesterol synthesis. Results of the SHARP trial in which CKD patients were randomized to receive simvastatin 20 mg plus ezetimibe 10 mg (n = 4650) or placebo (n = 4620) demonstrated that simvastatin and ezetimibe combination therapy conferred a 17% risk reduction compared with placebo at a median follow-up of 4.9 years.17 Limited studies suggest that statin and ezetimibe combination therapy is safe and effective in the treatment of dyslipidemia in kidney transplant patients who are refractory to statin therapy. In a study of 67 patients with posttransplantation hyperlipidemia resistant to statins, treatment with ezetimibe alone or with ezetimibe and statin significantly reduced total cholesterol and LDL cholesterol by 25% and 34%, respectively, during the first month of treatment.18 The 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines advocate adding

ezetimibe to statin therapy for solid organ transplant recipients who are refractory to the highest tolerated statin dose or as a second-line agent in those who are intolerant to statin. The AHA/ACC guidelines recommend adding ezetimibe to statin therapy in very high CVD risk patients if LDL-C level remains at least 70 mg/dL despite maximally tolerated statin therapy.

Protein convertase subtilisin/kexin type 9 inhibitors (PCSK9).

PCSK9 is a proprotein convertase involved in the degradation of

LDL receptors in the liver. PCSK9 inhibitors are human monoclonal antibodies that inhibit the binding of PCSK9 to the LDL receptors. Two large randomized, placebo-controlled trials involving high CV risk patients demonstrated that the PCSK9 inhibitors evolocumab (FOURIER trial, n = 27,564) and alirocumab (ODYSSEY trial, n = 18,924) reduced LDL-C levels significantly more than statins and significantly decreased CV morbidity and mortality (CV death, nonfatal myocardial infarction [MI], or stroke) independent of baseline LDL-C levels. Post hoc analysis of the ODYSSEY and FOURIER trials demonstrated that the efficacy and safety of alirocumab and evolocumab were comparable among subjects with and those without estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2 19 The role of PCSK9 inhibitors in the treatment of dyslipidemia or CV risk reduction in chronic kidney disease (CKD) patients and in kidney transplant patients remains to be studied.

Management of Hypertriglyceridemia

Initial management should include lifestyle changes, increased physical activity, weight reduction, dietary counseling (carbohydrate restriction),

BOX 111.2

Pharmacologic Therapy for Dyslipidemia in Kidney Transplant Recipients

KDIGO Guidelines

- Statins in all adult transplant recipients.
- In the absence of traditional risk factors, transplant recipients <30 years old could choose not to receive statins if priority is placed on minimizing polypharmacy and drug toxicity over the small absolute risk reduction.[a]
- Elevated TGs:
  - Therapeutic lifestyle changes: low-fat diet (<15% total calories), reduction of mono- and disaccharide intake, reduction in total amount of dietary carbohydrates, use of fish oil to replace some long-chain TGs
  - Fibrate use to prevent pancreatitis or reduce CV risk not recommended

ACC/AHA Guidelines

- Statin therapy should be based on clinical judgment (weigh risk and benefits) and patient preference
- Follow-up lipid profile at 4 and 12 weeks after treatment assess medical adherence, then every 3–12 months as clinically indicated
- Benefits outweigh risk in patients with:
  - Clinical ASCVD
  - LDL-C > 190 mg/dL
  - DM, age 40–75 years, LDL-C 70–189 mg/dL, no clinical ASCVD
  - Clinical ASCVD or diabetes, LDL-C 70–189 mg/dL, and estimated 10year ASCVD risk > 7.5%
- Elevated TGs not addressed; however, in nontransplant setting, ACC/AHA guidelines suggest adding n-3 polyunsaturated fatty acid (icosapent ethyl) to statin therapy in high-risk patients with TG ≥ 150 mg/dL[b]

2019 ESC/EAS Guidelines

- Treatment of dyslipidemias in transplant recipients similar to that for patients at high or very high CV risk
- Statins should be considered first-line agents
- Consider ezetimibe or ezetimibe-statin dual therapy in patients who are intolerant of statins or those with significant dyslipidemia despite maximally tolerated statin treatment, respectively[c]
- Elevated TGs[d]: consider adding omega-3 fatty acid to statin therapy in highrisk patients with TG 135–499 mg/dL (currently insufficient evidence to recommend routine use of fish oil in the transplant population)

[a] Rationale for recommendations: risk of coronary events is age dependent, and the ALERT trial did not enroll subjects <30 years.

[b] Approved by the US Food and Drug Administration for use as an adjunctive therapy to maximally tolerated statins to reduce the risk of CV events in adults with TG > 150 mg/dL. Patients must also have established CV disease or DM, and two more risk factors for CV disease.

[c] Cyclosporine can induce a 2- to 12-fold increase in the ezetimibe level. Concomitant ezetimibe and cyclosporine therapy can also raise cyclosporine concentration by 15%.

[d] Suggested lifestyle changes: reduce excessive body weight; increase physical activity; reduce alcohol, carbohydrate, and mono- and disaccharide intake; replace saturated fats with mono- or polyunsaturated fats.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; KDIGO, Kidney Disease Global Outcomes; LDL, low-density lipoprotein; TGs, triglycerides.

smoking cessation, and correction of secondary causes. The latter may include untreated DM, excess alcohol intake, or drug-induced causes. Severe hypertriglyceridemia (TG level > 500 mg/dL or 5.65 mmol/L) may occur with the use of sirolimus and everolimus. Management includes dose reduction, pharmacologic therapy, and, in refractory cases, switching of mTOR inhibitors to mycophenolic acid derivatives or tacrolimus.

Drug Therapy for Hypertriglyceridemia

Fibrates. Fibrates have the most pronounced effect on lowering plasma TG levels of available lipid-lowering agents. Of available options (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil), the first three can increase serum creatinine in cyclosporinetreated patients. Although all fibrates have been associated with creatinine kinase elevations (with or without overt rhabdomyolysis and myopathy) when used in combination with statins, gemfibrozil may have a greater risk for myopathy compared with fenofibrate or bezafibrate. In kidney transplant recipients, a daily dose exceeding 900 mg for gemfibrozil, 400 mg for bezafibrate, and 200 mg for fenofibrate is not recommended.16 Fenofibrate is contraindicated in patients with eGFR less than 30 mL/min/1.73 m2. Data on the safety of gemfibrozil in patients with advanced CKD are lacking.

Ezetimibe. Limited studies demonstrated that ezetimibe has TGlowering effects and is safe and effective in the transplant settings.

Bile acid sequestrants. Bile sequestrants are currently seldomly used given the available wide selection of highly effective lipid-lowering agents with more favorable side effect profiles.16 Notably, studies in the general population suggest that bile acid sequestrants may increase TG levels. Their use is contraindicated in individuals with TGs greater than 400 to 500 mg/dL.

Niacin. Two large RCTs showed that nicotinic acid use is of no benefit but is associated with serious adverse effects. Currently, no medication containing nicotinic acid is approved for use in Europe.20

Fish oil. The ESC/EAS guidelines recommend adding omega-3 polyunsaturated fatty acids (2 g icosapent ethyl twice daily) to statin therapy in high-risk patients with TG levels between 135 to 499 mg/dL. There is insufficient evidence to recommend routine use of fish oil in the kidney transplant population.16

Summary

Statins should be the first-line therapy for the treatment of nonhighdensity lipoprotein (non-HDL) cholesterol because of their wellestablished safety and efficacy in preventing CVD in the general population. Ezetimibe should be used as a second-line agent in patients intolerant of statins or in combination therapy with statin when the LDL-C level remains at least 70 mg/dL despite maximally tolerated statin therapy. Adherence to lifestyle changes and to statin therapy should be reemphasized before adding a nonstatin lipid-lowering agent to statin therapy. In patients with severe hypertriglyceridemia, adding omega-3 polyunsaturated fatty acids or fibrate to statin therapy may be considered. However, caution should be exercised because of potential fibrate and statin drug-drug interactions. The choice of one lipid-lowering agent over the other should be based on adverse effects and potential drug-drug interactions. Simvastatin and gemfibrozil combination therapy is associated with an increased risk for rhabdomyolysis and should be avoided. Whether PCSK9 inhibitors are safe and effective in the transplant setting remains to be studied.

POSTTRANSPLANTATION DIABETES MELLITUS (NEW-ONSET DIABETES AFTER TRANSPLANTATION)

Posttransplantation DM (PTDM) occurs in 4% to 25% of kidney transplant recipients. Variations in incidence may arise from differences in definition, duration of follow-up, and the presence of both modifiable and nonmodifiable risk factors. Over the years, PTDM has undergone changes in nomenclatures including steroid diabetes, PTDM, new-onset DM, transplant-associated hyperglycemia, and new-onset diabetes after transplantation (NODAT).21 In 2014 the International Expert Panel recommended changing the terminology

Risk Factors for Posttransplantation Diabetes Mellitus[1]

Nonmodifiable

- Black, Hispanic
- Age > 40–45 years
- 1st degree family hx of DM
- Gestational diabetes
- HLA mismatches
- HLA A30, B27, B42
- Acute rejection history
- APKD[2]
- Genetic polymorphism[3]
- Deceased donor
- Male recipient
- Male donor

Potentially modifiable

Modifiable

- HCV[4]
- CMV[5]
- Pretransplant IGT/IFG
- Proteinuria[2,6]
- HypoMg[2]

- Individualization of immunosuppressive therapy:
- Corticosteroids
- Tacrolimus
- Cyclosporine
- Sirolimus, everolimus
- Obesity (BMI ≥ 30 kg/m^2) or other component of metabolic syndrome
- Vitamin D deficiency

Fig. 111.1 Risk Factors for Posttransplantation Diabetes Mellitus. [1]Restoration of insulin metabolism by a functioning graft may unmask pretransplant impaired glucose tolerance or DM. [2]The associations between APKD, proteinuria, and hypomagnesia and PTDM have not been consistently observed. [3]Three genetic variants significantly associated with PTDM in random effects meta-analysis include CDKAL1 rs10946398, KCNQ1 rs2237892, and TCF7L2 rs7903146. [4]Antiviral therapy with direct-acting antiviral agents is discussed in Chapter 110. [5]Posttransplant CMV prophylactic and preemptive therapy is discussed in Chapter 110. [6]One study showed that moderately elevated early posttransplantation albuminuria is a risk factor for PTDM in a dose-dependent manner (increasing risk from normoalbuminuria to severely increased albuminuria). APKD, Autosomal dominant polycystic kidney disease; BMI, body mass index; CMV, cytomegalovirus; DM, diabetes mellitus; HCV, hepatitis C; HLA, human leukocyte antigen; Hx, history; HypoMg, hypomagnesemia; IGT/IFG, impaired glucose tolerance/impaired fasting glucose; PTDM, posttransplantation

diabetes mellitus.

NODAT back to PTDM, excluding transient posttransplantation hyperglycemia.22 Using the term NODAT is thought to be misleading because it seemingly excludes patients with pretransplant diabetes. Preexisting diabetes is often undiagnosed because of the effect of CKD on insulin metabolism and clearance and the lack of effective pretransplant screening.

Risk Factors

PTDM may arise from both transplant-related and traditional risk factors. The diabetogenic effect of corticosteroids, CNIs (tacrolimus > cyclosporine), and mTOR inhibitors have been well-described. Azathioprine, mycophenolic acid derivatives, and belatacept have not been shown to increase PTDM risk. Risk factors for PTDM are summarized in Fig. 111.1. They can be loosely categorized into those that are nonmodifiable, potentially modifiable, and modifiable.

Management

Management of PTDM follows the conventional approach and clinical guidelines for diabetes in the general population. Medical management usually involves a multidisciplinary team approach involving patients (and frequently family members), transplant coordinators, transplant physicians, and diabetic educators. A shared decision-making approach by which clinicians and patients exchange information and reach a consensus on treatment decisions can be helpful. The American Diabetes Association and European Association for the Study of Diabetes recommend a hemoglobin A1c (A1c) target of less than 7% in most patients to reduce the incidence of microvascular disease. More stringent control (A1c 6.0%–6.5%) might be considered in a subset of patients with short disease duration, long life expectancy,

and no significant CV disease, if this can be achieved without significant treatment-related adverse effects. For PTDM, the 2009 KDIGO clinical practice guidelines suggest a target A1c level from 7.0% to 7.5% but not less than 6.0%, particularly if hypoglycemic reactions are common.

Therapeutic Interventions

Nonpharmacologic Management

Obesity management is indicated because higher pretransplant BMI correlates with insulin resistance after transplantation. Lifestyle modifications in kidney transplant recipients include moderation of dietary sodium (<2400 mg sodium per day) and saturated fat intake (<7% calories from saturated fats, 2%–3% calories from trans-fatty acids), regular aerobic exercise, and weight reduction. Carbohydrate intake should be limited to 50% to 60% of caloric intake. The AHA guidelines for the general population recommend an intake of more than 25 g of dietary fiber per day and two servings of fish per week. Dietary guidelines for vegetarians are lacking. Flax seeds (or flaxseed oil) and chia seeds are alternative sources of omega-3 fatty acid. Dietitian referral is recommended. Defining realistic goals such as a target weight loss of 5% to 10% of total body weight and a patient-centered approach to education may be helpful.

Modification of Immunosuppression

Tacrolimus (TAC) has more consistently been shown to have a greater diabetogenic effect than CSA. A multicenter, prospective, randomized trial demonstrated that conversion from TAC to CSA resulted in reversal of diabetes, improved metabolic control, and reduced need for glucose lowering therapy. At 12-month follow-up, 34% of patients

(14/41) in the CSA arm were free of diabetes compared with 10% (4/39) in the tacrolimus arm (P = .01). During the follow-up period, 39% of patients in the CSA arm discontinued glucose lowering medication compared with 13% in the tacrolimus arm (P = .01). CSA conversion was associated with a mild increase in total and LDL-cholesterol and a greater reduction in eGFR (using the Modification of Diet in Renal Disease [MDRD] formula) compared with TAC maintenance immunosuppression at 12-month follow-up.23 A meta-analysis of controlled clinical trials to assess the safety and efficacy of early steroid withdrawal or avoidance, steroid avoidance, or steroid withdrawal was associated with a decrease in PTDM incidence among CSA- but not TAC-treated kidney transplant recipients.24 However, among CSA-treated patients, acute rejection episodes were more frequently observed in steroid avoidance compared with conventional steroid-treated groups.
A randomized trial of corticosteroid withdrawal (CSWD) demonstrated that CSWD has a limited impact in reducing PTDM compared with low-dose prednisone (5 mg/day from month 6–5 years). The proportion of PTDM patients requiring treatment was similar between CSWD and chronic corticosteroid (CCS) groups (CSWD 22.5% vs. CCS 21.5%). However, insulin use at 5 years was lower in the CSWD group (3.7% vs. 11.6%; P = .049).25 In the current era of transplantation, most transplant centers advocate rapid steroid taper and lower target CSA and TAC levels, which may improve PTDM risk. However, modification of immunosuppression to alleviate the incidence of PTDM should be tailored to each patient, with the benefits of better glycemic control weighed against the risk for acute rejection. Furthermore, CSA use is associated with worse lipid profile compared with TAC therapy.

Cigarette smoking in kidney transplant recipients is associated with perioperative complications, wound infections, increased risk of CVD, opportunistic infections, malignancies, and decreased patient and graft survival.29 A multifaceted approach including behavioral and pharmacologic strategies appears to be most effective at getting patients to stop smoking.

Pharmacologic Treatment

Obesity

When lifestyle modification fails to achieve glycemic control, medical intervention is necessary. Metformin is not widely used in transplant recipients because of the concern for lactic acidosis in the presence of dynamic kidney allograft function, particularly in the early posttransplant period. However, the potential beneficial effects of metformin, including weight neutral or weight loss, cardioprotection, and lack of significant drug-drug interactions renders metformin an attractive treatment option for selected patients.22 Experimental studies suggest that sulfonylureas are associated with beta cell apoptosis and beta cell exhaustion, raising theoretical concern about their use in PTDM, particularly in the early posttransplantation period. In contrast, the dipeptidyl peptidase-4 (DPP-4) inhibitors preserve pancreatic beta cell function in diabetic animal models. DPP-4 inhibitors are also safe and effective in the treatment of PTDM. Studies in patients with type 2 DM (T2DM) demonstrated that GLP-1 receptor agonists have a beneficial effect on CVD and weight loss. However, delayed gastric emptying associated with their use raises the concern for erratic immunosuppressant drug absorption in the transplant setting. Studies evaluating the safety and efficacy of GLP-1 inhibitors in kidney transplant recipients are lacking. One small single-center retrospective study showed that GLP-1 receptor agonist use allowed insulin dose reduction and ameliorated hypoglycemia risk. Allograft function was stable and no impact on TAC dosing was observed during the 12-month study period (n = 14).26 Further studies are needed. The sodium-glucose cotransporter type 2 (SGLT2) inhibitors are a new class of drugs that appear to reduce CV events and slow renal progression in the nontransplant population with diabetic CKD.27 In a single-center, prospective, randomized, placebo-controlled trial involving 44 kidney transplant recipients with PTDM randomized to receive either empagliflozin (n = 22) or placebo (n = 22) for 24 weeks, both A1C and weight loss were found to be significantly reduced in empagliflozin-treated patients compared with their placebo-treated counterparts (–0.2% vs. 0.1%, P = .025 and –2.5 kg vs. an increase of 1.0 kg, P = .014, respectively).28 No

Single-center and large registry studies in kidney transplant recipients demonstrated that obesity (generally defined as body mass index [BMI] > 30 kg/m2) at transplant is associated with increased risk of wound and surgical site infections, delayed graft function (DGF), acute rejection episodes, and graft loss. Posttransplant obesity also increases the risk of heart failure, atrial fibrillation, CVD, and cardiac death after transplant. Management of posttransplantation obesity can be a challenge because weight gain is common after transplant because of improved appetite related to resolving uremia, use of corticosteroid, liberation of dietary restrictions, and an overall improved sense of well-being. Early initiation of healthy lifestyle changes and counseling by a dietitian are important for successful weight management.

Corticosteroid reduction or withdrawal must be balanced against the risk of acute rejection and graft loss. The use of pharmacologic agents for weight reduction in the posttransplantation period is not recommended because of unknown potential drug-drug interactions. Data are inadequate regarding the safety and efficacy of posttransplantation gastric bypass surgery or adjustable gastric banding in ameliorating comorbid conditions such as hypertension, DM, and dyslipidemia. All studies reported to date were limited by lack of suitable comparison group, short follow-up, and heterogeneity in type of bariatric procedure and approach.30 However, with refinement in surgical techniques and advancement in postoperative care, posttransplantation bariatric surgery for morbid obesity should be considered on a case-by-case basis. Laparoscopic procedures are generally associated with fewer complications compared with open procedures.

significant differences in adverse events, immunosuppressive drug levels, or eGFR were observed between the two treatment groups except for one genital mycotic infection in the SGLT2 inhibitor treated group. Although the risk of genitourinary infectious complications associated with SGLT2 inhibitor use has not been consistently demonstrated, the US Food and Drug Administration warning labels regarding serious UTIs, including urosepsis and pyelonephritis, associated with its use remain in effect (updated March 2022). It is prudent to avoid SGLT2 inhibitor use in kidney transplant recipients with a history of recurrent UTIs, neurogenic bladder, or urologic abnormalities requiring chronic intermittent self-catheterization.

Evidence-based studies recommending one antidiabetic agent over the other in the context of transplantation are lacking. Hence, the choice should be based on the potential advantages and disadvantages of different classes of agents. Failure to achieve glycemic control despite glucose-lowering drug combination therapy requires initiation of basal-prandial insulin therapy. The 2014 international consensus guidelines on the screening, diagnosis, and management of early posttransplant hyperglycemia and PTDM is shown in Fig. 111.2.

Cigarette Smoking

UNCONVENTIONAL CARDIOVASCULAR DISEASE

RISK FACTORS

Proteinuria

Proteinuria occurs in 9% to 40% of kidney transplant recipients with a functioning graft. Proteinuria from native kidneys typically decreases

Detection, Diagnosis, and Management of PTDM

Time posttransplant (days)
Day 0–45

Time posttransplant (days)
Day 46–365

Time posttransplant (days)
> 365 days

Posttransplant hyperglycemia
(do not diagnose as PTDM)

Diagnostic tests
- OGTT[1]
- Fasting random glucose
- A1C[2,3]

Diagnostic tests
- OGTT[1]
- A1C[2]
- Fasting random glucose

PTDM

PTDM

Management

Management

- Day 0–7: Insulin
- Day 8–45: Insulin
- Oral antihyperglycemic agents

- Lifestyle modification
- Oral antihyperglycemic agents[4]
- Insulin

Fig. 111. 2 2014 International Consensus Guidelines on the Detection, Diagnosis, and Management of Posttransplantation Diabetes Mellitus (PTDM). [1]Seldom performed in clinical practice (time-consuming/cost). [2]A1C cannot be accurately interpreted within the first 3 months after transplantation because anemia and impaired graft function can directly interfere with the A1C assay. Recent blood transfusion and dapsone may alter A1C level. [3]A1C alone <365 days may underestimate PTDM and require confirmatory testing. [4]Over the past several years, newer injectable antidiabetic agents have increasingly been used (however, it should also be noted that evidence-based recommendations are lacking). A1C, Hemoglobin A1C; OGTT, oral glucose tolerance test; PTDM, posttransplantation diabetes mellitus.

rapidly after transplantation and resolves within the first month after transplantation. Persistent or worsening proteinuria is usually indicative of allograft pathology. Hence, monitoring the urine protein-to-creatinine ratio at each clinic visit and allograft biopsy should be performed in kidney transplant recipients with persistent or worsening proteinuria and in those whose primary renal disease is focal segmental glomerulosclerosis, to monitor for disease recurrence. As in the nontransplant setting, posttransplantation proteinuria increases the risk for CV events, graft loss, and mortality. In a single-center cohort analysis of 137 heart transplant recipients, the development of proteinuria after CNI to sirolimus conversion therapy was found to be associated with diminished benefit on cardiac allograft vasculopathy progression and higher all-cause mortality risk compared with those without proteinuria (hazard ratio [HR], 3.8; P = .01).31 Whether mTOR inhibitor-induced proteinuria similarly increases mortality in kidney transplant recipients is unknown and warrants further studies. Although controlled trials evaluating the beneficial effect of treating proteinuria in reducing CV risk in kidney transplant recipients are lacking, ACE inhibitors or ARBs should be considered in transplant recipients with proteinuria because of their well-established antiproteinuric and cardioprotective effects.

Hyperhomocysteinemia

Although hyperhomocysteinemia has long been recognized as a risk factor for CAD, systematic review and meta-analysis showed no beneficial effect of homocysteine-lowering therapy on CVD risk reduction in patients with ESKD or in kidney transplant recipients.32 The use of homocysteine-lowering agents for the primary prevention of CVD is not recommended.8

Belatacept Use

Phase III RCTs comparing the safety and efficacy of belatacept-based versus cyclosporine-based immunosuppression in recipients of standard donor kidneys (BENEFIT study) and in those of extended-criteria donor

kidneys (BENEFIT-EXT study) demonstrated that, compared with cyclosporine, belatacept-based regimens resulted in (1) lower BP, cholesterol levels, and incidence of PTDM, (2) significantly reduced death and graft loss, and (3) improved long-term renal function. However, whether improvement in CV risk factor profile translates into reduction in CVD remains to be studied. In one single-center retrospective cohort study involving kidney transplant recipients at high CV risk, belataceptbased immunosuppression (n = 35) was not found to be associated with CV risk reduction compared with CNI-based therapy (control, n = 150). However, the study had several limitations, including retrospective nature, small sample size, different baseline characteristics, and duration of follow-up between the two treatment groups.33

COMMON LABORATORY ABNORMALITIES

Anemia

In the immediate posttransplantation period, aggressive perioperative volume expansion may result in dilutional anemia. Refractory or severe anemia mandates aggressive evaluation to exclude the possibility of surgical postoperative bleeding, particularly in those with a rapid fall in hemoglobin (Hb) and hematocrit (Hct) levels.

Mild anemia is common in the early posttransplantation period when erythropoietin (EPO) therapy is typically discontinued but usually improves within several weeks to months. Suggested etiologic factors for posttransplantation anemia include iron deficiency, impaired graft function, acute rejection episodes, recent infection, and medications (e.g., azathioprine, mycophenolic acid derivatives, sirolimus, everolimus, dapsone, ACE inhibitors, and ARBs).

Assessment of baseline iron stores at the time of transplantation may be invaluable because iron deficiency is common in the dialysis population. Profound iron deficiency should be treated with intravenous (IV) iron as tolerated. The 2012 KDIGO anemia guidelines recommend initiating an erythropoiesis-stimulating agent in CKD patients when Hb values are less than 9 to 10 g/dL, provided iron stores are adequate. A target Hb level of 10 to 11 g/dL is recommended. Large CKD anemia trials demonstrated a possible harmful effect of higher Hb levels and high epoetin doses. Observational studies in kidney transplant recipients similarly suggested that mortality may be increased with Hb levels greater than 12.5 g/dL. Although evidence-based recommendations are lacking, management of posttransplantation anemia to keep Hb level in the range of 10 to 11 g/dL seems reasonable.

Refractory anemia or anemia that fails to rise gradually to a normal or near-normal level after the first few posttransplantation weeks can be a result of occult gastrointestinal (GI) bleeding, tertiary hyperparathyroidism, underlying inflammatory conditions, or parvovirus B19 infection. EPO-resistant anemia has been described in patients receiving sirolimus immunosuppression. In stable kidney transplant recipients, conversion from sirolimus to mycophenolic acid derivatives may help resolve anemia. Although uncommon, drug-induced hemolysis from agents such as dapsone should also be considered.

Leukopenia and Thrombocytopenia

Leukopenia and thrombocytopenia are most commonly due to medications, including lymphocyte-depleting agents (e.g., thymoglobulin or alemtuzumab), azathioprine, mycophenolic acid derivatives, sirolimus, everolimus, and trimethoprim-sulfamethoxazole, among others. Withholding or reducing the dose of the offending agent generally corrects these abnormalities. Severe leukopenia may be safely treated with granulocyte-stimulating factor (GSF). Thrombotic microangiopathy (TMA) or cytomegalovirus (CMV) infection should be excluded.

Parvovirus B19 infection may manifest with refractory anemia, pancytopenia, and TMA. Alemtuzumab can cause potentially fatal immune thrombocytopenia. Bortezomib has been reported to cause leukopenia and thrombocytopenia.

Posttransplantation Erythrocytosis

Posttransplantation erythrocytosis (PTE) may develop within the first 2 years and generally affects those with good allograft function. Its incidence appears to have decreased to less than 10% concomitant with the more frequent use of ACE inhibitors and ARBs. Spontaneous remission is observed in one-fourth of patients within 2 years from onset, whereas in the remaining three-fourths, erythrocytosis may persist for several years.

Risk factors for PTE include the presence of native kidneys, male sex, absence of rejection episodes, high pretransplantation Hb, and hypertension. Smoking and diabetes have been shown to be risk factors for PTE in some but not all studies. Other suggested risk factors include polycystic kidney disease and glomerulonephritis as the cause of end-stage kidney disease (ESKD). Although transplant renal artery stenosis has not consistently been shown to be a risk factor for PTE, imaging studies to evaluate the iliac and renal arteries should be considered in patients with refractory PTE (see Chapter 43). In addition, the possibilities of renal cell carcinoma in the native or transplanted kidneys should be excluded.

Treatment is generally recommended for an Hb level greater than 17 to 18 g/dL or an Hct level greater than 51% to 54% because of the associated risk for thromboembolic complications, hypertension, and headaches. Hb and Hct treatment range may vary depending on sex and institutional reference range. Treatment with ACE inhibitors or ARBs is often sufficient, although phlebotomy may occasionally be necessary. Relapse is common and often necessitates long-term ACE inhibitor or ARB treatment. We often prescribe low-dose aspirin 81 mg daily unless contraindicated.

Hyperkalemia

Mild hyperkalemia is commonly encountered in kidney transplant recipients, particularly in the early posttransplantation period when higher doses of CNI are used (TAC > CSA). It is often associated with mild hyperchloremic acidosis, a clinical presentation reminiscent of that of type 4 renal tubular acidosis. Other suggested mechanisms of CNI-induced hyperkalemia include activation of the sodium chloride cotransporter (NCC) in the distal convoluted tubule (leading to a decrease in the electrical gradient for potassium secretion via ROMK channels), inhibition of the ROMK channels and Na+/K+-ATPase in the distal tubule, and/or downregulation of mineralocorticoid receptor expression.34 In patients receiving CSA or TAC immunosuppression, a potassium level of 5.2 to 5.5 mmol/L is typical. Higher potassium levels, especially in the presence of concomitant use of drugs that may exacerbate hyperkalemia such ACE inhibitors, ARBs, and β-blockers, may require their discontinuation. Caution is needed when potassium-containing phosphorus supplements are prescribed. Although both high-dose and standard-dose trimethoprim can cause hyperkalemia via an amiloride-like effect, the routine use of low-dose trimethoprim-sulfamethoxazole (TMPSMX) prophylactic therapy is rarely the cause of severe or refractory hyperkalemia in kidney allograft recipients. Nonetheless, withholding of TMP-SMX should be considered in patients with severe or refractory hyperkalemia. In patients with recurrent hyperkalemia, consideration should be given to TMP-SMX dose reduction or TMPSMX to dapsone or atovaquone conversion therapy (see Chapter 110 for Pneumocystis jirovecii prophylaxis treatment options). Treatment of hyperkalemia is discussed in Chapter 10. Sodium polystyrene sulfonate (Kayexalate) or calcium resonium enemas should be avoided in the early posttransplantation period to avoid colonic dilation and perforation. Although large-scale clinical trials in kidney transplant recipients are lacking, the newer cation exchangers patiromer and sodium zirconium cyclosilicate appear safe and effective in the treatment of hyperkalemia in kidney transplant recipients.34 However, patiromer use in kidney transplant recipients may be hindered by potential drug-induced hypomagnesemia. This adverse drug effect may exacerbate the electrolyte abnormalities commonly seen in the posttransplantation period (discussed later). Limited studies suggest that patiromer may increase serum concentrations of TAC, whereas sodium zirconium cyclosilicate appears to have no impact on TAC pharmacokinetics.34

Hypophosphatemia

Hypophosphatemia is frequently encountered in the first months after transplantation. Concomitant hypercalcemia suggests posttransplantation hyperparathyroidism. In the absence of hypercalcemia, renal phosphate-wasting syndrome or malnutrition should be considered. Early after transplantation, hypophosphatemia has been attributed to a massive initial diuresis, particularly after a living-donor kidney transplant, defective renal phosphate reabsorption caused by ischemic injury, glucosuria (caused by hyperglycemia-induced osmotic diuresis), and corticosteroid use, the latter by inhibiting proximal tubular reabsorption of phosphate. Fibroblast growth factor-23 (FGF-23) may contribute to early posttransplantation hypophosphatemia independent of parathyroid hormone (PTH) level, and pretransplant FGF-23 is the main predictor of posttransplant phosphate levels. In contrast to hypophosphatemia occurring in the early posttransplant period, persistent hypophosphatemia beyond 1 year after transplant is mainly because of persistent hyperparathyroidism rather than increased FGF23 levels.

Hypercalcemia

Hypercalcemia is common after transplantation and is generally due to persistent secondary hyperparathyroidism. The concomitant presence of severe hypophosphatemia, particularly in patients

with excellent graft function, may exacerbate hypercalcemia through stimulation of renal proximal tubular 1 α-hydroxylase. Resolution of soft tissue calcifications and immobilization are potential contributing factors. Hypercalcemia may be masked by high-dose corticosteroid therapy but may manifest during tapering. In about two-thirds of patients, hypercalcemia resolves spontaneously within 6 to 12 months. However, spontaneous resolution occurs in less than half of those whose hypercalcemia existed before transplantation. Persistent hyperparathyroidism has generally been attributed to continued autonomous production of PTH from nodular hyperplastic glands, reduced density of calcitriol receptors, and decreased expression of the membrane calcium sensor receptors that render cells more resistant to physiologic concentrations of calcitriol and calcium. Persistently elevated FGF-23 levels after transplant may contribute to persistent hyperparathyroidism through inhibition of α1-hydroxylase activity leading to low calcitriol levels. The risk for persistent hyperparathyroidism is increased with the duration of dialysis and the severity of pretransplant hyperparathyroidism. Severe and persistent hypercalcemia (>11.5–12 mg/dL [2.87–3.0 mmol/L]) for longer than 6 months in the first posttransplant year requires further evaluation. Initial assessment should include an intact PTH level. Parathyroid technetium-99m (99mTc)-sestamibi scan is generally required to determine whether the hyperparathyroidism arises from parathyroid adenoma, parathyroid gland hyperplasia, or hyperplastic nodular formation. Treatment with cinacalcet can be considered in kidney transplant recipients with hyperparathyroidism-associated hypercalcemia in the early posttransplant period. Serum calcium, phosphorus, and alkaline phosphatase should be monitored at each clinic visit. Because spontaneous resolution of hyperparathyroidism may take time, it is generally advisable to delay parathyroidectomy to 1 year after transplant. However, severe hypercalcemia associated with parathyroid adenoma often necessitates surgical parathyroidectomy.

A multicenter, randomized, placebo-controlled trial demonstrated that cinacalcet use is safe and effective in the treatment of posttransplant hyperparathyroidism-associated hypercalcemia. Approximately 79% of cinacalcet, versus 3.5% of placebo-treated patients, achieved control of hypercalcemia (defined as calcium < 10.2 mg/dL; $P < .001$). Markers of bone density (alkaline phosphatase, osteocalcin, urine N-telopeptide) and measured bone mineral density (BMD) at the femoral neck at 1 year were comparable between the two treatment groups.35 Subtotal parathyroidectomy (or total parathyroidectomy with autotransplantation) is warranted in patients with tertiary hyperparathyroidism or persistent severe hypercalcemia refractory to medical management (>11.5–12 mg/dL [2.87–3.0 mmol/L]) for longer than 6 to 12 months, symptomatic or progressive hypercalcemia, nephrolithiasis, persistent osteitis fibrosa, calcium-related renal allograft dysfunction, or progressive vascular calcification and calciphylaxis.36 Clinicians should remain vigilant for the potential development of nephrocalcinosis associated with the use of cinacalcet.

Hypomagnesemia

CSA, TAC, and sirolimus can cause hypomagnesemia by inducing urinary magnesium wasting. Other factors that may contribute to posttransplantation hypomagnesemia include loop diuretics, recovery from acute tubular necrosis, postobstructive polyuria, renal tubular acidosis, and proton pump inhibitors. Hypomagnesemia may be more common in diabetics. In the first 3 months after transplantation, a magnesium level of less than 1.5 mg/dL (0.62 mmol/L) is common.

Dietary magnesium intake is usually insufficient, and high-dose oral magnesium supplementation may be required. IV magnesium should be considered in patients with severe hypomagnesemia (<1.0 mg/dL or 0.41 mmol/L), particularly patients with a history of CAD or cardiac arrhythmias and those taking digoxin.

Abnormal Liver Function Tests

Elevation of liver enzymes is common in the early posttransplantation period and is generally caused by drug-related toxicity (Fig. 111.3). CSA and, less commonly, TAC may cause transient, selflimited, dose-dependent elevations of transaminase levels and mild hyperbilirubinemia secondary to defective bile secretion. Elevated liver enzymes caused by drug-related adverse effects (such as from statin use) generally improve or resolve after drug discontinuation or dose reduction.

Persistent or profound elevation in liver enzymes should prompt further evaluation to exclude infectious causes, including CMV, hepatitis B, and hepatitis C infections. Preemptive therapy to prevent posttransplantation reactivation of HBV and treatment of hepatitis B and C are discussed in Chapter 110. A suggested algorithm for the management of kidney transplant recipients with elevated liver enzymes is shown in Fig. 111.3.

BONE AND MINERAL METABOLISM AFTER KIDNEY TRANSPLANTATION

Posttransplantation bone disease is common after kidney transplantation because of corticosteroid use, hypophosphatemia, and disturbances in the FGF-23-PTH-vitamin D axis. Corticosteroids directly inhibit osteoblastogenesis, induce apoptosis of osteoblasts and osteocytes, and increase bone resorption through osteoclast activation. Other adverse effects of corticosteroids include inhibition of intestinal calcium absorption, enhancement of renal calcium excretion, and direct suppression of gonadal hormone secretion.

Low plasma calcidiol (25(OH) vitamin D) level also may contribute to bone disease and is very common in kidney transplant recipients, with a reported prevalence of calcidiol deficiency of 30% (levels < 20 ng/mL) and insufficiency of 81% (levels < 30 ng/mL). Suggested causative factors include nutritional deficiency, malabsorption, decreased sun exposure, increased metabolism of calcidiol to calcitriol after a successful kidney transplant, and proteinuria (which may decrease levels of binding protein and total calcidiol levels).

Other potentially causal factors include “normal” age-dependent osteoporosis, persistent metabolic acidosis, phosphate depletion, DM, hypogonadism, smoking, and CNI therapy. Experimental murine models demonstrated that CSA increases both bone formation and bone resorption, leading to a high-turnover bone loss, whereas TAC increases bone resorption without affecting bone formation.37 In contrast, mTOR inhibitors may have a bone-sparing effect. Sirolimus was shown to inhibit osteoclast formation both in vitro and in vivo. One small European study showed that sirolimus decreased serum level of bone resorption markers in patients treated with sirolimus compared with those receiving a CNI-based regimen.38

Osteoporosis

Posttransplantation decline in BMD is most pronounced in the first 6 months and correlates with higher corticosteroid exposure. This early rapid decrease in BMD is usually followed by a slower rate of bone loss, which reflects cumulative corticosteroid dose. Bone loss in the first posttransplantation year ranging from 4% to 10% at the lumbar spine

Management of Elevated Liver Function Tests
in the Kidney Transplant Recipient

Elevated liver enzymes

Drug related: Common culprits: acyclovir, ganciclovir, valganciclovir, trimethoprim-sulfamethoxazole, statins,
proton pump inhibitors, isoniazid, cyclosporine or tacrolimus, 1 sirolimus or everolimus

Dose reduction or drug discontinuation

Improvement
Yes
Periodic laboratory reassessment at the
discretion of the clinicians

No
Non–drug-related etiologies

Noninfectious4

Infectious

CMV: Check CMV DNA PCR
In high-risk candidates for
primary infections or in case
of high clinical suspicion,
consider therapy initiation
before test results

HBV2: Check HBV DNA PCR
If positive, initiate antiviral
therapy and consider
hepatology consult

HCV3: Check HCV RNA PCR
If positive, hepatology
consult for consideration
of direct-acting
antiviral therapy

Nonalcoholic fatty
liver disease (obesity,
dyslipidemia, diabetes
mellitus), alcoholic
hepatitis, etc.

Fig. 111.3 Algorithm for the Management of Elevated Liver Enzymes in Kidney Transplant Recipients.
and, less commonly, tacrolimus may cause transient, self-limited, dose-dependent elevation
of aminotransferase levels and mild hyperbilirubinemia secondary to defective bile secretion. 2We advocate
antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation. 3Treatment of
HCV is discussed in Chapter 110. 4Appropriate evaluation and management similar to those in the nontransplant settings. CMV, Cytomegalovirus; HBV, hepatitis B; HCV, hepatitis C; PCR, polymerase chain reaction.

1Cyclosporine

and 5% to 8% at the hip have been reported. However, in more recent years, more modest bone loss or even no loss have been noted, perhaps due to lower corticosteroid doses and increased use of calcium and vitamin D.39 Evaluation of patients for bone loss or osteoporosis relies on dual-energy x-ray absorptiometry (DEXA) scan. One retrospective cohort study of 238 kidney transplant recipients with CKD stage 1 to 5 demonstrated that osteopenia (HR, 2.7; 95% CI, 1.6–4.6) and osteoporosis (HR, 3.5; 95% CI, 1.8–6.4) were associated with significantly increased hip fracture risk compared with normal BMD, independent of age, sex, and diabetes.40 The mean eGFR at the time of DEXA testing was 48 mL/min/1.73 m2 (range, 12–98 mL/min). In patients in the first 12 months after kidney transplant with eGFR greater than 30 mL/min/1.73 m2 and low BMD, the 2017 KDOQI guideline suggests initiating treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents. The choice of treatment can be influenced by abnormal levels of calcium, phosphate, PTH, alkaline phosphatase, and 25-OH Vitamin D as well as bone biopsy if required. Data are insufficient to guide treatment after the first 12 months.

Avascular Necrosis

Historically, posttransplantation avascular necrosis (AVN) occurs in up to 15% to 20% and most commonly affects the femoral head and neck. More recently its prevalence has decreased to approximately 3% to 5% concomitant with the use of lower corticosteroid dose and rapid steroid tapering. AVN usually occurs within the first few years after transplantation and may affect other joints, including the knees, the shoulders, and, less commonly, the ankles, elbows, and wrists. Predisposing factors for AVN include greater exposure to IV corticosteroid pulse therapy, cumulative doses of more than 2 g for longer than 3 months, low bone mass, hyperparathyroidism, increasing dialysis duration, excessive weight gain, hyperlipidemia, microvascular thrombosis, and a history of local trauma. Early AVN of the femoral head commonly presents with hip or groin pain or referred knee pain. Magnetic resonance imaging (MRI) is the most sensitive technique for early detection, and plain radiographs are of limited value. Corticosteroid dose reduction or discontinuation has little if any effect on altering the course of established AVN and may jeopardize graft function.

Prevention and Management of Posttransplantation Bone Diseases

Management of posttransplantation bone disease has largely been based on studies involving postmenopausal osteoporosis and corticosteroid-induced osteopenia in nontransplant settings. Studies in solid organ transplantation have yielded variable and conflicting results. Nonetheless, preventive measures to minimize posttransplantation bone loss should be initiated early after transplantation. Early ambulation and regular weight-bearing exercise should be encouraged. Adequate calcium supplementation (1000 mg/day) in nonhypercalcemic patients is recommended in the first posttransplantation year to prevent rapid bone loss resulting from corticosteroid-induced decreased intestinal calcium absorption. The 2017 KDIGO guideline recommends measuring calcidiol levels and correcting vitamin D deficiency and insufficiency using treatment strategies recommended for the general population. In patients at increased risk for fracture, consideration should be given to rapid corticosteroid taper or corticosteroid-free immunosuppressive protocols after weighing the risks and benefits of acute rejection. High pretransplantation PTH levels predict persistent hyperparathyroidism after transplantation, which may contribute to bone loss after transplantation. Hence, preexisting hyperparathyroidism associated with CKD should be treated according to the KDIGO guideline.

In patients with preexisting secondary hyperparathyroidism, hypercalcemia and hypophosphatemia may develop after transplantation because of persistent hyperparathyroidism and the newly elevated calcitriol level. Conservative management with phosphate replacement and suppression of hyperparathyroidism with cinacalcet has generally been recommended. Although no guidelines exist, phosphate supplementation should be considered in patients with a phosphate level of up to 1.5 to 1.7 mg/dL (0.5 mmol/L) to avoid complications associated with severe hypophosphatemia (e.g., rhabdomyolysis, left ventricular dysfunction, respiratory muscle weakness, and hemolysis). The indication for treatment may depend on the institutional reference range for serum phosphate. Patients should be encouraged to increase phosphate-rich food intake, and phosphate replacement should be discontinued when serum phosphate stabilizes at around 2.0 mg/dL (0.64 mmol/L). Overaggressive phosphate replacement is not recommended because it can result in worsening existing hyperparathyroidism and persistently elevated FGF-23 levels. Phosphate supplementation may also increase the risk of vascular and kidney allograft calcifications.

Bisphosphonates increase BMD in postmenopausal females and patients with corticosteroid-induced osteoporosis, particularly at the lumbar spine and trochanter. Studies evaluating the safety and efficacy of bisphosphonates in the treatment and prevention of bone disease after kidney transplantation have yielded mixed and even contradictory results, in part because of differences in study design, concomitant use of calcium or vitamin D, timing of treatment, duration of follow-up, and preexisting renal osteodystrophy, among others. The benefit of bisphosphonates for BMD may be skeletal site-specific. Several meta-analyses of RCTs showed a significant improvement in BMD with bisphosphonates compared with controls in the lumbar spine and femoral neck. No effect on fracture risk was observed. However, the low incidence of fracture events, small sample sizes, and short follow-up duration in all these studies might limit the ability to draw conclusions on fracture risk.39 The 2019 “Cochrane Kidney and Transplant Register of Studies” database involving RCTs and quasi-RCTs suggested that bisphosphonate therapy may reduce fracture and bone pain after kidney transplantation among all age groups based on evidence of low certainty.41 Bisphosphonates should be used with caution in patients with impaired kidney function and avoided in CKD stages 4 to 5.

Denosumab is a humanized monoclonal antibody that binds to and prevents RANKL (receptor activator of nuclear factor kappa-β ligand) from activating its receptor (RANK) on the surface of osteoclasts and their precursors. Denosumab has been shown to increase BMD and decrease fracture risk in postmenopausal females. Limited studies in kidney transplant recipients suggest that denosumab in combination with calcium and vitamin D may improve BMD compared with calcium and vitamin D alone.

Estrogen or androgen deficiencies also have been suggested to contribute to posttransplantation bone loss. However, no data support or refute the use of hormonal therapy to prevent posttransplantationrelated bone loss in postmenopausal females or in males with hypogonadism; hence, treatment should be individualized.

Teriparatide, a recombinant human parathyroid hormone 1 to 34, is the only osteoanabolic agent approved by the FDA for use in corticosteroid-induced osteoporosis in the general population. Little evidence exists to support its use after kidney transplantation.42

In summary, calcium supplementation, vitamin D, and bisphosphonates remain the backbone of treatment of abnormal bone and mineral metabolism after kidney transplantation. Persistent hyperparathyroidism or hypophosphatemia should be treated before considering additional therapies for osteoporosis. In the absence of evidenced-based recommendations, the use of bisphosphonates in the posttransplantation setting should be individualized. In our opinion, bisphosphonate therapy may be justifiable in high-risk individuals, including those with preexisting osteoporosis or documented overall low bone mass, those who are receiving high-dose corticosteroids or those with history of fractures, and those who are postmenopausal. Biochemical markers of low bone turnover (serum PTH and bone-specific alkaline phosphatase levels below or at the lower limits of normal) may be used to guide therapy. In high-risk individuals who are intolerant of bisphosphonates, denosumab can be used as an alternative treatment option. Profound hypocalcemia associated with the use of denosumab, particularly in patients with low GFR, has been reported and should not be overlooked.

GOUT

Potential risk factors for the development of posttransplantation hyperuricemia and gouty arthritis include pretransplantation hyperuricemia, graft impairment, obesity, diuretic use, and CSA compared with TAC. CSA may impair renal excretion of uric acid secondary to decreased GFR and increase net uric acid reabsorption by the proximal tubule.

Management of the acute gouty attack includes topical ice and rest of the inflamed joint. Pharmacologic treatments include colchicine, increased corticosteroid dose, or nonsteroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs should be avoided unless absolutely necessary. Progressive steroid tapering to low-dose maintenance antirejection therapy (usually over 2 to 3 weeks) is recommended to prevent rebound gout flare.

Management of chronic gout is directed at lowering uric acid levels. Allopurinol, a xanthine oxidase inhibitor, should be started at 100 to 200 mg/day, particularly in the presence of impaired allograft function, because lower eGFR predisposes to severe allopurinol toxicity from retention of the metabolite oxypurinol. The dose can be increased by 50-mg increment (adjusted for renal function) every 4 weeks to maintain uric acid level less than 6 mg/dL in symptomatic patients. We do not recommend allopurinol in asymptomatic patients based on uric acid level alone. Febuxostat, a nonpurine analog xanthine oxidase inhibitor, can be considered in allopurinol-allergic patients. It is administered as 40 or 80 mg/day with no dose adjustment required for patients with renal impairment. However, one large randomized trial involving high CV risk patients (defined as patients with a history of major cardiovascular disease before randomization) demonstrated higher all-cause and CV mortality among febuxostat-treated compared with allopurinol-treated patients.43 Both allopurinol and febuxostat should be used cautiously in patients taking azathioprine because of the inhibition of azathioprine metabolism by xanthine oxidase inhibitors (e.g., when used in combination therapy with allopurinol or febuxostat, consider azathioprine dose reduction by 25% and close monitoring of complete blood counts). Alternatively, azathioprine to mycophenolic acid derivative conversion therapy may be considered. The latter does not interact with allopurinol or febuxostat. Recombinant pegylated uricase (pegloticase), which converts uric acid to the more soluble and readily excreted purine end-product allantoin, rapidly reduces uric acid levels in patients refractory to conventional therapy. Pegloticase was approved by the FDA in 2010 for treatment of refractory gout, but high titers of antibodies against the drug is associated with loss of efficacy and

infusion reactions. Recent studies suggest that posttransplantation immunosuppressive therapy may reduce immunologic response to pegloticase therapy by inhibiting the development of antipegloticase antibodies. Successful treatment of a heart transplant recipient with polyarticular tophaceous gout and hyperuricemia with a 38-week course of pegloticase has been reported.44 Whether immunosuppressive therapy in the transplant setting may prevent antipegloticase antibody development and retain the urate-lowering efficacy among organ transplant recipients warrants further studies.

OUTPATIENT CARE

We recommend that patients be seen two times a week for the first 4 weeks after transplantation and weekly for the next month. After the first 2 months, the frequency of outpatient visits depends on the complexity of the patients’ early postoperative course. Patients with stable graft function and an uneventful postoperative course can return to work or their regular daily activities 2 to 3 months after transplantation. Laboratory assessment during the first month after transplantation should include serum creatinine and electrolyte values, fasting glucose level, liver enzymes, immunosuppressive drug levels, and complete blood count with platelets. Urinalysis and, if clinically indicated, urine culture, and urine protein-to-creatinine ratio (see proteinuria section) also should be performed. At our institution, the patient’s care will generally be returned to the referring nephrologist after 3 months. However, continued annual follow-up at the transplantation center is recommended.

SELF-ASSESSMENT QUESTIONS

1. Management of posttransplantation hypertension should include lifestyle modifications and which one of the following?

A. Stringent blood pressure control to a goal of less than 130/80 mm HG should begin in the early posttransplantation period.

B. An ACE inhibitor is the antihypertensive agent of choice after kidney transplantation because it improves patient and graft survival.
C. The KDIGO guidelines suggest a blood pressure goal of less than 130/80 mm Hg if albuminuria is present.
D. None of the above.
2. Which of the following drug combination therapies is more likely to cause myopathy and rhabdomyolysis?
A. High-dose statin and ezetimibe
B. High-dose statin and tacrolimus

C. High-dose statin and cyclosporine
D. Both B and C
3. Which one of the following statements is correct?
A. Cyclosporine (CSA) is more diabetogenic than tacrolimus (TAC).
B. Belatacept is less diabetogenic than both TAC and CSA.
C. Unlike the calcineurin inhibitors (CSA and TAC), mTOR inhibitors (sirolimus and everolimus) are nondiabetogenic.
D. Among currently available immunosuppressive agents, mTOR inhibitor use is associated with the worst lipid profile followed by CSA and TAC.
E. The mycophenolic acid derivatives mycophenolate mofetil and mycophenolate sodium are less diabetogenic than azathioprine.

REFERENCES

1. Paoletti E, Gherzi M, Amidone M, et al. Association of arterial hypertension with renal target organ damage in kidney transplant recipients: the predictive role of ambulatory blood pressure monitoring. Transplantation. 2009;87(12):1864–1869.
2. Gluskin E, Tzukert K, Levi IM-Y, et al. Ambulatory monitoring unmasks hypertension among kidney transplant patients: single center experience and review of the literature. BMC Nephrol. 2019;20(1):284.
3. Kasiske BL, Anjum S, Shah R, et al. Hypertension after kidney transplantation. Am J Kidney Dis. 2004;43(6):1071–1081.
4. Carpenter MA, John A, Weir MR, et al. BP, cardiovascular disease, and death in the folic acid for vascular outcome reduction in transplantation trial. J Am Soc Nephrol. 2014;25(7):1554–1562.
5. Shumate AM, Bahler CD, Goggins WC, et al. Native nephrectomy with renal transplantation is associated with a decrease in hypertension medication requirements for autosomal dominant polycystic kidney disease. J Urol. 2016;195(1):141–146.
6. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13–e115.
7. Weir MR, Burgess ED, Cooper JE, et al. Assessment and management of hypertension in transplant patients. J Am Soc Nephrol. 2015;26(6): 1248–1260.
8. Rangaswami J, Mathew RO, Parasuraman R, et al. Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. Nephrol Dial Transplant. 2019;34(5):760–773.
9. Hiremath S, Fergusson DA, Fergusson N, et al. Renin-angiotensin system blockade and long-term clinical outcomes in kidney transplant recipients: a meta-analysis of randomized controlled trials. Am J Kidney Dis. 2017;69(1):78–86.
10. Watorek E, Szynczak M, Boratynska M, et al. Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. Transplant Proc. 2011;43:2967–2969.
11. Holdaas H, Potena L, Saliba F. mTOR inhibitors and dyslipidemia in transplant recipients a cause for concern? Transplant Rev. 2015;29(2): 93–102.
12. van Dijk M, van Roon AM, M Yusof Said MY. Long-term cardiovascular outcome of renal transplant recipients after early conversion to everolimus compared to calcineurin inhibition: results from the randomized controlled MECANO trial. Transpl Int. 2018;31(12):1380–1390.
13. Asleh R, Briasoulis A, Pereira NL, et al. Hypercholesterolemia after conversion to sirolimus as primary immunosuppression and cardiac allograft vasculopathy in heart transplant recipients. J Heart Lung Transplant. 2018;37(11):1372–1380.
14. Holdaas H, Fellström B, Jardin AG, et al. Beneficial effects of early initiation of lipid-lowering therapy following renal transplantation. Nephrol Dial Transplant. 2005;20:974–980.
15. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation. 2019;73:e285–e350.
16. Ponticelli C, Arnaboldi L, Moroni G, et al. Treatment of dyslipidemia in kidney transplantation. Expert Opin Drug Saf. 2020 Mar;19(3):257–267.
17. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebocontrolled trial. Lancet. 2011;377(9784):2181–2192.
18. Savvidaki E, Koukoulaki M, Benou A, et al. Ezetimibe is effective in the treatment of persistent hyperlipidemia of renal allograft recipients. Clin Nephrol. 2011;75:107–112.
19. Schmit D, Fliser D, Speer T. Proprotein convertase subtilisin/kexin type 9

in kidney disease. Nephrol Dial Transplant. 2019;34(8):1266–1271.

20. Mach F, Baigent C, Catapano AL, et al. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019;41:111–188.
21. Pham PT, Sarkar M, Pham PM, et al. Diabetes mellitus after solid organ transplantation. Endotext. July 13, 2022.
22. Sharif A, Hecking M, de Vries AP, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2022;14(9):1992–2000.
23. Wissing KM, Abramowicz D, Weekers L, et al. Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. Am J Transplant. 2018;18(7):1726–1734.
24. Pascual J, Royuela A, Galeano C, et al. Very early steroid withdrawal or avoidance for kidney transplant recipients: a systematic review. Nephrol Dial Transplant. 2012;27:825–832.
25. Pirsch JD, Henning AK, First MR, et al. New-onset diabetes after transplantation: results from a double-blind early corticosteroid withdrawal trial. Am J Transplant. 2015;15(7):1982–1990.
26. Kukla A, Hill J, Merzkani M, et al. The use of GLP1R agonists for the treatment of type 2 diabetes in kidney transplant recipients. Transplant Direct. 2020;6(2):e524.
27. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31–39.
28. Halden TAS, Kvitne KE, Midtvedt K, et al. Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. Diabetes Care. 2019;42(6):1067–1074.
29. Khalil MAM, Tan J, Said Khamis S, et al. Cigarette smoking and its hazards in kidney transplantation. Adv Met Med. 2017;2017:6213814.
30. Hadjievangelou N, Kulendran M, McGlone ER, et al. Is bariatric surgery in patients following renal transplantation safe and effective? A best evidence topic. Int J Surg. 2016;28:191–195.
31. Asleh R, Alnsasra H, Lerman A, et al. Effects of mTOR inhibitorrelated proteinuria on progression of cardiac allograft vasculopathy and outcomes among heart transplant recipients. Am J Transplant. 2021;21(2):626–635.
32. Kang A, Nigwekar SU, Perkovic V, et al. Interventions for lowering plasma homocysteine levels in kidney transplant recipients. Cochrane Database Syst Rev. 2015;5:CD007910.
33. Neuwirt H, Leitner-Lechner I, Julia Kerschbaum J, et al. Efficacy and safety of belatacept treatment in renal allograft recipients at high cardiovascular risk: a single center experience. J Clin Med. 2019;8(8): 1164.
34. Rizk J, Quan D, Gabardi S, et al. Novel approaches to management of hyperkalaemia in kidney transplantation. Curr Opin Nephrol Hypertens. 2021;30(1):27–37.
35. Evenepoel P, Cooper K, Holdaas H, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. Am J Transplant. 2014;14(11): 2545–2555.
36. Pham PC, Pham PT. Parathyroidectomy. In: Nissenson AR, Fine RN, eds. Handbook of Dialysis Therapy. 5th ed. Philadelphia: Elsevier; 2017: 709–718.
37. Kanda J, Izumo N, Furukawa M, et al. Effects of the calcineurin inhibitors cyclosporine and tacrolimus on bone metabolism in rats. Biomed Res. 2018;39(3):131–139.
38. Westenfeld R, Schlieper G, Wöltje M, et al. Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis-implications for post-transplantation bone disease. Nephrol Dial Transplant. 2011;26:4115–4123.

39. Anastasilakis AD, Tsourdi E, Makras P, et al. Bone disease following solid organ transplantation: a narrative review and recommendations for management from the European Calcified Tissue Society. Bone. 2019;127:401–418.

References

40. S1 A, Simonsen O, Lindergård B, et al. Can DXA predict fractures in renal transplant patients? Am J Transplant. 2008;8(12):2647–2651.
41. Palmer SC, Chung EY, McGregor DO, et al. Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev. 2019;10(10):CD005015.
42. Santos RD, Rossi A, Coyne D, et al. Management of post-transplant hyperparathyroidism and bone disease. Drugs. 2019;79(5):501–513.

43. White WB, Saag KG, Becker MA, et al. CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378(13):1200–1210.
44. Freyne B. A case report of immunosuppressant medication-associated polyarticular tophaceous gout successfully treated using the polyethylene glycol-conjugated uricase enzyme pegloticase. Transplant Proc. 2018;50(10):4099–4101.

112

Chronic Allograft Injury

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DEFINITIONS AND EPIDEMIOLOGY

The results after kidney transplantation have steadily improved over the past 30 years with a 1-year overall graft survival rate of about 94% and acute rejection rates within the first year after transplantation of 12%.1 Loss of an allograft from acute rejection is now rare and is predominantly found in patients who are presensitized against human leukocyte antigens (HLAs).2 Today, most allografts are lost by chronic antibody-mediated rejection that is a consequence of (de novo) development of donor-specific HLA antibodies (DSAs) but also non-HLA antibodies.3 4 5 Every year, about 4% of kidney grafts are lost (Fig. 112.1). Only 2 decades ago, it was believed that nonimmunologic causes were the main factors leading to chronic allograft injury and graft loss.6 Today, HLA alloantibodies are believed to be the main culprit, accounting for more than half of graft losses in the long term.7 With the acknowledgment of alloantibodies as main factors that contribute to graft failure, the term chronic allograft nephropathy has been replaced by more specific terminology in the Banff classification of kidney allograft pathology (Table 112.1).8 9

Although immunologic causes are mainly responsible for late allograft injury and graft failure, nonimmunologic causes still represent significant risk factors for (late) graft injury and graft loss. The donor graft may present with significant preexisting disease limiting long-term graft survival.10 In addition, chronic interstitial fibrosis and tubular atrophy (IFTA) may result from early damage to the allograft such as ischemia/reperfusion injury or early acute rejection. Calcineurin-inhibitor (CNI) nephrotoxicity, recurrent or de novo glomerular disease, BK virus infection, and IFTA originating from other causes further contribute to graft damage and graft loss over the long term.

Although some allografts are lost because of one specific cause, others accumulate damage from several different causes with gradual loss of functioning nephrons. Main contributors to late graft injury and late graft loss are summarized in Box 112.1

PATHOGENESIS: NONIMMUNOLOGIC FACTORS

Donor Age, Donor Sex, and Donor-Recipient Size Mismatching

Long-term graft survival is reduced in kidneys from older donors, an effect that is more pronounced in deceased compared with living kidney transplant recipients.11 Impaired graft survival is attributed to a differential response of the older organ to injury, an impaired capacity to withstand stress, a limited ability to repair structural damage, or amplification of external injury because of preexisting structural abnormalities.12

Reduced nephron mass resulting in glomerular hyperfiltration and hypertension with accelerated senescence is also a postulated mechanism for a progressive decline in kidney graft function.13 The effect of kidney size mismatching is thought to be related to insufficient numbers of nephrons within the donor kidney, which, in turn, leads to compensatory hyperfiltration.14 Although some experimental data support this hypothesis, the extent to which an inadequate number of nephrons contributes to chronic injury in clinical transplantation is unknown.

Female donor sex has a negative impact on kidney graft survival, with reduced survival when female grafts are transplanted into male recipients (risk ratio [RR], 1.22). This may be the result of reduced nephron mass of female donor kidneys (nephron underdosing). Other mechanisms may include possible differences in the immunogenicity of male and female grafts.15 16

Ischemia/Reperfusion Injury and Delayed Graft Function

Graft survival is lower in recipients with longer ischemia times, and longer cold ischemia time represents a risk factor for the development of IFTA at 6 months after transplantation.17 Ischemia-reperfusion injury also may trigger immune-mediated injury because ischemia and oxidative injury resulting from reperfusion are associated with activation of the adaptive immune response, antigen-presenting cells and Toll-like receptors, and release of proinflammatory cytokines—all of which can lead to acute rejection and subsequent IFTA.18 Pretreatment of the deceased organ donor with low-dose dopamine (aiming to reduce ischemia/reperfusion injury) reduced the need for dialysis early after kidney transplantation but failed to improve long-term kidney graft survival.19 20 Similarly, therapeutic hypothermia compared with normothermia of the deceased organ donor was associated with a lower incidence of delayed graft function in the kidney transplant recipient (28% vs. 39%).21 Another promising approach to reduce ischemia/reperfusion injury and improve early kidney graft function is the replacement of cold storage of kidneys by pulsatile machine perfusion during transportation. This strategy has been tested in clinical trials and is now routine practice in some centers.22

Delayed graft function, commonly defined by the need for dialysis in the first week after transplantation, is a risk factor for IFTA.23 There are also independent associations between delayed graft function and late graft failure and between delayed graft function and graft failure that is mediated by acute rejection. Major risk factors for delayed graft function are prolonged cold ischemia time, donor age older than 50 years, diabetes mellitus as a cause of end-stage kidney disease (ESKD), time on dialysis of more than 5 years, and the presence of HLA alloantibodies.24 The risk for delayed graft function is reduced when the donor or recipient is of female sex or when trauma is the cause of donor death. Ischemia and oxidative injury resulting from reperfusion of an ischemic kidney may cause an upregulation of major histocompatibility complex (MHC) antigens or proinflammatory cytokines, predisposing to acute rejection.

Graft Survival for Recipients of a First
Deceased Donor Kidney Transplant,
by Year of Transplant
2013-15, n = 20,393

1997-00, n = 34,849

2009-12, n = 32,425

1993-96, n = 39,820

2005-08, n = 33,029

1989-92, n = 39,812

2001-04, n = 34,790

1985-88, n = 35,184

100
95

Graft survival (%)

90
85
80
75
70
65
0

0

1
2
3
Posttransplant time (years)

Fig. 112.1 Graft Survival for Recipients of a First Deceased Donor Kidney Transplant According to Year of Transplantation. Graft survival has steadily improved over the past years but mainly as a result of reduction of early graft loss. (Courtesy Prof. Gerhard Opelz, CTS Study.)

BK Virus Nephropathy

BK virus is an endemic polyomavirus that is usually acquired during childhood and persists in the urinary tract. Although it is asymptomatic in the immunocompetent host, it becomes activated in the immunocompromised patient. Viremia may be found in 10% to 30% of patients within the first 6 months after transplantation with biopsyproven BK virus–associated nephropathy in 1% to 10% of patients. BK virus–associated nephropathy mimics the pattern of interstitial cellular rejection but may be distinguished in immunohistochemistry by positive staining for the SV40 antigen. The Banff working group identified two histologic markers predictive for graft function and graft survival. The Banff interstitial fibrosis (ci) score and a new score termed “the intrarenal polyomavirus load level (pvl).” The pvl score is based on the fraction of tubules with evidence of BK replication by light microscopy or immunohistochemical staining of epithelial cell nuclei for SV40 antigen. The pvl and ci scores were used to define the following three BK virus–associated nephropathy classes: pvl1 up to 1%, pvl2 greater than 1%, and less than 10%, and pvl3 of 10% or greater.25 BK virus–associated nephropathy, if untreated, may lead to severe IFTA and graft loss in most patients. The mainstay of therapy is the reduction of immunosuppression.26 The diagnosis and management of BK virus nephropathy are discussed further in Chapter 110

Calcineurin Inhibitor Toxicity

CNI nephrotoxicity affects all histologic compartments of the transplanted kidney. Although not specific for CNI toxicity, CNI lesions include medial arteriolar hyalinosis, striped interstitial fibrosis, global glomerulosclerosis, and tubular microcalcification unrelated to other causes, such as tubular necrosis and hyperparathyroidism.27 28 CNIinduced arteriolopathy is characterized by nodular hyaline deposits in the media of afferent arterioles sufficient to cause narrowing of the vascular lumen.29 30 It is attributed to eosinophilic transformation and vacuolization of smooth muscle cells with subsequent necrosis. Arteriolar hyalinosis is the most reliable diagnostic marker of CNI nephrotoxicity. Confirmation of the diagnosis is made by exclusion of other causes, such as donor hyalinosis (which can be detected on the implantation biopsy specimen), diabetes, and hypertensive nephrosclerosis. Striped fibrosis is subjectively defined by a dense stripe of cortical fibrosis and atrophic tubules adjacent to normal cortex and is traditionally regarded as pathognomonic of CNI nephrotoxicity but can be seen in any cause of fibrosis, especially those associated with microvascular injury. It is likely that the associated arteriolopathy and narrowing of the lumen contribute to development of fibrosis and atrophy after watershed infarcts within areas of ischemia. Local hypoxia leads to formation of free oxygen radicals, which promote cellular death by apoptosis. In addition, upregulation of transforming growth factor-β is considered an important etiologic factor in CNI toxicity.28

Today, CNI nephrotoxicity is believed to be responsible for only a small proportion of graft failures. The Study of Long-term Deterioration of Kidney Allograft Function (DeKAF) demonstrated that 70% of patients with a primary or secondary histologic diagnosis of CNI nephrotoxicity had evidence of deposition of the complement split-product C4d and had DSA linking chronic graft failure to alloimmunity rather than CNI nephrotoxicity.31 32

Recurrent and De Novo Glomerular Diseases

Recurrent glomerulonephritis (GN) is diagnosed by exclusion of donor-transmitted disease and de novo GN. Its relative importance for graft loss increases as graft survival lengthens.33 Given that it is a relatively common occurrence and has implications for treatment and retransplantation, clinicians should carefully search for recurrence in patients with prior GN. Diagnosis and management of recurrent disease are discussed further in Chapter 113

Cardiovascular Risk Factors

The vasculopathy in chronic allograft injury resembles systemic vascular disease, raising the possibility that conventional cardiovascular (CV) disease risk factors may be implicated. Hypertension occurs in about 70% to 90% of transplant recipients and predisposes to graft failure.34 Dyslipidemias, including raised total cholesterol, low-density lipoprotein cholesterol, and triglycerides and cigarette smoking, have also been associated with late graft failure. The management of CV risk factors in the transplant recipient is discussed in Chapter 111

PATHOGENESIS: IMMUNOLOGIC FACTORS

T-Cell–Mediated Rejection

Acute T-cell–mediated rejection, vascular or corticosteroid-resistant rejection, subclinical rejection, and late (chronic-active) T-cell–mediated rejection all contribute to the burden of chronic allograft injury. Early acute T-cell–mediated rejection (within 3 months of transplantation) that is adequately diagnosed and treated usually has no impact on long-term graft survival, but late chronic-active T-cell–mediated rejection in which serum creatinine does not return to baseline usually translates into IFTA and/or vascular damage, contributing to graft injury. Multiple and severe late acute T-cell–mediated rejection episodes are predictive of chronic graft dysfunction more than early cellular rejection and acute vascular rejection, which have stronger associations with acute graft loss.35 There is some evidence from

TABLE 112.1

Updated 2019 Banff Classification Categories

Category 1: Normal Biopsy or Nonspecific Changes
Category 2: Antibody-Mediated Changes Active ABMR
All three features must be present for diagnosis.
1. Active ABMR
1. Histologic evidence of acute tissue injury, including one or more of the following:
2. Chronic active ABMRb
3. Chronic ABMR
🐧 •🐧 Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo
4. C4d staining without evidence of rejection
glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1
alone is not sufficient and g must be ≥ 1
🐧 •🐧 Intimal or transmural arteritis (v >0)a
🐧 •🐧 Acute TMA in the absence of any other cause
🐧 •🐧 Acute tubular injury in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the
following:
🐧 •🐧 Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d > 0 by IHC on
paraffin sections)
🐧 •🐧 At least moderate microvascular inflammation ([g + ptc] ≥ 2), although in the presence of acute TCMR,
borderline infiltrate, or infection; ptc ≥ 2 alone is not sufficient, and g must be ≥ 1
🐧 •🐧 Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if
thoroughly validated
3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). C4d staining
or expression of validated transcripts/classifiers as noted previously in criterion 2 may substitute for
DSA; however, thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is
negative, is strongly advised whenever criteria 1 and 2 are met.
Chronic Active ABMR
All three features must be present for diagnosis. As with active ABMR, biopsy samples showing histologic
features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but
not both, may be designated as suspicious, and it should be noted if the lesion is C4d positive or C4d
negative, based on the criteria listed:
1. Histologic evidence of chronic tissue injury, including one or more of the following:
🐧 •🐧 TG (cg > 0), if no evidence of chronic TMA; includes changes evident by EM only (cg1a; see Table 112.4)
🐧 •🐧 Severe peritubular capillary basement membrane multilayering (requires EM)c
🐧 •🐧 Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima
favor chronic ABMR if there is no history of biopsy-proven TCMR with arterial involvement but are not
required

2. Identical to criteria for active ABMR

3. Serologic evidence of DSAs (HLA or other antigens):

🐧 •🐧 Biopsy results suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited

DSA testing

Chronic ABMR

All three features must be present for diagnosis:

1. cg > 0 and/or severe ptcml (ptcml1)

2. Absence of criterion 2 of recurrent/recent antibody interaction with the endothelium

3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior evidence of DSA

C4d Staining Without Evidence of Rejection

All four features must be present for diagnosisd:

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on

paraffin sections)

2. Criterion 1 for active or chronic active ABMR not met

3. No molecular evidence for ABMR as in criterion 2 for active and chronic active ABMR

4. No acute or chronic active TCMR, or borderline changes

🐧•🐧 Foci of tubulitis (t1, t2, or t3) with mild interstitial inflammation (i1), or mild tubulitis (t1) with interstitial

Category 3: Borderline Changes

Suspicious for Acute TCMR

inflammation (i2, i3)

🐧•🐧 No intimal arteritis (v = 0)

TABLE 112.1

Updated 2019 Banff Classification Categories—cont’d

Category 4: TCMR
1. Acute TCMR
2. Chronic active TCMR

Category 5: Interstitial Fibrosis and Tubular Atrophy (IFTA)

Category 6: Other Changes Not Considered Caused by Acute or Chronic Rejection

Acute TCMR
IA. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of moderate tubulitis (t2)
IB. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of severe tubulitis (t3)
IIA. Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis
IIB. Severe intimal arteritis comprising > 25% of the luminal area (v2) with or without interstitial inflammation and tubulitis
III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
Chronic active TCMR
IA. Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out
IB. Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out
II. Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)
Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima); note that such lesions may represent chronic active ABMR and TCMR; the latter also may be manifest in the tubulointerstitial compartment
I. Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area)
II. Moderate interstitial fibrosis and tubular atrophy (26%–50% of cortical area)
III. Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)

- BK virus nephropathy
- Posttransplant lymphoproliferative disorders
- Calcineurin inhibitor nephrotoxicity
- Acute tubular injury
- Recurrent disease
- De novo glomerulopathy (other than transplant glomerulopathy)

- Pyelonephritis
- Drug-induced interstitial nephritis

[a] These arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. The v lesions are scored in arteries only having a continuous media with two or more smooth muscle layers.

[b] Lesions of chronic, active ABMR can range from primarily active lesions with early TG evident only by EM to those with advanced TG and other chronic changes in addition to active microvascular inflammation. In the absence of evidence of current/recent antibody interaction with the endothelium (those features in the second section of Table 112.3), the term “active” should be omitted; in such cases, DSAs may be present at the time of biopsy or at any previous time after transplantation.

[c] Seven or more layers in one cortical peritubular capillary and five or more in two additional capillaries, avoiding portions cut tangentially.

[d] The clinical significance of these findings may be quite different in grafts exposed to anti–blood group antibodies (ABO-incompatible allografts), in which they do not appear to be injurious to the graft and may represent accommodation; however, with anti-HLA antibodies, such lesions may progress to chronic ABMR and more outcome data are needed.

ABMR, Antibody-mediated rejection; cg, glomerular double contours; DSA, donor-specific antibody; EM, electron microscopy; g, glomerulitis; i, inflammation; IF, immunofluorescence; IHC, immunohistochemistry; ptc, peritubular capillaritis; t, tubulitis; TCMR, T-cell–mediated rejection; TG, transplant glomerulopathy; TMA, thrombotic microangiopathy; v, intimal arteritis.

From Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney meeting report (I): Updates on and clarification of criteria for T cell- and antibodymediated rejection. Am J Transplant. 2020;20:2318–2331.

protocol biopsy studies that subclinical T-cell–mediated rejection may be an important factor contributing to chronic graft injury.[36] [37]

Besides the direct effects of T-cell–mediated rejection on graft function, acute T-cell–mediated rejection may be linked to the development of DSA and subsequent antibody-mediated rejection.[38]

Antibody-Mediated Rejection

Chronic active antibody-mediated rejection is the leading cause of graft loss, together with death with a functioning graft, recurrent kidney disease, and IFTA of unknown origin.[39]

For the diagnosis of antibody-mediated kidney graft rejection, histologic features of antibody-mediated rejection in the biopsy sample (Figs. 112.2–112.4), together with evidence of current or recent antibody interaction with the vascular endothelium (see Fig. 112.3) and the detection of circulating DSA (either HLA or non-HLA), are required. Because C4d in peritubular capillaries is not detectable in more than 50% of patients with chronic antibody-mediated rejection, C4d-positivity is no longer a prerequisite for the diagnosis of antibodymediated rejection.[9] This finding, together with the observation that chronic antibody-mediated rejection may occur in the absence of complement activation (e.g., the occurrence of transplant glomerulopathy in patients during effective therapeutic complement inhibition by eculizumab), led to the hypothesis that complement-independent mechanisms such as direct endothelial cell activation and infiltration of natural

BOX 112.1 Main Factors Contributing to Late Graft Injury and Late Graft Loss

Donor Factors
- Deceased donor kidney (DBD or DCD)
- Older donor age, female donor
- Donor vascular disease
- Ischemia/reperfusion injury and long ischemia time
- Delayed graft function

Recipient Risks (Nonimmune)
- Obesity
- Urinary tract infection
- Transplant ureteral obstruction
- BK virus nephropathy
- Calcineurin inhibitor toxicity
- Recurrent kidney disease or de novo glomerulonephritis
- Hypertension, dyslipidemia, smoking
- Diabetes (preexisting or posttransplantation)

A

Recipient Risks (Alloimmune)
- Child or adolescent recipient
- Variable immunosuppressive medication trough concentrations from malabsorption or nonadherence
- HLA mismatches, presensitization status (donor-specific HLA alloantibodies)
- Acute rejection that is severe, corticosteroid resistant, vascular, antibody mediated, or late occurring
- Late de novo donor-specific antibodies and chronic (antibody-mediated) rejection

DBD, Donation after brain death; DCD, donation after cardiac death; HLA, human leukocyte antigen. Modified from Nankivell BJ, Kuypers DRJ. Diagnosis and prevention of chronic kidney allograft loss. Lancet. 2011;378:1428–1437.

killer (NK) cells or monocytes may contribute to chronic antibodymediated allograft injury. C4d-negative antibody-mediated rejection shares the same histologic and ultrastructural features as C4d-positive rejection. To improve the diagnosis of antibody-mediated rejection, a molecular microscope strategy was adopted in the 2013 update of the Banff classification.40 This means that in the absence of C4d positivity or microvascular inflammation, antibody interaction with the vascular endothelium is also suggested by detection of an increased expression of specific gene transcripts in the biopsy tissue indicative of endothelial injury (the “molecular microscope”), although this approach still needs further validation.

Unrecognized DSAs, if strongly reactive and complementactivating, can cause hyperacute rejection or accelerated antibodymediated rejections in the early phase after kidney transplantation.

Acute antibody-mediated rejection in the early phase occurs in about 1% to 6% of patients overall, but in as many as 21% to 55% of patients who had detectable DSAs already before transplantation and who received desensitization therapy.41–43 Weakly positive DSAs have been associated with rather subtle types of graft damage, often leading to delayed graft function.2 Early damage can lead to chronic rejection, most probably because the structure of the endothelium is no longer intact and new antigenic epitopes are expressed on the surface of transplanted tissue. During later phases after transplantation, insufficient immunosuppression can facilitate the development of de novo DSAs against these new epitopes and result in chronic antibody-mediated rejection and failure of the transplanted organ. De novo DSAs, but

B

Fig. 112.2 Transplant Glomerulopathy: Light Microscopy. (A) Note the mesangial expansion and thickening of the glomerular basement membrane (GBM). (B) Note the GBM reduplication in capillary loops (between arrows).

to a lesser extent also persistence or reemergence of DSAs that were detectable before transplantation, are associated with poor allograft outcome.

Chronic active antibody-mediated rejection is found more frequently in patients who are nonadherent to immunosuppressive medication or in whom immunosuppression was reduced for other reasons, such as conversion to CNI-free or steroid-free immunosuppressive protocols, recurrent infection, or malignancy.44–46 In these patients, antibody-mediated lesions and T-cell–mediated lesions are often found in kidney graft biopsy samples at the same time. Additional risk factors for the development of de novo DSAs and antibody-mediated rejection are HLA class II DR mismatches between donor and recipient, prior cellular rejection episodes, and younger recipient age. In many patients with late antibody-mediated graft loss, even when HLA class I alloantibodies are detectable, HLA class II de novo DSAs are considered to be mainly responsible for rejection. In a recent study on the evolution of HLA alloantibodies after transplantation, de novo DSAs appeared at a mean of 4.6 years after transplantation, and the prevalence of de novo DSAs after 10 years was 20% in those adherent to the immunosuppressive regimen, compared with 60% in nonadherent graft recipients.46 In another study, DSAs were found in 37% of patients who had an indication biopsy 7 days to 31 years after transplant.7 De novo DSAs that were directed against HLA class II antigens had an especially strong association with strongly impaired graft survival. A recent development for the detection of harmful DSAs is the introduction of solid-phase assays into a clinical routine, which

A
A

CL

GBM

B

B

Fig. 112.3 C4d Immunoperoxidase Staining in Association With Chronic Antibody-Mediated Rejection. Staining of glomerular capillaries (A) and circumferential staining of peritubular capillaries (B) are typical.

enables the distinction of complement-binding (C1q assay) HLA antibodies from antibodies that do not bind complement. In a cohort of more than 1000 patients, it was recently demonstrated that the posttransplant occurrence of complement-binding DSA is associated with adverse events. The 5-year graft survival in patients with complementbinding antibodies was 54% compared with 93% in patients with DSAs that were not able to bind complement. The higher risk for graft loss in patients with complement-binding DSAs was attributable to a higher risk for chronic antibody-mediated rejection.47 Recent preliminary data also suggest that DSAs of different immunoglobulin G subclasses may be associated with different distinct injury phenotypes in kidney allograft biopsies.

Other antibodies that may contribute to chronic antibody-mediated rejection are MHC class I–related chain A antibodies, angiotensin II type 1 receptor–activating antibodies, and other antiendothelial cell antibodies.48 49

Insufficient Immunosuppression and Nonadherence to Medication

The recognition that HLA alloantibodies are responsible for a great proportion of late graft losses37 50 has focused attention on insufficient immunosuppression and nonadherence to immunosuppressive medication (Fig. 112.5).44 51

Fig. 112.4 Transplant Glomerulopathy: Electron Microscopy. (A) Section of a glomerular capillary loop (×24,000) demonstrating mesangial interposition (asterisks), subendothelial expansion and new lamina densa (double arrow), and endothelial hypertrophy (line). (B) A complete glomerular capillary loop (CL) with glomerular basement membrane (GBM) thickening (single arrow), endothelial hypertrophy (double arrow), expanded subendothelial space, and new lamina densa (single arrow). Apparent GBM duplication is a result of mesangial interposition and formation of new lamina densa.

A retrospective analysis of more than 25,000 kidney transplant recipients showed that reduction or discontinuation of cyclosporine, tacrolimus, or mycophenolate mofetil after the first posttransplant year in patients with good graft function was associated with significantly reduced subsequent kidney graft survival.44 In a recent study in which 64% of graft losses in a cohort with indication biopsies were attributable to (antibody-mediated) rejection, about half of the patients with rejection-associated allograft loss were identified as nonadherent.51

Young adults who are in transition from pediatric to adult nephrology care are at high risk for nonadherence. Other risk factors are previous nonadherence, psychiatric disorders, substance abuse, insufficient socioeconomic support, and adverse effects from immunosuppressive medication. Insufficient immunosuppression may also occur during immunosuppressive minimization (tapering) or CNIavoidance trials. In a recent study, 14 of 61 patients (23%) who were converted from cyclosporine to everolimus at 3 to 4.5 months after transplantation developed DSA, compared with only 7 of 65 patients (11%) who continued on cyclosporine.41 Eight patients on everolimus but only two patients on cyclosporine developed antibody-mediated rejection. Therefore, such patients should be rigorously evaluated for alloantibodies and antibody-mediated allograft injury according to Transplantation Society Guidelines (see later).52

CLINICAL MANIFESTATIONS

Insufficient Immunosuppression
Contributes to Late Graft Loss
Nonadherence

Inadequate dosing

Insufficient immunosuppression

Acute cellular rejection

Development of
de novo donor-specific antibodies

Acute antibodymediated rejection

Chronic antibodymediated rejection

Late graft failure

Fig. 112.5 Insufficient immunosuppression contributes to late graft loss.

Routine laboratory evaluation of graft function does not facilitate the early diagnosis of chronic allograft injury. A rise in serum creatinine is a late marker of allograft dysfunction. Reduction in the glomerular filtration rate is usually estimated by equations such as the Modification of Diet in Renal Disease (MDRD) formula or the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. However, substantial nephron loss may occur before a rise in serum creatinine becomes evident.

Persistent or worsening proteinuria is also a late sign of chronic allograft injury. Proteinuria greater than 1 g/day typically occurs with recurrent or de novo GN or with severe chronic antibodymediated changes such as transplant glomerulopathy (see Figs. 112.2–112.4). A definite diagnosis of antibody-mediated rejection requires transplant kidney biopsy together with serologic testing for alloantibodies and viral disease such as BK virus or cytomegalovirus (CMV) infection. So far, no noninvasive tests can reliably diagnose antibody-mediated rejection. The evolution of antibody-mediated graft damage from the binding of DSAs to graft loss is given in Fig. 112.6

Recently a risk prediction score for long-term kidney allograft failure has been developed and validated. The “iBox” combines functional, histologic, and immunologic allograft parameters together with HLA antibody profiling and showed good performance in predicting the risk of long-term kidney allograft failure.53

The Evolution of Antibody-Mediated
Graft Damage
DSA
Direct endothelial cell activation, complement activation, lymphocyte recruitement (NK cells and monocytes), coagulation cascade activation

Chronic antibody-mediated rejection
Peritubular capillarities, glomerulitis, ±C4d-positivity

Transplant glomerulopathy
Basement membrane remodeling, mesangial matrix expansion, capillary obliteration, foot process effacement

Clinical manifestations
Reduced graft function, proteinuria

Allograft loss

Fig. 112.6 Evolution of antibody-mediated graft damage from the binding of donor-specific antibodies (DSA) to graft loss. NK, Natural killer.

activation occur long before GBM duplication and graft dysfunction are evident, implying that endothelial injury is the initial insult that resulted in GBM remodeling.55 An association between transplant glomerulopathy and peritubular capillary basement membrane duplication has been well described, suggesting that the process resulting in transplant glomerulopathy involves the entire glomerular and peritubular capillary beds.56 57 It is currently debated whether transplant glomerulopathy represents scarring that is refractory to treatment.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A

B

Fig. 112.7 Histologic Features of Chronic Allograft Injury and Interstitial Fibrosis–Tubular Atrophy With No Evidence of Specific Cause. (A) Interstitial fibrosis and glomerulosclerosis. (Trichrome stain.) (B) Fibrointimal proliferation in an intrarenal artery. (PAS stain.)

PATHOLOGY

Chronic IFTA (Fig. 112.7) represents the final pathway of nephron injury and is not specific for any graft disease. IFTA is found in most late graft biopsies, whether a result of early graft damage (e.g., tubular injury from ischemia reperfusion injury, overt or subclinical rejection, or even preexisting disease of the donor) or later graft damage (secondary to CNI toxicity, hypertension and hyperlipidemia, recurrent glomerular disease, or immune-mediated injury) or of unknown origin (IFTA).

Chronic antibody-mediated rejection is characterized by structural remodeling of glomerular basement membranes (GBMs; so-called transplant glomerulopathy) and similar changes in the peritubular capillaries together with IFTA and fibrous thickening of arteries (see Figs. 112.2–112.4). Transplant glomerulopathy is characterized by duplication of glomerular capillary basement membranes and mesangial matrix expansion, in the absence of immune deposits. In addition, deposition of C4d in peritubular and glomerular capillaries can sometimes occur (see Fig. 112.3). Clinicopathologic studies suggest that transplant glomerulopathy is a manifestation of capillary injury occurring in conjunction with interstitial, peritubular capillary, and glomerular inflammation, although it also may occur independently of IFTA or transplant arteriopathy.54 On electron microscopy (EM), there is expansion of the subendothelial space with deposition of flocculent or fibrillary material, interposition of mesangial cell cytoplasm in the lamina densa, and mesangial matrix expansion (see Fig. 112.4). EM may be used to diagnose transplant glomerulopathy at its earliest stages. Ultrastructural abnormalities characteristic of endothelial

When chronic allograft injury has been identified by a gradual rise in serum creatinine and/or by new or worsening proteinuria, ultrasound should be performed to exclude ureteral or vascular problems and assess the Doppler resistive index. The Doppler resistive index gives an estimate of intrarenal (but also systemic) compliance and is most useful in longitudinal studies in the same patient to assess progressive graft vascular injury.

In addition, testing for BK virus in plasma is also advised during deteriorating graft function and for all kidney transplant recipients at 3-month intervals during the first 2 years after transplantation.

Circulating HLA alloantibodies also should be documented during graft dysfunction and may further guide diagnostics and therapy.

Many centers now perform routine HLA alloantibody screening in stable graft recipients at different time points after transplantation to facilitate early diagnosis of antibody-mediated rejection. According to the 2013 The Transplantation Society Consensus Guidelines, nonsensitized first kidney transplant recipients should be tested for DSAs at least once 3 to 12 months after transplantation.52 In presensitized patients, more frequent testing is recommended. Although there is consensus that HLA alloantibodies are responsible for a significant proportion of late graft losses and that HLA antibodies in the context of deteriorating graft function are harmful, the significance of HLA alloantibodies that are detected solely during routine testing is uncertain.58 59

Allograft biopsy is required to rule out a specific allograft pathology together with specific staining, such as C4d, for detection of antibodymediated allograft injury in all patients and SV40 if there is suspicion for BK virus nephropathy. Other specific examinations of the biopsy specimen for immunoglobulins, complement components, or EM may in addition be useful to rule out recurrence of primary kidney disease or de novo GN. The role of protocol biopsies in the early detection of chronic allograft injury remains controversial.

Diagnosing allograft injury from blood samples represents a new area of research. For example, donor-derived cell-free DNA (ddcfDNA) comes from the transplanted organ and is exogenous to the respective kidney transplant recipient. An increase of dd-cfDNA levels in the peripheral blood seems to occur even before the serum creatinine level starts rising, which may enable early diagnosis of transplant injury und ultimately avoid premature graft loss.60 However, randomized controlled trials are still lacking and no firm recommendations can be made.61

Because the etiology of chronic allograft dysfunction is multifactorial, any specific diagnosis is made by combination of a biopsy with a review of the patient’s history to identify important etiologic factors, such as preexisting donor disease, prior rejection, and high-titer antiHLA antibodies, as well as issues not related to alloimmunity, such as CNI nephrotoxicity, de novo GN, or recurrent kidney disease. Chronic allograft dysfunction is common and can have many causes. If it is left untreated, it can ultimately result in kidney injury, which, in turn, will heal by scarring and interstitial fibrosis and progress to ESKD.

Prevention of Antibody-Mediated Allograft Injury

In the absence of established treatments of circulating DSAs and chronic antibody-mediated rejection, only prevention of antibody-mediated allograft injury is effective in preventing future graft loss.

Once harmful HLA antibodies such as C1q-binding DSA are detectable, it becomes very difficult to avoid allograft injury and decline of kidney function. Preventive measures include avoidance of sensitization by limitation of blood transfusions and poor HLA matching during first transplantations.62 63 The introduction of epoetin led to a dramatic decrease of recipient sensitization by a significant reduction in blood transfusions.64 Sensitization should especially be avoided in young patients who may require retransplantation during their lifetime. New measures, such as matching for antibody epitopes in addition to whole HLA alleles, may further help preventing sensitization.

When the patient is already sensitized, antibody-mediated allograft injury can best be prevented by transplantation of the patient with an organ against which the recipient has not developed HLA alloantibodies. This may be achieved by inclusion of patients in special programs such as Eurotransplant Acceptable Mismatch Program or by kidney-paired donation.64 65 However, successful transplantation in patients with preexisting HLA alloantibodies usually requires desensitization in combination with other measures.66

After transplantation, chronic antibody-mediated allograft rejection is best prevented by conventional triple-drug therapy including a CNI (preferably tacrolimus), an antiproliferative agent (preferably mycophenolic acid–based therapy), and corticosteroids. Induction therapy, with an interleukin-2 receptor antagonist or antithymocyte globulin, should be used to prevent early acute cellular rejection. Insufficient immunosuppression and nonadherence may lead, unless a patient is prone to tolerance, to cellular rejection and then, via development of de novo DSA, to antibody-mediated rejection and graft loss. Precise knowledge of the patient's alloantibody status before and after transplantation is a prerequisite for early diagnosis of allograft injury and early and targeted treatment to prevent antibody-mediated rejection and ensure long-term graft survival. HLA alloantibodies should be tested at least once after transplantation in all patients. In immunologically high-risk patients, desensitized patients, patients with suspected rejection, and during therapy of antibody-mediated rejection, antibodies need to be monitored more frequently with the goal of recognizing allograft injury in its early stages and preventing its progression to chronic rejection.52 Additional patient groups who may benefit from HLA alloantibody monitoring are patients who receive reduction, withdrawal, or change of immunosuppressive drugs, especially in the context of CNI- or steroid-free regimens. Protocol biopsies may further help in guiding posttransplant therapy at least in high-risk recipients, although definitive proof is lacking.

Strategies for the prevention of chronic allograft injury are summarized in Box 112.2

Treatment of Chronic Allograft Injury

Although reduction of blood pressure to less than 130/80 mm Hg is believed to be beneficial, the preferred agent for blood pressure reduction remains controversial; in particular the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor

BOX 112.2 Strategies for the Prevention of Chronic Allograft Injury

- Avoid sensitization in future organ recipients (e.g., avoid blood transfusions, avoid poor HLA matching during first transplantation).
- Obtain complete donor and recipient typing and precise knowledge on HLA

alloantibodies at time of transplantation.
- Minimize ischemia/reperfusion injury (e.g., short cold ischemia time).
- Avoid insufficient immunosuppression.
- Perform prophylaxis for CMV (first 3–6 months).
- Test for BK virus after transplantation.
- Monitor donor-specific HLA alloantibodies after transplantation (at least in presensitized patients or during drug minimization).
- Perform protocol biopsies to detect subclinical rejection (at least in presensitized patients or during drug minimization).
- Review for nonadherence.

CMV, Cytomegalovirus; HLA, human leukocyte antigen.

BOX 112.3

Injury

Treatment of Chronic Allograft

Treatment (Nonimmune)
- Treat hypertension (consider ACE inhibitors or AT1 receptor antagonists)
- Lifestyle modification (stop smoking, control lipids)
- Control diabetes
- Prevention and treatment of urinary tract infection
- Target CNI toxicity by reduction or replacement of CNI (caveat: risk for insufficient immunosuppression)

Treatment (Alloimmune)
- Diagnose and treat early acute cellular rejection by steroids or antithymocyte globulin
- Diagnose and treat acute antibody-mediated rejection by means such as plasmapheresis or immunoadsorption ± anti-CD20 therapy
- Diagnose and treat chronic antibody-mediated rejection by means such as intravenous immunoglobulins ± anti-CD20 therapy
- Consider proteasome inhibitor, CD38 inhibitors, IL-6 receptor inhibitor, complement blockade, or the cysteine protease imlifidase (no clear evidence).

ACE, Angiotensin-converting enzyme; AT1, angiotensin 1 receptor;
CNI, calcineurin inhibitor.

blockers (ARBs) has not uniformly shown benefit.[67,68] Nor have there been specific studies confirming the benefits of reducing proteinuria in chronic allograft injury, although by extrapolation for other progressive proteinuric diseases, there is strong a priori evidence for the benefits of renin-angiotensin system blockade with dietary salt restriction.

A beneficial effect of treating dyslipidemia with statins in the transplant recipient also remains controversial,[69,70] and the adverse effects of statins such as rhabdomyolysis when used with CNIs must be considered. After a specific diagnosis had been established, targeted treatments can be initiated. These are summarized in Box 112.3

SELF-ASSESSMENT QUESTIONS

1. Which one of the following is believed to be mainly responsible for late kidney graft loss?
A. Hypertension and hyperlipidemia
B. New-onset diabetes after transplantation
C. Recurrence of primary disease
D. HLA alloantibodies
E. Calcineurin inhibitors
2. Chronic antibody-mediated rejection:
1. may be C4d negative in graft biopsy samples.
2. has specific histopathologic features.
3. is found more often in patients nonadherent to immunosuppressive medication.
4. can be mediated only by HLA alloantibodies.
5. is targeted by reduction of immunosuppression.
A. 1 and 2 are correct

B. 1, 2, 3, and 4 are correct
C. 1, 2, and 3 are correct
D. All are correct
E. No answer is correct
3. Clinical manifestations of chronic antibody-mediated rejection are:
1. a rise in serum creatinine.
2. a rise in protein excretion.
3. specific for chronic antibody-mediated rejection.
4. often late signs that occur after significant allograft damage has already occurred.
A. Only 1 is correct
B. 1 and 2 are correct
C. All are correct
D. 1, 2, and 3 are correct
E. 1, 2, and 4 are correct

REFERENCES

1. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357:2562–2575.
2. Süsal C, Döhler B, Sadeghi M, et al. HLA antibodies and the occurrence of early adverse events in the modern era of transplantation: a collaborative transplant study report. Transplantation. 2009;87:1367–1371.
3. Dragun D, Müller DN, Bräsen JH, et al. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. N Engl J Med. 2005;352(6):558–569.
4. Reindl-Schwaighofer R, Heinzel A, Kainz A, et al. Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: genome-wide analysis in a prospective cohort. Lancet. 2019;393(10174):910–917.
5. Lefaucheur C, Louis K, Philippe A, Loupy A, Coates PT. The emerging field of non-human leukocyte antigen antibodies in transplant medicine and beyond. Kidney Int. 2021;100(4):787–798.
6. Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349:2326–2333.
7. Hidalgo LG, Campbell PM, Sis B, et al. De novo donor-specific antibody at the time of kidney transplant biopsy associates with microvascular pathology and late graft failure. Am J Transplant. 2009;9:2532–2541.
8. Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney meeting report (I): Updates on and clarification of criteria for T cell- and antibodymediated rejection. Am J Transplant. 2020;20:2318–2331.
9. Mengel M, Sis B, Haas M, et al. Banff 2011 meeting report: new concepts in antibody-mediated rejection. Am J Transplant. 2012;12:563–570.
10. Bos EM, Leuvenink HG, van Goor H, Ploeg RJ. Kidney grafts from brain dead donors: inferior quality or opportunity for improvement? Kidney Int. 2007;72:797–805.
11. Young A, Kim SJ, Speechley MR, et al. Accepting kidneys from older living donors: impact on transplant recipient outcomes. Am J Transplant. 2011;11:743–750.
12. Kainz A, Perco P, Mayer B, et al. Gene-expression profiles and age of donor kidney biopsies obtained before transplantation distinguish medium term graft function. Transplantation. 2007;83:1048–1054.
13. Halloran PF, Melk A, Barth C. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. J Am Soc Nephrol. 1999;10:167–181.
14. Saxena AB, Busque S, Arjane P, et al. Preoperative renal volumes as a predictor of graft function in living donor transplantation. Am J Kidney Dis. 2004;44:877–885.
15. Gratwohl A, Dohler B, Stern M, Opelz G. H-y as a minor histocompatibility antigen in kidney transplantation: a retrospective cohort study. Lancet. 2008;372:49–53.
16. Zeier M, Dohler B, Opelz G, Ritz E. The effect of donor gender on graft survival. J Am Soc Nephrol. 2002;13:2570–2576.
17. Schwarz A, Mengel M, Gwinner W, et al. Risk factors for chronic allograft nephropathy after renal transplantation: a protocol biopsy study. Kidney Int. 2005;67:341–348.
18. Kim IK, Bedi DS, Denecke C, et al. Impact of innate and adaptive immunity on rejection and tolerance. Transplantation. 2008;86:889–894.
19. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. JAMA. 2009;302:1067–1075.
20. Schnuelle P, Schmitt WH, Weiss C, et al. Effects of dopamine donor pretreatment on graft survival after kidney transplantation: a randomized trial. Clin J Am Soc Nephrol. 2017;12:493–501.
21. Niemann CU, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. N Engl J Med. 2015;373:405–414.
22. Kuypers DR, Chapman JR, O’Connell PJ, et al. Predictors of renal transplant histology at three months. Transplantation. 1999;67:1222–1230.
23. Nickeleit V, Singh HK, Randhawa P, et al. The Banff Working Group classification of definitive polyomavirus nephropathy: morphologic

definitions and clinical correlations. J Am Soc Nephrol. 2018;29(2):680–693.
24. Hirsch HH, Randhawa P. Bk polyomavirus in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):179–188.

25. Nankivell BJ, Borrows RJ, Fung CL, et al. Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. Transplantation. 2004;78:557–565.
26. Benigni A, Bruzzi I, Mister M, et al. Nature and mediators of renal lesions in kidney transplant patients given cyclosporine for more than one year. Kidney Int. 1999;55:674–685.
27. Antonovych TT, Sabnis SG, Austin HA, et al. Cyclosporine a-induced arteriolopathy. Transplant Proc. 1988;20:951–958.
28. Austin 3rd HA, Palestine AG, Sabnis SG, et al. Evolution of ciclosporin nephrotoxicity in patients treated for autoimmune uveitis. Am J Nephrol. 1989;9:392–402.
29. Mengel M, Mihatsch M, Halloran PF. Histological characteristics of calcineurin inhibitor toxicity—there is no such thing as specificity. Am J Transplant. 2011;11:2549–2550.
30. Gaston RS, Cecka JM, Kasiske BL, et al. Evidence for antibodymediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90:68–74.
31. Briganti EM, Russ GR, McNeil JJ, et al. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002;347:103–109.
32. Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Collaborative transplant study. Kidney Int. 1998;53:217–222.
33. Kasiske BL, Kalil RS, Lee HS, Rao KV. Histopathologic findings associated with a chronic, progressive decline in renal allograft function. Kidney Int. 1991;40:514–524.
34. Nankivell BJ, Borrows RJ, Fung CL, et al. Natural history, risk factors, and impact of subclinical rejection in kidney transplantation. Transplantation. 2004;78:242–249.
35. Rush D, Nickerson P, Gough J, et al. Beneficial effects of treatment of early subclinical rejection: a randomized study. J Am Soc Nephrol. 1998;9:2129–2134.
36. Schaefer SM, Susal C, Sommerer C, et al. Current pharmacotherapeutical options for the prevention of kidney transplant rejection. Expert Opin Pharmacother. 2013;14:1029–1041.
37. Einecke G, Sis B, Reeve J, et al. Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009;9:2520–2531.
38. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14:272–283.
39. Amico P, Honger G, Mayr M, et al. Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads. Transplantation. 2009;87:1681–1688.
40. Gloor JM, Winters JL, Cornell LD, et al. Baseline donor-specific antibody levels and outcomes in positive crossmatch kidney transplantation. Am J Transplant. 2010;10:582–589.
41. Lefaucheur C, Loupy A, Hill GS, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol. 2010;21:1398–1406.
42. Opelz G, Dohler B. Effect on kidney graft survival of reducing or discontinuing maintenance immunosuppression after the first year posttransplant. Transplantation. 2008;86:371–376.
43. Liefeldt L, Brakemeier S, Glander P, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. Am J Transplant. 2012;12:1192–1198.
44. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant. 2012;12:1157–1167.
45. Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med.

2013;369:1215–1226.
46. Zou Y, Stastny P, Süsal C, et al. Antibodies against mica antigens and kidney-transplant rejection. N Engl J Med. 2007;357:1293–1300.
47. Dragun D, Muller DN, Brasen JH, et al. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. N Engl J Med. 2005;352:558–569.
48. Terasaki PI. Humoral theory of transplantation. Am J Transplant. 2003;3:665–673.

49. Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2011.
50. Tait BD, Süsal C, Gebel HM, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. Transplantation. 2013;95:19–47.
51. Loupy A, Aubert O, Orandi BJ, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. BMJ. 2019;366:l4923.
52. Gloor JM, Sethi S, Stegall MD, et al. Transplant glomerulopathy: subclinical incidence and association with alloantibody. Am J Transplant. 2007;7:2124–2132.
53. Wavamunno MD, O’Connell PJ, Vitalone M, et al. Transplant glomerulopathy: ultrastructural abnormalities occur early in longitudinal analysis of protocol biopsies. Am J Transplant. 2007;7:2757–2768.
54. Ivanyi B. Transplant capillaropathy and transplant glomerulopathy: ultrastructural markers of chronic renal allograft rejection. Nephrol Dial Transplant. 2003;18:655–660.
55. Regele H, Bohmig GA, Habicht A, et al. Capillary deposition of complement split product c4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: a contribution of humoral immunity to chronic allograft rejection. J Am Soc Nephrol. 2002;13:2371–2380.
56. Süsal C, Morath C. Current approaches to the management of highly sensitized kidney transplant patients. Tissue Antigens. 2011;77:177–186.
57. Morath C, Opelz G, Zeier M, Susal C. Prevention of antibody-mediated kidney transplant rejection. Transpl Int. 2012;25:633–645.
58. Oellerich M, Shipkova M, Asendorf T, et al. Absolute quantification of donor-derived cell-free DNA as a marker of rejection and graft injury in kidney transplantation: results from a prospective observational study. Am J Transplant. 2019;19(11):3087–3099.
59. Filippone EJ, Farber JL. The monitoring of donor-derived cell-free DNA in kidney transplantation. Transplantation. 2021;105(3):509–516.
60. Meier-Kriesche HU, Scornik JC, Susskind B, et al. A lifetime versus a graft life approach redefines the importance of HLA matching in kidney transplant patients. Transplantation. 2009;88:23–29.

61. Vella JP, O’Neill D, Atkins N, et al. Sensitization to human leukocyte antigen before and after the introduction of erythropoietin. Nephrol Dial Transplant. 1998;13:2027–2032.
62. Claas FH, Rahmel A, Doxiadis II . Enhanced kidney allocation to highly sensitized patients by the acceptable mismatch program. Transplantation. 2009;88:447–452.
63. Montgomery RA. Renal transplantation across HLA and ABO antibody barriers: Integrating paired donation into desensitization protocols. Am J Transplant. 2010;10:449–457.
64. Morath C, Beimler J, Opelz G, et al. An integrative approach for the transplantation of high-risk sensitized patients. Transplantation. 2010;90:645–653.
65. Opelz G, Zeier M, Laux G, et al. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. J Am Soc Nephrol. 2006;17:3257–3262.
66. Heinze G, Mitterbauer C, Regele H, et al. Angiotensin-converting enzyme inhibitor or angiotensin ii type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol. 2006;17:889–899.
67. Wiesbauer F, Heinze G, Mitterbauer C, et al. Statin use is associated with prolonged survival of renal transplant recipients. J Am Soc Nephrol.

2008;19:2211–2218.
68. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003;361:2024–2031.
69. Seron D, Oppenheimer F, Pallardo LM, et al. Fluvastatin in the prevention of renal transplant vasculopathy: results of a prospective, randomized, double-blind, placebo-controlled trial. Transplantation. 2008;86:82–87.
70. Nankivell BJ, Kuypers DRJ. Diagnosis and prevention of chronic kidney allograft loss. Lancet. 2011;378:1428–1437.

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Recurrent Disease in Kidney Transplantation

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Kidney transplantation is a treatment, not a cure. Although transplantation can restore kidney function, it rarely removes the cause of the original kidney disease and recurrence is dreaded by patients and clinicians alike. Globally, glomerulonephritis (GN) and diabetes are the two leading causes of kidney failure and are the most common primary diseases in patients undergoing kidney transplantation. That both GN and diabetes can recur after transplantation is a source of consternation for recipients and clinicians.

Recurrence is typically a time-dependent phenomenon. The likelihood of recurrence increases as the graft ages. With increased graft survival rates over the past 30 years, the apparent incidence of recurrence has grown.[1,2] An analysis of U.S. Renal Allograft Disease Registry data examining GN recurrence demonstrated a prevalence of 2.8% at 2 years, 9.8% at 5 years, and 18.5% at 8 years of follow-up after transplantation, and such patients were twice as likely to experience graft failure compared with those without recurrence.[3]

Recurrence has a powerful adverse impact on transplant survival, which is increasingly apparent as time since transplantation lengthens. In an analysis of data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) including more than 7968 patients with GN who received a kidney transplant, biopsy-proven recurrence was found in approximately 10% over the median follow-up time of 8.6 years, with 45% of those losing their graft within 5 years of the recurrence[2] (Fig. 113.1). For those with GN, recurrent disease is the third most common cause of graft loss after the first year after transplantation, behind death with a functioning graft and chronic rejection (CR) but substantially ahead of acute rejection (see Fig. 113.1).[4]

However, for those with known recurrent disease, it is the most common cause of graft loss.[2]

De novo GN and new-onset diabetes after transplantation (NODAT) may affect the transplanted kidney, although both are relatively uncommon causes of graft failure and may be difficult to distinguish from recurrence or from CR. Like recurrent disease, the prevalence of both appears to increase with time after transplantation. Given the high incidence of NODAT and increasing graft survival in recent eras, de novo diabetic nephropathy may become a significant clinical problem in the future. However, the major impact of NODAT in the first 10 years after transplantation is an increase in cardiovascular (CV) mortality with little impact on death-censored graft failure.[5]

DEFINITIONS

Diagnosis of recurrence requires histologic demonstration of the same disease involving both the native and transplanted kidneys. Diagnosis of recurrence causing graft failure requires a clinical decision that recurrence was the dominant contributor to graft loss (other contributors, such as CR, may be present).

The incidence of recurrent disease is probably underestimated because a histologic diagnosis of the primary kidney disease is not always obtained, and many transplant biopsies are not done with recurrent disease in mind, so immunohistologic and electron microscopic (EM) examination (mandatory for optimal diagnosis of recurrent disease) may not be undertaken.[1] In addition, a clinical diagnosis of CR is often made in patients with declining graft function and proteinuria, so that recurrent disease is not properly excluded.

Additional factors confound the available evidence. Many reports of disease recurrence are retrospective, single-center studies. Recall bias and incomplete documentation, changes in practice over time, and peculiarities of local patient populations and local practices may limit relevance to other populations. The most definitive reports have come from analyses of the large registry databases of Europe, the United States, and Australasia (the latter registry being known as ANZDATA). Registries capture data on large numbers of patients but are still subject to bias because of factors including unit participation rates, quantity and type of data collected, accuracy, consistency of reporting, and reliability of data entry. How recurrence is defined and diagnosed and which outcomes are measured is crucial. For example, immunoglobulin A nephropathy (IgAN) recurred in 58% of patients in one series in which all recipients underwent biopsy,6 but in approximately 25% of cases in which biopsy was performed only when clinically indicated.7 When graft loss from IgAN recurrence is the outcome measure, the risk decreased to approximately 10% at 10 years of follow-up.4 Thus, definition of recurrence, outcome measures, study design, era, and source of data all need to be considered in assessing the published literature.

RECURRENT GLOMERULONEPHRITIS

Many types of GN may recur after transplantation; however, the rate and consequences of recurrence vary enormously. For example, anti–glomerular basement membrane disease (anti-GBM; Goodpasture disease) recurs only rarely, but when it does, it is likely to cause rapid graft loss. In contrast, C3 glomerulopathy (formerly known as dense deposit disease and/or type II membranoproliferative glomerulonephritis [MPGN]) recurs in over 80% of patients; however, the disease tends to be very slowly progressive, and graft survival beyond 10 years is typical. Recurrence of focal segmental glomerulosclerosis (FSGS), IgAN, and membranous nephropathy (MN) are the most frequently encountered clinical problems (Fig. 113.2).

Several factors may influence the risk for recurrence in addition to the type of GN. Time since transplantation is clearly important and may be related to the duration of graft exposure to the nephritogenic factors responsible for GN.1 Those grafts that survive long term are exposed to nephritogenic factors for longer and are more likely to develop recurrent GN. Consistent with this, recipients of human leukocyte antigen (HLA)-identical transplants rarely experience rejection

Recurrent Glomerulonephritis and
Other Causes of Kidney Allograft Failure
1.00

Graft survival

0.95
0.90
0.85
Acute rejection
Glomerulonephritis recurrence
Death with allograft function
Chronic rejection

0.80
0.75

0

1

2

3

4
5
6
7
Years posttransplant

8

9

10

Fig. 113.1 Recurrent Glomerulonephritis (GN) and Other Causes of Kidney Allograft Failure. Kaplan-Meier analysis of the relative contributions of acute rejection, GN recurrence, death, and chronic rejection to graft loss during the first 10 years after transplantation among patients who underwent transplantation because of end-stage kidney disease caused by GN. (Modified from Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002;347[2]:103–109.)

Primary Glomerulonephritis
and Kidney Allograft Failure
1.00

Graft survival

0.95
0.90
0.85

MPGN type I
FSGS
MN
IgAN
PIC GN

0.80
0.75

0

1

2

3

4
5
6
7
Years posttransplant

8

9

10

Fig. 113.2 Primary Glomerulonephritis (GN) and Kidney Allograft Failure. Kaplan-Meier analysis of freedom from graft loss caused by recurrent GN during the first 10 years after kidney transplantation among patients with a primary diagnosis of GN. FSGS, Focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; PIC GN, pauciimmune crescentic glomerulonephritis. (Modified from Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002;347[2]:103–109.)

and enjoy prolonged graft survival but have a high rate of recurrent GN.8 In one report of HLA-identical recipients, recurrent GN was present in 36% to 42% of those in whom biopsy was performed and resulted in 24% of graft losses, being the second most frequent cause of graft loss after death in this group.8 Patients sustaining first graft loss from recurrent GN are also at higher risk for recurrence in a subsequent graft.

Improvements in immunosuppression over the past 40 years have led to reduced rates of acute rejection. Such improvements also may have had an impact on rates of graft loss from IgAN recurrence, which

has declined by nearly 50% over the past 10 years according to one ANZDATA registry analysis.9

U.S. Renal Data System (USRDS) registry data failed to demonstrate that any individual immunosuppressive agent is superior for preventing recurrence.10 Nevertheless, the immunosuppressive regimen may be important. For example, one small retrospective study found that induction therapy with rabbit antithymocyte globulin was associated with a lower risk for IgAN recurrence compared with either anti-CD25 antibodies or no induction.11 Corticosteroid withdrawal may lead to increased rates of recurrence,12 especially in recipients with IgAN, in whom a twofold increase in the risk for graft failure from recurrence of IgAN has been reported.9 Similarly, inclusion or addition of cyclophosphamide to immunosuppressive regimens may treat recurrent vasculitis affecting the graft.13 Sirolimus or everolimus may result in proteinuria and kidney dysfunction, especially in patients with underlying GN, suggesting that mammalian target of rapamycin (mTOR) inhibition may accelerate preexisting glomerular injury in the graft.14 Effects of individual agents are likely to be disease-specific, but the necessary data remain sparse.

Strategies to reduce the risk for recurrence have been reported. Bilateral native nephrectomy to eliminate persistent antigenic stimulation appears unhelpful; indeed, nephrectomized patients experienced a higher incidence of recurrence compared with those with native kidneys left in situ in one large single-center retrospective study.15 Induction of disease remission before transplantation and prolonged time on dialysis pretransplantation (both aimed at permitting disease “burnout”) do not appear to be effective except in the case of antiGBM disease, in which a delay in transplantation until the patient has been serologically negative for at least 6 months virtually eliminates the risk for recurrence.4 Avoiding living related donation to recipients with FSGS has been debated for years but overall appears not to have any impact on risk of recurrence.16

As with GN in native kidneys, proteinuria, deterioration in kidney function and, to a lesser extent, hematuria are the cardinal manifestations of recurrent GN.17 The pattern of kidney and extrarenal manifestations is frequently similar to that of the native disease, except that the overall rate of progression may be slower. Extrarenal features of the primary condition may recur, such as thrombocytopenia and hemolysis in hemolytic uremic syndrome (HUS) and extrarenal vasculitis in recurrent antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Serology may be helpful in some patients, such as anti-GBM antibody detection in those with Goodpasture disease, but not necessarily in others, such as those with recurrent lupus nephritis (LN).

The differential diagnosis of recurrent GN is clinically important because it may influence management (Table 113.1). Chronic rejection and diabetic nephropathy, recurrent or de novo, may manifest with progressive graft dysfunction, proteinuria, and hypertension and may therefore be clinically indistinguishable from recurrence. De novo GN also should be considered. Viral diseases of the kidney should be considered (particularly BK nephropathy) because reducing immunosuppression, and in selected instances, antiviral drugs may provide benefit. Obstructive uropathy and tumors involving the graft should be excluded by an ultrasound scan. Finally, recurrence may coexist with chronic rejection or calcineurin inhibitor (CNI) toxicity. Indeed, every condition that can lead to chronic graft dysfunction should be considered in the differential diagnosis of recurrence (see Table 113.1 and Chapters 109 and 110).

Histologic evidence of recurrence is required in all patients. Biopsy can provide the diagnosis, exclude alternative diagnoses that may require different approaches to treatment, and provide important prognostic information pertinent to the affected graft and also relevant to any future consideration of retransplantation. Full evaluation of

TABLE 113.1

Differential Diagnosis of Recurrent Glomerulonephritis

Diagnosis

Frequency and Timing

Recurrent glomerulonephritis

De novo glomerulonephritis
Chronic rejection

Graft pyelonephritis

BK nephropathy

Clinical Features

Laboratory Features Biopsy Features

Management

Common; variable timing, days to years

Proteinuria, hematuria, kidney impairment, hypertension

Same as primary glomerulonephritis5

Disease specific

Uncommon; variable timing but typically later than recurrence
Very common; increasing incidence with time

Proteinuria, hematuria, kidney impairment

Similar to primary glomerulonephritis; serology may be negative
Type specific

Type specific5,8

Antiprogression strategies (see Chapter 82)
Minimize calcineurin

inhibitor and
antiprogression
strategies (see
Chapter 82)
Antibiotics

Uncommon; typically
early after
transplantation
Uncommon; typically
1–5 y after
transplantation

Acute rejection

Common; early

Kidney tumor/PTLD

Uncommon, rare; early
or late

Hypertension,
proteinuria,
kidney impairment
Calcineurin inhibitor
exposure
Fever, pyuria, kidney
impairment

Tubulointerstitial
fibrosis, arteriolar
hyalinosis, transplant
glomerulopathy
Positive blood or urine
cultures

Neutrophil infiltration

Kidney impairment,
decoy cells in urine

Serum BK PCR positive

Kidney impairment,
oliguria
Kidney impairment,
kidney mass

Nonspecific

Tubulitis with tubular
cell atypia and
inclusions, normal
glomeruli
Tubulitis with or without
vasculitis[15]
Atypical cells, mitoses,
monoclonality

Anemia, EBV positive

Minimize
immunosuppression

and consider antiviral
drugs
Increase
immunosuppression
Minimize
immunosuppression,
consider
chemotherapy

EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PTLD, posttransplantation lymphoproliferative disease.

the biopsy specimen by light microscopy, immunohistology, and EM is desirable and, in many patients, essential to confirm recurrence.18 Light microscopy and immunohistology are necessary to differentiate recurrent from de novo GN, rejection, and CNI toxicity. The presence of tubulitis should suggest acute rejection. Chronic rejection may produce chronic interstitial inflammation and transplant glomerulopathy, which may be indistinguishable from MPGN on light microscopy (Fig. 113.3; see also Chapter 109). The use of immunohistology to define the immunoglobulin and complement component content of immune deposits and EM to establish the structure of basement membrane and location of deposits may clarify the diagnosis.18 The risk of recurrence for common histologic types of kidney disease is summarized in Table 113.2

RECURRENCE OF SPECIFIC GLOMERULAR DISEASES

Immunoglobulin A Nephropathy and IgA Vasculitis (Henoch-Schönlein Purpura)

IgAN is the most common form of GN leading to kidney failure, and affected patients frequently become transplant recipients. Histologic recurrence is frequent and increases with time since transplantation. Published recurrence rates vary greatly (from 8%–53%). Much of this variation appears to be because of study differences in biopsy indication (protocol or clinical) and length of posttransplant follow-up.19

The highest published recurrence rates are from centers performing protocol biopsies in addition to those that are clinically indicated. This is likely because the early stages of IgAN recurrence are frequently not accompanied by clinical changes, such as proteinuria, hematuria, or graft dysfunction.19

Recurrence is difficult to predict. No large prospective multicenter cohort studies demonstrate risk factors for histologic and/or clinical recurrence. Single-center studies and registry analyses suggest that younger age at transplantation, rapid progression of the native IgAN, degree of proteinuria, and donor factors (including HLA matching) may be associated with higher risk.17 The suspicion that living donor grafts have higher rates of recurrence than deceased donors has not been confirmed.17 Thus, patients with IgAN should not be precluded from consideration for living donor transplantation. The number of HLA mismatches between donor and recipient also may have a role in recurrence rates. Two Australian registry studies have found that those with zero mismatch kidneys have higher rates of recurrence than those with one or more HLA mismatches.9 20 Similarly, ABO-incompatible transplants have been found to have lower rates of recurrence, possibly because of differences in immunosuppression regimens.21

Choice of immunosuppression after transplantation is controversial. One large USRDS registry analysis suggested that individual drug choices did not affect the risk for graft loss attributed to recurrence.10 In contrast, a retrospective analysis of ANZDATA found that continuation of corticosteroids was strongly associated with protection from graft loss caused by recurrence of IgAN, although not from other types of GN.9 Observational data also suggest that induction with antithymocyte globulin may afford relative protection.[11]

The clinical expression of recurrent disease is variable and time dependent. Graft loss within the first 3 years after transplantation is uncommon (see Fig. 113.2), although it can occur, particularly when IgAN in the native kidney was rapidly progressive or after previous graft loss from recurrence.[7] An Italian cohort study of 190 patients followed for 15 years reported that of the 22% of patients who developed recurrence, almost a third ultimately lost their graft because of IgAN

A
B

C

Fig. 113.3 Transplant Glomerulopathy and Membranoproliferative Glomerulonephritis (MPGN). Transplant biopsy specimen from a patient with end-stage kidney disease caused by biopsy-proven idiopathic MPGN type I, who received a kidney transplant and had a progressive reduction in glomerular filtration rate with proteinuria 1.5 g/day and hypertension. (A) Light microscopy. Glomerular hypercellularity and lobulation on a background of chronic interstitial inflammation and fibrosis, with protein casts within dilated tubules. (Hematoxylin-eosin stain; ×100.) (B) Subendothelial deposits and basement membrane reduplication (arrow). (Methenamine silver stain; ×400.) (C) Electron microscopy showing subendothelial electron-dense deposits (arrows) (×7500). There were also prominent C3 deposits on immunofluorescence (not shown). Light microscopy was therefore suggestive of recurrent MPGN but was also consistent with chronic rejection (CR) with transplant glomerulopathy associated with CR. Immunofluorescence and electron microscopy (subendothelial deposits) confirmed recurrence of MPGN. Compare these images with Figs. 112.3 and 112.4. (A–B, Courtesy Dr. Paul McKenzie, Royal Prince Alfred Hospital, Sydney, Australia.)

recurrence during follow-up.22 Death-censored graft survival at 15 years was approximately 10% lower in patients who had IgAN than in controls, largely attributable to IgAN recurrence.

Recurrence of IgA vasculitis (IgAV) is less well characterized but appears to be similar to IgAN. An analysis of the United Network for Organ Sharing (UNOS) database including 339 patients with kidney failure caused by IgAV who received a first kidney allograft reported a frequency of graft loss caused by recurrence of 13.6% and no difference in 10-year graft survival between recipients with IgAN (58.4%) or IgAV (59.3%) as their primary kidney disease.23

Treatment of recurrent IgAN and IgAV has not been systematically evaluated. The addition of corticosteroid maintenance in corticosteroid-free patients with recurrence is unproven but reasonable. A change to mycophenolate mofetil (MMF) or the use of fish oil, antiplatelet agents, and tonsillectomy cannot be recommended. The use of nonspecific measures to prolong kidney survival is appropriate,

TABLE 113.2

Recurrent Diseases in Kidney Transplants and Effects on Graft Survival

Disease

Clinical Recurrence Rate (%)

Graft Loss in Recurrent Disease (%)

Primary focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis type 1
Dense deposit disease
Hemolytic uremic syndrome (HUS)
Classic D+ HUS
Atypical D− HUS
Familial HUS
IgA nephropathy

20–50 (children), 10–15 (adults)
20–30
80

40–50
30–40
20, often late

0–13
30–50
57
30–40, increases with longer duration of follow-up
(30%–60% histologic recurrence rate)
Rare (despite 50% histologic recurrence rate)
10–29 (histologic recurrence may be more common)
10–20

Uncommon
55–100
Approaching 100
16–33

<5
1–30
25

50
Rare
10–20

IgAV (Henoch-Schönlein purpura)
Membranous nephropathy
Systemic vasculitis, including granulomatosis and
microscopic polyangiitis
Anti-GBM disease (Goodpasture disease)
Systemic lupus erythematosus
Amyloidosis

Rare
Up to 50
20–50

GBM, Glomerular basement membrane; IgA, immunoglobulin A; IgAV, IgA vasculitis.

including tight blood pressure control, renin-angiotensin system (RAS) blockade, and avoidance of nephrotoxins.

Membranous Nephropathy

Histologic recurrence of MN can be found in up to 40% of grafts,24 and for those with documented recurrence, graft loss rates of over 50% at 3 years of follow-up have been reported.25 26 Patients who have previously lost a graft to recurrence are at higher risk on retransplantation, but disease course, duration of dialysis, HLA genotype, graft source, and immunosuppression have not been found to predict recurrence risk.26

In 2009 M-type phospholipase A2 receptor (PLA2R) was identified as the antigen targeted in 70% to 80% of idiopathic MN.27 This has spurred interest in the use of anti-PLA2R antibody titers in monitoring disease activity and predicting recurrence. A number of small single-center and multicenter observational studies suggested a role for the adoption of PLA2R measurement as a clinical tool in transplantation, with higher levels at transplantation associated with higher rates of recurrence.28–31 The largest of these studies reported a recurrence rate of 57% among patients with primary MN, with a median time to recurrence of 4.1 months.28 The positive predictive value of pretransplant anti-PLA2R antibodies was 83% (10 of 12), and the negative predictive value was 42% (5 of 12).28

Current data show that the presence of anti-PLA2R at the time of transplant increases the risk for recurrence; however, both sensitivity and specificity are imperfect and larger studies are required. At present, there is insufficient evidence to recommend delaying transplantation until anti-PLA2R antibody status is negative; however, rising titers should warrant caution and consideration of a delay in transplantation.

Management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. There has been some success with rituximab reported in small case series, but the findings await confirmation in a randomized trial. Spontaneous remission appears to be less common than is seen in MN affecting native kidneys. The cumulative exposure to immunosuppressive therapy should be considered because these patients may be at increased risk for lymphoma. Living donor transplantation appears warranted for first grafts but in our opinion should probably be avoided for second grafts if the first was lost early because of recurrence.

To diagnose recurrence requires a native kidney biopsy showing MN and a graft biopsy showing MN. This is especially important in MN, in which de novo MN has been reported in 2% to 15% of transplant recipients and tends to manifest more insidiously and later than recurrent MN.32

Focal Segmental Glomerulosclerosis

FSGS recurs in 20% to 30% of first transplants.33–35 FSGS is a heterogeneous group of conditions and those with familial or sporadic forms associated with mutation of slit-diaphragm proteins such as podocin do not recur, although rare cases of posttransplant nephrotic syndrome caused by the development of antibodies directed against the “neoantigen” within the donor kidney have been reported. FSGS secondary to obesity, vascular disease, or reflux nephropathy and those with a very slow rate of progression are at very low risk for recurrence. In contrast, patients with primary FSGS and in particular those with an aggressive initial course (heavy proteinuria and kidney failure within 3 years of onset), age younger than 15 years, mesangial hypercellularity on biopsy, or with recurrence in a previous graft are at greatest risk.34 35 The rate of recurrence is higher than 75% in subsequent grafts when the first graft was lost because of recurrence.36

Living related donor transplantation has previously been implicated as a risk factor for recurrence; however, a large USRDS analysis refutes this notion,16 and ANZDATA data show improved graft survival from living donors.37

Recurrence may occur early (typically within the first month posttransplantation) and initially manifests with heavy proteinuria, followed by hypertension and graft dysfunction. Patients with recurrent disease appear more susceptible to acute rejection and acute kidney injury38 and graft loss. Recurrence has been associated with early graft loss in up to 50% of patients33 34 37; however, treatment with plasma exchange appears to have delayed graft loss in many patients and decreased the incidence of overall graft failure4 33 (see Fig. 113.2).

Primary FSGS appears to be caused by a circulating factor that targets podocytes, although the specific factor(s) involved remain unknown. Soluble urokinase plasminogen activator receptor (suPAR) and the costimulatory protein B7-1 (CD80) have been proposed to mediate recurrence; however, reports have been anecdotal and subsequent studies have failed to prove the role of either molecule or consistently demonstrate success with therapies targeting them.39–43

Plasma exchange or immunoadsorption with either a protein A or anti-IgG column is effective for some patients who develop recurrent FSGS, presumably because it removes the circulating permeability factor.44 45 Although not studied in a randomized controlled trial (RCT), several series have reported disease remission in the majority of patients who receive treatment within 2 weeks of recurrence.45 46 The potential for positive publication bias and the absence of RCT evidence make prognostic information speculative; however, response rates appear likely to exceed 50% when therapy is commenced within 2 weeks of clinical recurrence, with lower response rates anticipated when therapy is delayed.46 Given that graft survival appears to be significantly prolonged in patients who respond to therapy, a course of plasma exchange is warranted in all patients without contraindications (see Chapter 104).

Immunosuppression should include a CNI, and the addition of an angiotensin-converting enzyme (ACE) inhibitor should be considered. A minority of patients with an incomplete response or relapse after cessation of initial therapy will require repeated or long-term plasma exchange47 or concurrent treatment with secondary agents such as rituximab or cyclophosphamide.45 47–49 For such patients, we recommend a course of rituximab 500 mg weekly for 4 weeks, in addition to existing immunosuppression and weekly plasma exchange. Pretransplantation plasma exchange has not been shown to be beneficial for preventing recurrence. See Fig. 113.4 for an approach to the management of recurrent FSGS.

Minimal change disease is a far less frequent cause of kidney failure. Recurrence of disease after transplantation has been reported; however, it is difficult to be sure that the underlying disease was not FSGS.

Membranoproliferative Glomerulonephritis

Glomerular diseases with an MGPN pattern of injury are classified into immune complex (IC-MPGN) and complement-mediated forms (see Chapters 22 and 23).50 51 Recurrent MPGN bears major clinical and histologic similarities with the subgroup of patients with CR who have transplant glomerulopathy, and comprehensive assessment of transplant biopsy specimens (see Fig. 113.3 and compare Figs. 112.3 and 112.4), as well as accurate diagnosis of the native kidney disease, is crucial in making this distinction (see Table 113.1). IC-MPGN, rather than transplant glomerulopathy, is suggested by the presence of crescents on light microscopy, stronger staining for C3 and weaker staining for IgM on immunohistologic examination, and subendothelial electron-dense deposits on EM.18 This distinction has important clinical implications, particularly because recurrence carries a higher risk for subsequent recurrence should retransplantation be considered. A

Approach to the Detection and Management of FSGS Recurrence

PRETRANSPLANTATION
Measure proteinuria
unless anuric

POSTTRANSPLANTATION
Measure proteinuria
Weekly for 4 weeks
Monthly for 6 months
or
whenever nephrosis suspected (edema, hypoalbuminemia)

Significant proteinuria
Increase compared with pretransplantation
by .1 g/24 h (uPCR .50 mg/mmol)

Transplant biopsy

Light microscopy
Immunohistology
Electron microscopy

If biopsy does not show FSGS
and patient not nephrotic
Monitor protein excretion weekly
and treat only if increasing
proteinuria
Note: If proteinuria is from
native kidneys, this will decline
over time

Consider treatment if
FSGS confirmed by biopsy
Biopsy unavailable but clinical nephrotic syndrome
Biopsy does not confirm FSGS, but increasing proteinuria/nephrotic syndrome

Treatment
Plasma exchange—9 treatments: daily for 3 days, then 3 times a week for 2 weeks
Immunosuppression—use CNI + corticosteroids + mycophenolate or azathioprine
(avoid sirolimus, everolimus)
Renin-angiotensin blockade—ACE inhibitor/ARB

Remission
1 g/24 h or uPCR

.

.

Proteinuria

Withhold plasma exchange
Monitor proteinuria monthly

50

1259

No remission
Proteinuria .1 g/24 h or uPCR .50
Further plasma exchange—weekly for 6 weeks,
titrate to response
Consider switch to cyclophosphamide 1-2 mg/kg/day
for 3-6 months or addition of rituximab 500 mg IV
weekly for 4 cycles to current regimen
If no response and severely nephrotic, consider
transplant nephrectomy

Fig. 113.4 Approach to the Detection and Management of Focal Segmental Glomerulosclerosis (FSGS)
Recurrence. Authors’ recommendation based on Davenport. 47 ACE, Angiotensin-converting enzyme; ARB,
angiotensin receptor blocker; CNI, calcineurin inhibitor; uPCR, urine protein-to-creatinine ratio.

retrospective analysis of kidney biopsies that included 70 patients with MPGN suggested that the severity of histologic lesions is predictive of recurrence.52

Immune Complex Membranoproliferative Glomerulonephritis

IC-MPGN appears to be mediated by glomerular deposition of immune complexes, triggered by exposure to endogenous or exogenous (e.g., hepatitis C virus [HCV]) antigens or related to a monoclonal gammopathy. Because the antigens are not necessarily removed by transplantation, recurrence of disease is possible and is seen in 20% to 45% of kidney recipients.50,53–56 Graft loss has been reported in up to 50% of those with recurrence, and the risk for recurrence in subsequent grafts approaches 80%.50,57–59 Significant geographic diversity in the risk for recurrence is evident, with much higher rates of graft loss resulting from recurrence in areas where the majority of patients with IC-MPGN are HCV positive, such as Spain,53 compared with lowHCV prevalence areas, such as Australia.4

No form of treatment for recurrent IC-MPGN has been proven effective, and the underlying cause of MPGN should be considered in each patient. In HCV-associated IC-MPGN, direct-acting antiviral therapy is effective for virus elimination and should provide substantial protection from HCV viremia and IC-MPGN recurrence after transplantation. Other forms of IC-MPGN have been successfully treated with immunosuppression or plasma exchange.

C3 Glomerulopathy

Complement-mediated MPGN, also referred to as C3 glomerulopathy, is a disease process secondary to dysregulated complement activation (see Chapter 23). There are two subtypes determined by EM appearance: C3 GN and dense deposit disease (DDD).51 DDD has clinical and histologic similarities to transplant glomerulopathy. It is suggested by granular staining for C3 on capillary loops without immunoglobulin deposits, and the characteristic ribbonlike intramembranous dense deposits on EM (see Fig. 22.2).18,60

DDD has been found to recur in 50% to 80% of grafts, typically manifesting with proteinuria, hematuria, and slowly progressive loss of kidney function.61 The disease course tends to be slow, and whereas graft loss caused by recurrence is ultimately seen in the majority of patients, this generally occurs beyond the first 10 years after transplantation.4,61 Graft loss has been associated with male sex, crescents on biopsy, and heavy proteinuria.61 No effective therapy is known, and although plasma exchange and immunosuppression have been described, these are not supported by good evidence, and control of blood pressure and proteinuria with RAS blockade is the preferred therapy. Given the role of alternate complement pathway mutations in DDD (see Chapter 23), administration of complement antagonists such as eculizumab may be beneficial but remain unproven, with inconsistent results reported in published case series to date.59,62–64

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome of the Finnish type has been reported to recur after transplantation and cause graft loss; however, the mechanism of kidney damage is likely different between primary and recurrent disease. The primary disorder in some cases is caused by a mutation of the NPHS1 gene that results in the complete absence of nephrin, and therefore transplantation causes de novo exposure to nephrin in the transplanted kidney. Neoantigen exposure may cause antibody development and deposition that damages the slit diaphragm and produces a type of MN with podocyte fusion on EM and a clinical picture of heavy proteinuria and ultimately graft failure. Cyclophosphamidebased rescue therapy may be successful.65

Antineutrophil Cytoplasmic Antibody–Associated PauciImmune Vasculitis

Kidney transplantation for ANCA-associated vasculitis (AAV) is associated with a reduction in the frequency of disease relapse by approximately 50% compared with patients remaining on dialysis, and patient and graft survival posttransplantation is similar to that in other transplant recipients.66

Recurrence rates in AAV appear to be declining over time. A 1998 pooled analysis of reported case series examining recurrence of AAV detected recurrence in 17% of the 127 included patients, with kidney involvement demonstrated in approximately 60% and graft losses reported in 25% of these.66 More recently, a review of transplant outcomes in AAV show a decline in recurrence rates to 1% to 2% per year in contemporary studies, possibly because of the improvement in immunosuppression regimens since the 1990s.67,68

Clinical parameters have not been found to be useful in predicting those patients most likely to relapse. Pretransplantation disease course, duration of dialysis, ANCA titers at time of transplantation and during follow-up, cytoplasmic ANCA (c-ANCA) or perinuclear ANCA (p-ANCA) pattern, antibody specificity to PR3 or MPO, disease subtype (granulomatous polyangiitis, microscopic polyangiitis, or kidney-limited vasculitis), and donor source have not been found to significantly impact recurrence rates.66,67

The prevention and management of relapse has not been prospectively examined. In most reports, patients did not receive a transplant until they were in clinical remission; however, successful transplantation in the face of persisting ANCA positivity is well recognized. In the absence of firm evidence, we recommend that clinical remission be maintained for 6 to 12 months before transplantation to reduce the risk for recurrence and also to avoid risks associated with performing transplantation in a debilitated patient, especially if kidney failure has occurred soon after presentation with systemic vasculitis.69 Monitoring ANCA to indicate AAV recurrence is commonly performed; however, the test performance characteristics in this context have not been reported. Patients with kidney relapses have generally been managed with cyclophosphamide-based regimens, as used for kidney vasculitis in native kidneys, which have been reported to be successful in inducing remission in 11 of 16 (69%) cases.66,67 No negative impact of the use of cyclophosphamide to treat relapse has been reported, but cumulative dose, if it had also been used pretransplant, would significantly increase the risk for bladder cancer and infertility. Significant interest exists in the use of rituximab for AAV recurrence posttransplant. Although current literature is limited to case reports, in our opinion, rituximab is a reasonable second-line alternative to cyclophosphamide in this context.67,70

Anti–Glomerular Basement Membrane Disease

Histologic recurrence of anti-GBM disease is seen in 50% of patients who receive a transplant while circulating anti-GBM antibodies persist but rarely when patients undergo transplantation 6 months or more after the disappearance of anti-GBM antibodies. With delayed transplantation, the rate of clinical recurrence is very low, and since the implementation of this practice in Australia, no grafts were lost after transplantation in 47 patients followed for up to 10 years.4 Rare episodes of recurrence should be treated as for native kidney disease with corticosteroids, cyclophosphamide, and aggressive plasma exchange (see Chapter 25).

Recurrent anti-GBM disease is distinct from de novo anti-GBM disease, which is seen in up to 15% of transplant recipients with Alport syndrome who develop anti-GBM antibodies in response to neoantigen exposure (α chain of type IV collagen) via the transplant.71 This is discussed further in Chapter 25.

Lupus Nephritis

The reported recurrence rate of LN has varied from 2% to 54% depending on the diagnostic criteria used.72 73 Recurrence has been reported early (days) and late (years) after transplantation, with a median time to recurrence of approximately 4 years.72 73 The clinical and histologic pattern of recurrence is variable but is typically more benign in histology and clinical expression than the patient's original disease. Although the majority of patients with kidney failure caused by lupus have had diffuse proliferative (class III or IV) LN, mesangial proliferative (class II) LN is the most commonly described lesion after transplantation, followed by class III and membranous LN (class V).73 Duration of dialysis and serologic activity before transplantation do not predict recurrence, and antinuclear antibody titer and complement levels are unreliable markers of disease recurrence. There is no consistent relationship between recurrence of nephritis and activity of extrarenal lupus after transplantation.

The long-term outcome for lupus patients after transplantation is controversial but appears similar to that of the general posttransplantation population.72 74 Although recurrence is an uncommon cause of graft loss within the first 10 years after transplantation, with no cases of graft loss reported from 86 recipients in one registry analysis,4 late graft losses do occur. It is clear that lupus patients, particularly those with a lupus anticoagulant, are at increased risk for thrombotic events after transplantation, including graft thrombosis.75

Management of recurrent LN has not been systematically studied; corticosteroids, cyclophosphamide, MMF, and plasma exchange have been used, with variable results reported. Anticoagulation during the perioperative and early posttransplantation phases should be considered for those with a history of thrombosis or lupus anticoagulant positivity. Successful retransplantation has been reported after graft loss caused by recurrence.75

Thrombotic Microangiopathy and Hemolytic Uremic Syndrome

Recurrence risk is dependent on the underlying cause of thrombotic microangiopathy (TMA). Typical childhood Shiga toxin–associated HUS seldom recurs, whereas recurrence of atypical HUS (aHUS), which is associated with dysregulation of the alternative complement pathway, occurs in up to 80% of patients depending on the mutations involved.76 77 The diagnosis of recurrent TMA, including HUS, is complicated by the fact that de novo TMA is seen in 1% to 5% of kidney transplant recipients, most commonly associated with the use of CNIs (both tacrolimus and cyclosporine carry a similar risk), sirolimus, or with acute vascular rejection. Drug-induced de novo TMA is generally observed within 14 days of drug commencement.

The risk for aHUS recurrence and its impact on graft survival is dependent on the complement pathway mutation responsible. Mutations in complement factor H are associated with a recurrence risk of approximately 75%, and more than 90% of those with recurrence incur graft failure, typically within the first year.76 78 In contrast, mutations of membrane cofactor protein are associated with a recurrence rate of only 20% and substantially better survival rates than in patients with factor H or I mutations.79 Given these variations in risk for recurrence, genotypic evaluation of the recipient and any potential living donors before transplantation is advisable for all patients with kidney failure caused by atypical HUS.80 Combined liver-kidney transplantation may be considered in selected candidates with defined mutations.81 Recurrence is generally within the first 6 months after transplantation, thought to be because of ischemia-reperfusion driven endothelial injury; however, late recurrences have been reported.77 The clinical presentation may be gradual or abrupt, with thrombocytopenia, hemolysis, and progressive kidney dysfunction.

Historically, treatment for recurrent aHUS has relied on withdrawal of any potential causative agent such as CNIs (with a temporary increase in the dose of corticosteroids to reduce the risk of acute rejection), and plasma exchange. This strategy was only modestly effective, for both first episode and posttransplant aHUS.76,82 The development of eculizumab, a humanized monoclonal antibody targeting C5 of the complement membrane attack complex, has revolutionized treatment for aHUS. In the last few years, a number of cohort studies and a large registry analysis have shown that the preemptive use of eculizumab in patients with aHUS leads to greatly reduced recurrence rates and improved graft survival.83–85 A meta-analysis of 13 cohort studies and five case series that included a total of 380 patients confirmed protection against recurrence when eculizumab was used preemptively, with recurrence seen in under 6% of cases. Commencement of eculizumab after development of posttransplant aHUS recurrence was also relatively effective, with graft loss reported in approximately 20% of 192 cases.86 Both outcomes were vastly superior to historical rates of recurrence and graft loss in those with recurrence. Although the responsible mutations were frequently not identified in this meta-analysis, where it was recorded, the most common mutations were complement factor H and I mutations, which have recurrence rates preeculizumab approaching 80%, with graft loss in those with recurrence of more than 90%, typically within the first year.78 A subsequent retrospective analysis of the impact of eculizumab found prophylactic use to be superior to initiation after recurrence in terms of graft survival.87 We recommend that eculizumab be commenced pretransplant (day of surgery or prior) for high-risk mutations including complement factor H, complement factor B, and C3 and/or previous graft recurrence, and considered for moderate risk mutations such as complement factor I or anticomplement factor H antibody.87 This position is supported by the 2016 KDIGO guidelines.80

There is less evidence to guide the decision on if and when to cease eculizumab. It is likely that this decision will differ for patients with different gene mutations. Recurrence rates decline after 12 to 24 months,76 so we would recommend waiting 24 months posttransplant before attempting cessation. After cessation, intensive monitoring of graft function, hemoglobin and platelet count, blood film, and serum LDH appear warranted in our opinion; however, this strategy has not been scientifically examined. Prompt reintroduction of eculizumab should be considered in cases of recurrence after eculizumab cessation.

Scleroderma

Few patients with scleroderma undergo kidney transplantation. The largest analysis of transplanted scleroderma patients consisted of 86 patients reported to the UNOS registry and showed graft survival of 62% at 1 year, 47% at 5 years after transplantation, and 27% at 10 years; 24% of recipients died during the 10-year observation period.88 The recurrence rate could not be accurately determined; however, recurrence was responsible for graft loss in 21% of patients in whom the cause was identified. A more recent analysis of 22 patients from the ANZDATA registry reported similar graft survival of 78% at 1 year, 53% at 5 years, and 28% at 10 years.89 The management of scleroderma after transplantation is unstudied; however, the use of RAS blockade after transplantation to treat hypertension would seem appropriate. Overall, kidney transplantation appears to be an appropriate treatment for those with scleroderma and kidney failure, in the absence of contraindications to transplantation such as severe scleroderma gut or lung disease.90

AMYLOID, LIGHT-CHAIN DISEASE, AND FIBRILLARY AND IMMUNOTACTOID GLOMERULOPATHIES

Amyloidosis

The risk and impact of recurrence for patients who undergo transplantation because of systemic amyloidosis are dependent on its

cause. Management of AL amyloid is primarily directed at treating the underlying plasma cell dyscrasia, most commonly by high-dose chemotherapy and autologous stem cell or allogeneic bone marrow transplantation. Recurrence after transplantation is likely if the malignancy is not fully controlled but may be susceptible to further chemotherapy. The largest reported series by Heybeli et al. includes 60 patients who received a kidney transplant for AL amyloid-induced kidney failure, roughly half of whom (28 patients) had asymptomatic cardiac involvement.91 Before kidney transplant, 51 of the 60 patients had received treatment for amyloidosis, which resulted in complete remission for 37 (62%) and partial remission in 11 (19%) patients.91 Of 9 patients who were treatment naïve at the time of kidney transplant, 7 were treated with melphalan and autologous stem cell transplant after kidney transplant, all of whom had complete remission.91 Death-censored graft survival was 98.3% at 1 year and 95.8% at 5 years. No grafts were lost through recurrence.91 Protocol biopsies were performed out to 10 years and revealed amyloid recurrence in the graft in 13 (22%) patients, with an estimated median time to recurrence of 122 months.91 Recurrence was predominantly observed in those with a poor response to initial chemotherapy. This paper built on previous work with small patient cohorts that revealed similar findings.92 93 Thus transplantation appears to be a viable option for patients with kidney failure caused by AL amyloidosis, provided they have achieved a good hematologic response to treatment.90

Secondary (AA) amyloidosis is typically a more insidious disease; kidney failure is a relatively frequent complication, and kidney transplantation is frequently effective.92 The risk for recurrence of AA amyloid depends on the ability to eradicate the underlying cause of chronic inflammation. In AA amyloid, recurrence as a result of chronic infection is unlikely if the infection can be eradicated pretransplantation, whereas conditions such as rheumatoid arthritis may persist after transplantation and lead to recurrent amyloid in the graft. Less than 5% of patients with AA amyloid associated with familial Mediterranean fever (which can be managed with colchicine after transplantation) have recurrence at 10 years after transplantation.94 A Norwegian series of 62 transplants in patients with AA amyloid, mostly secondary to rheumatic diseases, demonstrated a recurrence rate of 10% at an average of 5 years of follow-up, with recurrence causing graft loss in two patients only. Overall, patient and graft survival rates were 65% and 62%, respectively, at 5 years, with most losses resulting from infection.95

Light-Chain Nephropathy

Patients with light-chain nephropathy have occasionally received transplants, and recurrence is common; one case series reported recurrence in five of seven patients at a range of 2 to 45 months after transplantation. Those with recurrence developed proteinuria, hypertension, and progressive graft dysfunction. One of seven has had longterm graft function, and one died soon after transplantation because of myeloma.96 Kidney transplantation is therefore generally inadvisable for patients with this disease, unless performed in conjunction with bone marrow transplantation as a means of curing the underlying disease. Rituximab and bortezomib have been used with success in patients with light-chain nephropathy recurrence in the graft, but insufficient evidence exists to recommend either agent as a standard of care.

graft function is most commonly slow and does not appear to have an impact on 5-year graft survival rates.97

RECURRENCE OF METABOLIC DISEASES AFFECTING THE KIDNEY TRANSPLANT

Diabetes Mellitus

Diabetes mellitus is the most common cause of kidney failure in most parts of the world. However, these patients undergo transplantation less commonly than those with GN because of a higher prevalence and severity of CV comorbidity and inferior survival in registry studies.98 99 Recurrence of diabetic nephropathy affects at least 25% of recipients at an average follow-up of 6 years and with some patients diagnosed within 3 years of transplantation.100 Histologic and clinical features are similar to those of native kidney diabetic nephropathy. The risk of graft loss from recurrence has not been well documented but appears to be significantly less than with GN, probably because of the competing risk of death from CV disease. NODAT is also common and has been reported to cause nephropathy in the graft, also manifesting within 5 years of transplantation in a small proportion of cases. The extent to which this contributes to graft loss also awaits clarification, although one registry analysis suggested that the impact on graft failure is insignificant compared with the impact on premature death with a functioning graft.5

Primary Hyperoxaluria

Primary hyperoxaluria (see Chapter 60) is a rare autosomal recessive disease caused by defective or absent hepatic production of alanine glyoxylate aminotransferase, resulting in systemic accumulation of calcium oxalate (oxalosis). Kidneys and blood vessels in particular are affected. Kidney transplantation alone is frequently complicated by hyperoxaluria and rapid deposition of oxalate crystals within the graft causing graft failure within weeks to months from transplantation (Fig. 113.5). By contrast, combined liver-kidney transplantation corrects the underlying metabolic deficit and permits long-term kidney graft survival, provided the total body burden of oxalate present at the time of transplantation can be managed. In an analysis of the USRDS that included 190 adults with oxalosis who went on to undergo kidney transplantation, 134 patients who received a kidney transplant alone experienced 48% 8-year death-censored graft survival. This was inferior to 56 patients who also received a liver (76%) and inferior to a control group with a primary diagnosis of GN (61%).101 Aggressive removal of residual oxalate before transplantation by dialysis and after transplantation by maintenance of high urine volumes, urinary alkalinization,

Fibrillary and Immunotactoid Glomerulopathies

Fibrillary glomerulopathy (DNAJB9 Deposition Disease) and immunotactoid glomerulopathies are known to recur in approximately 50% of those undergoing transplantation for these diseases, and although early graft loss as a result of recurrence has been reported, decline in

Fig. 113.5 Recurrent Primary Hyperoxaluria. Light microscopy demonstrates oxalate crystals within the tubular lumen (arrows) with a secondary interstitial inflammatory infiltrate.

and pyridoxine supplementation for pyridoxine-sensitive patients also may decrease the risk for graft damage.

Fabry Disease

Fabry disease results from a defect in the lysosomal α-galactosidase A enzyme, which results in tissue accumulation of trihexosylceramide, eventually causing kidney failure (see Chapter 48). Recurrent Fabry disease has been documented within the graft; however, graft survival does not appear to be affected. Treatment with recombinant α galactosidase A, should this become widely available, is likely to reduce the risk for kidney failure and also for recurrence.

RECURRENCE OF VIRUS-ASSOCIATED NEPHROPATHIES AND TUMORS IN THE TRANSPLANTED KIDNEY

Virus-associated kidney diseases may recur after transplantation. Hepatitis B and C virus–associated IC-MPGN and MN are known to recur; however, the risk for this can be substantially decreased by successful antiviral therapy before transplantation (see Chapter 58).

Retransplantation has been reported in patients experiencing graft loss because of BK virus nephropathy. In the largest series with documented recurrence, BK viral replication was found in 11 of 31 (35%) recipients, and BK virus-associated nephritis (BKVAN) in 2

of the 31 (6%) at an median follow-up of 30 months after retransplantation.102 Rates of BK recurrence were lower when viral clearance had been achieved before retransplantation, with recurrence seen in 15% of BK-negative recipients versus 100% who remained BK positive at the time of transplantation.102 In a recently published study of the UNOS/OPTN database between 2005 and 2016, there were 46 (14%) regraft failures in 341 patients who had lost their first graft because of BKVAN. Of these, 7 (15%) lost their regraft because of BKVAN compared with 55 (2%) of the 2458 regrafts who had lost a previous graft for another reason.103 There was no difference in overall regraft survival between those who lost their first graft to BKVAN compared with another cause over the median follow-up time of 4.7 years.103 Thus, retransplantation, ideally delayed until BK virus is not detectable in serum by polymerase chain reaction, appears to be safe and effective.

Patients with posttransplantation lymphoproliferative disease (PTLD) who incur graft loss secondary to direct infiltration or rejection after the withdrawal of immunosuppression may safely and successfully undergo retransplantation after they recover. In an analysis of patients with second kidney transplants in the UNOS registry between 2000 and 2019, 254 patients were found to have had PTLD in their first transplant. These patients were found to have higher rates of PTLD in their second transplant (2.8% vs. 0.1% without previous PTLD, $P = .001$), but there was no difference in graft or patient survival at a median of 4.5 years of follow-up.104

SELF-ASSESSMENT QUESTIONS

1. Risk for graft loss because of recurrent disease is highest for kidney transplant recipients whose kidney failure was caused by:
A. IgAN.
B. FSGS.
C. Type 1 diabetes.
D. Lupus nephritis.
E. Reflux nephropathy.
2. A diagnosis of recurrent disease affecting the allograft requires which of the following pieces of information?
A. Allograft biopsy confirming the disease
B. Biopsy diagnosis of the native kidney disease

C. Clinical features of the original kidney disease recurring after transplant
D. Allograft failure caused by the disease
E. Both A and B

3. Which one of the following statements is true regarding management of recurrent FSGS?
A. First-line therapy includes a 3-day course of daily intravenous pulses of methylprednisolone.
B. Cyclophosphamide should be started once recurrence is confirmed.
C. In a patient who develops nephrotic-range proteinuria 2 weeks after transplant, a biopsy specimen that is normal on light microscopy excludes the diagnosis of recurrent FSGS.
D. Plasma exchange should be started once a diagnosis of recurrent FSGS is made, with a plan to complete approximately nine cycles of therapy.

REFERENCES

1. Chadban S. Glomerulonephritis recurrence in the renal graft. J Am Soc Nephrol. 2001;12(2):394–402.
2. Allen PJ, Chadban SJ, Craig JC, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. Kidney Int. 2017;92(2):461–469.
3. Hariharan S, Adams MB, Brennan DC, et al. Recurrent and de novo glomerular disease after renal transplantation: a report from Renal Allograft Disease Registry (RADR). Transplantation. 1999;68(5):635–641.
4. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002;347(2):103–109.
5. Cole EH, Johnston O, Rose CL, Gill JS. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clin J Am Soc Nephrol. 2008;3(3):814–821.
6. Odum J, Peh CA, Clarkson AR, et al. Recurrent mesangial IgA nephritis following renal transplantation. Nephrol Dial Transplant. 1994;9(3):309–312.
7. Ohmacht C, Kliem V, Burg M, et al. Recurrent immunoglobulin A nephropathy after renal transplantation: a significant contributor to graft loss. Transplantation. 1997;64(10):1493–1496.
8. Andresdottir MB, Hoitsma AJ, Assmann KJ, Koene RA, Wetzels JF. The impact of recurrent glomerulonephritis on graft survival in recipients of human histocompatibility leucocyte antigen-identical living related donor grafts. Transplantation. 1999;68(5):623–627.
9. Clayton P, McDonald S, Chadban S. Steroids and recurrent IgA nephropathy after renal transplantation. Am J Transplant. 2011;11:1645–1649.
10. Mulay A, Van Walraven C, Knoll G. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. Am J Transplant. 2009;9:1–8.
11. Berthoux F, El Deeb S, Mariat C, Diconne E, Laurent B, Thibaudin L. Antithymocyte globulin (ATG) induction therapy and disease recurrence in renal transplant recipients with primary IgA nephropathy. Transplantation. 2008;85(10):1505–1507.
12. Ibrahim H, Rogers T, Casingal V. Graft loss from recurrent glomerulonephritis is not increased with a rapid steroid discontinuation protocol. Transplantation. 2006;81:214–219.
13. Nachman PH, Segelmark M, Westman K, et al. Recurrent ANCAassociated small vessel vasculitis after transplantation: a pooled analysis. Kidney Int. 1999;56(4):1544–1550.
14. Ruiz JC, Campistol JM, Sanchez-Fructuoso A, et al. Increase of proteinuria after conversion from calcineurin inhibitor to sirolimusbased treatment in kidney transplant patients with chronic allograft dysfunction. Nephrol Dial Transplant. 2006;21(11):3252–3257.
15. Odorico JS, Knechtle SJ, Rayhill SC, et al. The influence of native nephrectomy on the incidence of recurrent disease following renal transplantation for primary glomerulonephritis. Transplantation. 1996;61(2):228–234.
16. Cibrik D, Kaplan B, Campbell D, Meier-Kriesche H. Renal allograft survival in transplant recipients with focal segmental glomerulosclerosis. Am J Transplant. 2003;3:64–67.
17. Wyld M, Chadban S. Recurrent IgA nephropathy after kidney transplantation. Transplantation. 2016;100(9):1827–1832.
18. Andresdottir M, Assmann K, Koene R, Wetzels J. Immunohistological and ultrastructural differences between recurrent type I membranoproliferative glomerulonephritis and chronic transplant glomerulopathy. Am J Kidney Dis. 1998;32:582–588.
19. Wyld MLR, De La Mata NL, Masson P, O’Lone E, Kelly PJ, Webster AC. Cardiac mortality in kidney transplant patients: a population-based cohort study 1988–2013 in Australia and New Zealand. Transplantation. 2021;105(2):413–422.
20. McDonald S, Russ G. Recurrence of IgA nephropathy among renal allograft recipients from living donors is greater among those with zero

HLA mismatches. Transplantation. 2006;82:759–762.

21. Sato Y, Ishida H, Shimizu T, Tanabe K. Evaluation of tonsillectomy before kidney transplantation in patients with IgA nephropathy. Transpl Immunol. 2014;30(1):12–17.
22. Moroni G, Longhi S, Quaglini S, et al. The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. Nephrol Dial Transplant. 2013;28(5):1305–1314.
23. Samuel JP, Bell CS, Molony DA, Braun MC. Long-term outcome of renal transplantation patients with Henoch-Schonlein purpura. Clin J Am Soc Nephrol. 2011;6(8):2034–2040.
24. Dabade TS, Grande JP, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy after kidney transplantation: a surveillance biopsy study. Am J Transplant. 2008;8(6):1318–1322.
25. Yang W, Bose B, Zhang L, et al. Long-term outcomes of patients with end-stage kidney disease due to membranous nephropathy: a cohort study using the Australia and New Zealand Dialysis and Transplant Registry. PLoS One. 2019;14(8):e0221531.
26. Cosyns JP, Couchoud C, Pouteil-Noble C, Squifflet JP, Pirson Y. Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. Clin Nephrol. 1998;50(3):144–153.
27. Beck L, Bonegio R, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;261(1):11–21.
28. Kattah A, Ayalon R, Beck Jr LH, et al. Anti-phospholipase A(2) receptor antibodies in recurrent membranous nephropathy. Am J Transplant. 2015;15(5):1349–1359.
29. Quintana LF, Blasco M, Seras M, et al. Antiphospholipase A2 receptor antibody levels predict the risk of posttransplantation recurrence of membranous nephropathy. Transplantation. 2015;99(8):1709–1714.
30. Gupta G, Fattah H, Ayalon R, et al. Pre-transplant phospholipase A2 receptor autoantibody concentration is associated with clinically significant recurrence of membranous nephropathy post-kidney transplantation. Clin Transplant. 2016;30(4):461–469.
31. Debiec H, Martin L, Jouanneau C, et al. Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. Am J Transplant. 2011;11(10):2144–2152.
32. Schwarz A, Krause PH, Offermann G, Keller F. Impact of de novo membranous glomerulonephritis on the clinical course after kidney transplantation. Transplantation. 1994;58(6):650–654.
33. Uffing A, Perez-Saez MJ, Mazzali M, et al. Recurrence of FSGS after kidney transplantation in adults. Clin J Am Soc Nephrol. 2020;15(2):247–256.
34. Artero M, Biava C, Amend W, Tomlanovich S, Vincenti F. Recurrent focal glomerulosclerosis: natural history and response to therapy. Am J Med. 1992;92(4):375–383.
35. Senggutuvan P, Cameron JS, Hartley RB, et al. Recurrence of focal segmental glomerulosclerosis in transplanted kidneys: analysis of incidence and risk factors in 59 allografts. Pediatr Nephrol. 1990;4(1):21–28.
36. Stephanian E, Matas AJ, Mauer SM, et al. Recurrence of disease in patients retransplanted for focal segmental glomerulosclerosis. Transplantation. 1992;53(4):755–757.
37. Francis A, Trnka P, McTaggart SJ. Long-term outcome of kidney transplantation in recipients with focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2016;11(11):2041–2046.
38. Kim E, Striegel J, Kim Y, Matas A, Najarian J, Mauer S. Recurrence of steroid resistant nephrotic syndrome in kidney transplants is associated with increased acute renal failure and acute rejection. Kidney Int. 1994;45(5):1440–1445.
39. Wei C, El Hindi S, Li J, al e. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med. 2011;17:952–960.
40. Franco Palacios C, Lieske J, Wadei H, al e. Urine but not serum soluble urokinase receptor (suPAR) may identify cases of recurrent FSGS in

kidney transplant candidate. Transplantation. 2013;96:394–399.
41. Sinha A, Bajpai J, Saini S, al e. Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. Kidney Int. 2014;85:649–658.

42. Yu CC, Fornoni A, Weins A, et al. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med. 2013;369(25):2416–2423.
43. Garin EH, Reiser J, Cara-Fuentes G, et al. Case series: CTLA4IgG1 therapy in minimal change disease and focal segmental glomerulosclerosis. Pediatr Nephrol. 2015;30(3):469–477.
44. Dantal J, Godfrin Y, Koll R, et al. Antihuman immunoglobulin affinity immunoadsorption strongly increases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol. 1998;9:1709–1715.
45. Andresdottir MB, Ajubi N, Croockewit S, Assmann KJ, Hibrands LB, Wetzels JF. Recurrent focal glomerulosclerosis: natural course and treatment with plasma exchange. Nephrol Dial Transplant. 1999;14(11):2650–2656.
46. Kashgary A, Sontrop JM, Li L, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. BMC Nephrol. 2016;17(1):104.
47. Davenport RD. Apheresis treatment of recurrent focal segmental glomerulosclerosis after kidney transplantation: re-analysis of published case-reports and case-series. J Clin Apher. 2001;16(4):175–178.
48. El-Zoghby ZM, Grande JP, Fraile MG, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy: early diagnosis by protocol biopsies and treatment with anti-CD20 monoclonal antibodies. Am J Transplant. 2009;9(12):2800–2807.
49. Sprangers B, Lefkowitz GI, Cohen SD, et al. Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. Clin J Am Soc Nephrol. 2010;5(5):790–797.
50. Alasfar S, Carter-Monroe N, Rosenberg A, Montgomery R, Alachkar N. Membranoproliferative glomerulonephritis recurrence after kidney transplantation: using the new classification. BMC Nephrol. 2016;17(1).
51. Pickering MC, D’Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84(6):1079–1089.
52. Little M, Dupont P, Campbell E, et al. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. Kidney Int. 2006;69:504–511.
53. Cruzado JM, Gil-Vernet S, Ercilla G, et al. Hepatitis C virus-associated membranoproliferative glomerulonephritis in renal allografts. J Am Soc Nephrol. 1996;7(11):2469–2475.
54. Green H, Rahamimov R, Rozen-Zvi B, et al. Recurrent membranoproliferative glomerulonephritis type I after kidney transplantation: a 17-year single-center experience. Transplantation. 2015;99(6):1172–1177.
55. Lorenz E, Sethi S, Leung N, Dispenzieri A, Fervenza F, Cosio F. Recurrent membranoproliferative glomerulonephritis after kidney transplantation. Kidney Int. 2010;77:721.
56. Wilson GJ, Cho Y, Teixiera-Pinto A, et al. Long-term outcomes of patients with end-stage kidney disease due to membranoproliferative glomerulonephritis: an ANZDATA registry study. BMC Nephrol. 2019;20(1):417.
57. Andresdottir MB, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Recurrence of type I membranoproliferative glomerulonephritis after renal transplantation: analysis of the incidence, risk factors, and impact on graft survival. Transplantation. 1997;63(11):1628–1633.
58. Moroni G, Casati C, Quaglini S, et al. Membranoproliferative glomerulonephritis type I in renal transplantation patients: a singlecenter study of a cohort of 68 renal transplants followed up for 11 years. Transplantation. 2011;91(11):1233–1239.
59. Regunathan-Shenk R, Avasare RS, Ahn W, et al. Kidney transplantation in C3 glomerulopathy: a case series. Am J Kidney Dis. 2019;73(3):316–323.
60. Levine AP, Chan MMY, Sadeghi-Alavijeh O, et al. Large-scale WholeGenome

Sequencing Reveals the genetic Architecture of primary membranoproliferative GN and C3 glomerulopathy. J Am Soc Nephrol. 2020;31(2):365–373.
61. Andresdottir MB, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Renal transplantation in patients with dense deposit disease: morphological characteristics of recurrent disease and clinical outcome. Nephrol Dial Transplant. 1999;14(7):1723–1731.

62. Le Quintrec M, Lapeyraque AL, Lionet A, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis. 2018;72(1):84–92.
63. Noris M, Remuzzi G. Glomerular diseases dependent on complement activation, including atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis, and C3 glomerulopathy: core curriculum 2015. Am J Kidney Dis. 2015;66(2):359–375.
64. Ruggenenti P, Daina E, Gennarini A, et al. C5 Convertase blockade in membranoproliferative glomerulonephritis: a single-arm clinical trial. Am J Kidney Dis. 2019;74(2):224–238.
65. Patrakka J, Ruotsalainen V, Reponen P, et al. Recurrence of nephrotic syndrome in kidney grafts of patients with congenital nephrotic syndrome of the Finnish type: role of nephrin. Transplantation. 2002;73(3):394–403.
66. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener’s granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol. 1998;9(5):842–852.
67. Hruskova Z, Geetha D, Tesar V. Renal transplantation in anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrol Dial Transplant. 2015;30(suppl 1):i159–i163.
68. Kuhnel L, Hawley CM, Johnson DW, Gobe GC, Ellis RJ, Francis RS. Allograft failure in kidney transplant recipients who developed kidney failure secondary to ANCA-associated vasculitis. Clin Transplant. 2021:e14235.
69. Little M, Hassan B, Jaques S, et al. Renal transplantation in systemic vasculitis: when is it safe. Nephrol Dial Transplant. 2009;25(10):3219–3225.
70. Geetha D, Seo P, Specks U, Fervenza FC. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post-kidney transplant: report of two cases. Am J Transplant. 2007;7(12):2821–2825.
71. Gobel J, Olbricht CJ, Offner G, et al. Kidney transplantation in Alport’s syndrome: long-term outcome and allograft anti-GBM nephritis. Clin Nephrol. 1992;38(6):299–304.
72. Contreras G, Mattiazzi A, Guerra G, et al. Recurrence of lupus nephritis after kidney transplantation. J Am Soc Nephrol. 2010;21(7):1200–1207.
73. Norby GE, Strom EH, Midtvedt K, et al. Recurrent lupus nephritis after kidney transplantation: a surveillance biopsy study. Ann Rheum Dis. 2010;69(8):1484–1487.
74. Moroni G, Tantardini F, Gallelli B, et al. The long-term prognosis of renal transplantation in patients with lupus nephritis. Am J Kidney Dis. 2005;45(5):903–911.
75. Goss JA, Cole BR, Jendrisak MD, et al. Renal transplantation for systemic lupus erythematosus and recurrent lupus nephritis. A singlecenter experience and a review of the literature. Transplantation. 1991;52(5):805–810.
76. Le Quintrec M, Zuber J, Moulin B, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. Am J Transplant. 2013;13(3):663–675.
77. Artz MA, Steenbergen EJ, Hoitsma AJ, Monnens LA, Wetzels JF. Renal transplantation in patients with hemolytic uremic syndrome: high rate of recurrence and increased incidence of acute rejections. Transplantation. 2003;76(5):821–826.
78. Bresin E, Daina E, Noris M, et al. Outcome of renal transplantation in

patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol. 2006;1(1):88–99.
79. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2007;18(8):2392–2400.
80. Goodship T, Cook H, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney Int. 2017;91(3):539–551.

81. Remuzzi G, Ruggenenti P, Codazzi D, et al. Combined kidney and liver transplantation for familial haemolytic uraemic syndrome. Lancet. 2002;359(9318):1671–1672.
82. Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol. 2013;8(4):554–562.
83. Legendre CM, Campistol JM, Feldkamp T, et al. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. Transpl Int. 2017;30(12):1275–1283.
84. Siedlecki A, Isbel N, Walle J, et al. Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome. Kidney International Reports. 2019;4(3):434–446.
85. Levi C, Fremeaux-Bacchi V, Zuber J, et al. Midterm outcomes of 12 renal transplant recipients treated with eculizumab to prevent atypical hemolytic syndrome recurrence. Transplantation. 2017;101(12):2924–2930.
86. Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with eculizumab: a systematic review and meta-analysis. J Clin Med. 2019;8(7).
87. Zuber J, Frimat M, Caillard S, et al. Use of Highly Individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2019;30(12):2449–2463.
88. Chang YJ, Spiera H. Renal transplantation in scleroderma. Medicine (Baltim). 1999;78(6):382–385.
89. Siva B, McDonald SP, Hawley CM, et al. End-stage kidney disease due to scleroderma—outcomes in 127 consecutive ANZDATA registry cases. Nephrol Dial Transplant. 2011;26(10):3165–3171.
90. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation. 2020;104(4S1):S11–S103.
91. Heybeli C, Bentall A, Wen J, et al. A study from the Mayo Clinic evaluated long-term outcomes of kidney transplantation in patients with immunoglobulin light chain amyloidosis. Kidney Int. 2020.
92. Pinney JH, Lachmann HJ, Sattianayagam PT, et al. Renal transplantation in systemic amyloidosis-importance of amyloid fibril type and precursor protein abundance. Am J Transplant. 2013;13(2):433–441.

93. Angel-Korman A, Stern L, Sarosiek S, et al. Long-term outcome of kidney transplantation in AL amyloidosis. Kidney Int. 2019;95(2):405–411.
94. Sherif AM, Refaie AF, Sobh MA, Mohamed NA, Sheashaa HA, Ghoneim MA. Long-term outcome of live donor kidney transplantation for renal amyloidosis. Am J Kidney Dis. 2003;42(2):370–375.
95. Hartmann A, Holdaas H, Fauchald P, et al. Fifteen years' experience with renal transplantation in systemic amyloidosis. Transpl Int. 1992;5(1):15–18.
96. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in light-chain deposition disease. Am J Kidney Dis. 2004;43(1):147–153.
97. Pronovost PH, Brady HR, Gunning ME, Espinoza O, Rennke HG. Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy. Nephrol Dial Transplant. 1996;11(5):837–842.
98. Chadban S, Staplin D. Is it time to increase access to transplantation for those with diabetic end-stage kidney disease? Kidney Int. 2014;86(3):464–466.
99. Lim WH, Wong G, Pilmore HL, McDonald SP, Chadban SJ. Longterm outcomes of

kidney transplantation in people with type 2 diabetes: a population cohort study. Lancet Diabetes Endocrinol. 2017;5(1):26–33.
100. Bhalla V, Nast CC, Stollenwerk N, et al. Recurrent and de novo diabetic nephropathy in renal allografts. Transplantation. 2003;75(1):66–71.
101. Cibrik DM, Kaplan B, Arndorfer JA, Meier-Kriesche HU. Renal allograft survival in patients with oxalosis. Transplantation. 2002;74(5):707–710.
102. Geetha D, Sozio SM, Ghanta M, et al. Results of repeat renal transplantation after graft loss from BK virus nephropathy. Transplantation. 2011;92(7):781–786.
103. Leeaphorn N, Thongprayoon C, Chon W, Cummins L, Mao M, Cheungpasitporn W. Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents. Am J Transplant. 2020;20:1334–1340.
104. Leeaphorn N, Thongprayoon C, Chewcharat A, et al. Outcomes of kidney retransplantation in recipients with prior posttransplant lymphoproliferative disorders: an analysis of the 2000-2019 UNOS/OPTN database. Am J Transplant. 2021;21(2):846–853.

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Outcomes of Kidney Transplantation: Identification, Measures, and Evaluation

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INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem that imposes a substantial burden on patients, families, and healthcare systems.1 Kidney transplantation provides superior survival compared with dialysis but does not fully correct quality of life (QOL) and survival2,3 compared with the general population. The overall risk of death in transplant recipients is at least three times higher than the general population, and transplant recipients have significantly reduced QOL, even compared with patients with other chronic disease. Strategies such as optimization of matching, crossmatching, and surgical techniques; improvement in perioperative care; effective antiviral, antifungal, and antibacterial prophylaxis; and contemporary immunosuppression have led to improvement in patient and allograft outcomes over the past two decades. Improvement in short-term outcomes is accompanied by evidence from the United Kingdom, Australia, and Europe on gains in long-term graft survival. Data from the Collaborative Transplant Study have shown that between 1985 and 1996, the 1- and 10 year-graft loss hazard rates have declined by 64% (95% confidence interval [CI], 61%–66%) and 45% (39%–50%), respectively. Between 2000 to 2015, the reduction in graft loss hazard rates at 1 and 10 years were 22% (12%–30%) and 64% (45%–76%), respectively.4

Despite these improvements, there are important challenges in improving the health and overall well-being of transplant recipients. Current immunosuppression regimens cannot completely prevent rejection and graft loss and can lead to undesirable complications such as cancer and infection. Importantly, the outcomes that researchers study and clinicians target often do not align with those that patients prioritize.5 Patient engagement is a critical element of clinical research that can enhance the credibility of the findings and improve their translation into practice.

This chapter describes outcomes after transplantation including graft health, mortality, and long-term complications of immunosuppression and includes a brief description of the tools used to assess these outcomes. The chapter explicitly focuses on outcomes that are prioritized by patients and families, especially those that are not frequently considered by clinicians and health professionals, such as life participation.

GRAFT HEALTH AND PATIENT SURVIVAL

Graft health is a broad umbrella term for direct outcomes of the kidney transplant. Important aspects of graft health include patient survival, short- and long-term graft survival, graft rejection, and graft function.

Definitions that characterize patient and allograft survival include the following:

- ✔•✔ Patient survival refers to the overall survival (OS) of the transplanted person measured from the time of transplantation to the time of death; censor at the end of follow-up time or the time the person was lost to follow.
- ✔•✔ Death with a functioning graft is a major cause of graft loss after kidney transplantation. This occurs when a patient has sufficient graft function and does not need either retransplantation or dialysis at the time of death. The date of death is recorded as the last follow-up visit with function.
- ✔•✔ Graft survival is the absence of irreversible graft failure, meaning

the requirement for retransplantation or long-term dialysis therapy. This can be further divided:

✓ •✓ Death-censored graft survival is time from date of transplantation to the occurrence of irreversible graft loss; censor on the date at which the patient was lost to follow-up, died, or at the end of follow-up time.

✓ •✓ Overall graft survival is time from transplant to graft loss and/or death; censor on the date at which the patient was lost to follow-up or end of follow-up time for recipients with a functioning graft.

Measures of patient or graft survival can be reported with or without adjustment for potential confounders and typically at a specified time point (such as 30-day, 1-year, 5-year, or 10-year). Transplant data registries, such as the International Registry in Organ Donation (IRODaT), Organ Procurement and Transplantation Network (OPTN), United Network for Organ Sharing (UNOS), Scientific Registry of Transplant Recipients (SRTR), United States Renal Data System (USRDS), European Dialysis and Transplant Association Registry (ERA-EDTA), Collaborative Transplant Study (CTS), and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), provide important data regarding the country-specific graft and patient survival (both short- and long-term) over the past 50 years.

Early Posttransplant Outcomes

There are high upfront risks associated with kidney transplantation, driven by surgical complications and adverse effects of intense immunosuppression early in the transplant course. A longitudinal, observational study of over 200,000 patients on long-term dialysis in the United States[6] showed that patients who were listed for transplantation (46,164) and received a first deceased-donor transplant (23,275) experienced a 2.8-fold higher risk of death in the first 2 weeks after the transplant compared with those who remained on the waitlist. The risk of death became similar between transplanted and waitlisted patients around 106 days, and a net survival benefit was seen after 244 days posttransplantation.[6] Importantly, the study showed a substantially lower annual death rate for those transplanted (3.8 deaths per 100 patient-years) compared with those who remained waitlisted on dialysis (6.3 per 100 patient years) and on dialysis but not suitable for waitlisting (16.1 per 100 patient years), with beneﬁts particularly favoring young patients (20–39 years old) and young diabetic patients.

Long-Term Posttransplant Outcomes

Interpretation of longer-term outcomes needs careful consideration of the case mix (such as recipient comorbidities, organ quality, immunologic risks, donor-recipient matching), transplant era (evolution of immunosuppression protocols and practices), and country-speciﬁc and resource-related factors (such as the impact of socioeconomic factors, access to care, and affordability of medications, which may vary between countries; Fig. 114.1). These factors may have accounted for the between-country differences in the adjusted graft loss rates in the United States, United Kingdom, and Australia and New Zealand, with the risk of graft loss at 1 year posttransplant being highest in the United Kingdom (Hazard ratio [HR] 1.22), followed by the United States from year 2 onward. The risk of allograft loss remains the lowest in Australia across all eras.7 Other studies have reported a wide range of 10-year patient survival, ranging from 34% to 78% for transplants performed after the year 2000.8–11 The impact of regional and ethnic differences was again highlighted in a study comparing European versus North American kidney transplant recipients from the UNOS and CTS for Europe databases. The 10-year graft survival rates between

2005 to 2008 were 56% in Europe, and 46%, 48%, and 34% for White, Hispanic, and Black Americans, respectively.10

Data from the Netherlands Organ Transplant Registry suggested that deceased-donor criteria (brain vs. circulatory death) were not a predictor for patient- or death-censored graft survival.9 However, donor comorbid diseases, such as type 2 diabetes and hypertension, were risk factors for allograft survival.12 For transplants performed in 2014 to 2015, the death-censored graft survival rates at 1 and 5 years were 98% and 83%, respectively, for deceased-donor grafts, and 99% and 91% for living-donor kidney grafts in Australia13 (Fig. 114.2A). The rate of graft failure (censored for death) was approximately 3 per 100 graft-years, with chronic allograft injury being the dominant cause of graft loss13 (Fig. 114.3).

Patient OS after transplantation differs by era and recipient age. The 5- and 15 year patient survivals after primary living-donor kidney transplant varied from 89% in the 1990–94 period to 94% in the 2000–04 period and 75% in the 1990–94 period to 80% in 2000–04. For primary deceased-donor kidney transplants, the 5- and 15- year survivals were 84% in 1990–94 and 89% in 2004–09 and 53% in 1990–94 and 64% in 2000–04, respectively (see Fig. 114.2B). The reported 5-year graft patient survival for older kidney transplant recipients (≥65 years old) transplanted between 2006 to 2016 was 79%.14 Older transplant recipients also incur a survival advantage compared with age- and

Predictive Factors for Patient Survival and Graft Outcomes of Survival, Acute Rejection, and Overall Function

- Death- and non–death-censored... graft survival

Patient survival and outcomes

- Overall death
- Death with functioning graft

Donor type: living, deceased (after brain death, circulatory death, and extended criteria donor)

Kidney Donor Profile Index (KDPI) which

accounts for donor age, BMI, vascular risk
(diabetes, hypertension, smoking), cause of
death, HCV status, terminal serum creatinine
and DCD criteria
Donor need for inotropic support, concurrent
infection, need for kidney replacement therapy,
prior to retrieval
Donor surgery warm ischemic time
(particularly with multiorgan retrieval surgery),
cold ischemic time, and use of ex-vivo
machine perfusion

Graft survival

and

- Banff criteria biopsy proven rejection

Graft rejection

- Conventional measures of graft function

Graft function

- Newer biomarkers: predictive of prognosis
for rejection and long-term graft survival

Surgical issues such as graft thrombosis,
ureteric obstruction, collection causing mass
effect compromising the graft viability
Immunological matching: HLA matches,
anti-HLA antibodies, donor-specific antibodies
pretransplant and de novo, panel reactive
antibodies (PRA). Episodes of acute rejection
(cell mediated or antibody mediated)
Immunosuppression protocols and side
effects: infections, malignancy, metabolic
disturbances of cardiovascular disease,
dyslipidemia, and new-onset diabetes

Recipient vascular risks: BMI, diabetes,
hypertension, prior cerebrovascular or
cardiovascular disease, age, ethnicity
genetic risks, length on dialysis
pretransplant
Other insults such as:

- calcineurin inhibitor toxicity
- recurrent/chronic rejection
- recurrence of primary renal disease

Other determinants
- socioeconomic factors
- access to affordable healthcare
- region- or country-specific models of care

Delayed graft function either from ischemiareperfusion injury, donor-related or recipientrelated acute kidney injury from any cause

Fig. 114.1 Predictive factors for patient survival and graft outcomes of survival, acute rejection, and overall function. BMI, Body mass index; DCD, donation after cardiac death; HCV, hepatitis C virus; HLA, human leukocyte antigen. (Created using Biorender.com.)

Graft and Patient Survival for Deceased and Living Donor Kidney Transplantation Across Eras in Australia
Graft Survival: Living Donor

Graft Survival: Deceased Donor
1.00

1.00

0.75

0.75

0.50

0.50

0.25

0.25

0.00

0.00
0

10
20
Years posttransplant

30

0

A
Patient Survival: Deceased Donor

10
20
Years posttransplant

30

Patient Survival: Living Donor

1.00
1.00

0.75

0.75

0.50

0.50

0.25

0.25

0.00

0.00
0

10
20
Years posttransplant

30

0

10
20
Years posttransplant

30

B
2015–2019
2010–2014
2005–2009
2000–2004
1995–1999
1990–1994

Fig. 114.2 Graft and Patient Survival for Deceased and Living Donor Kidney Transplantation Across Eras in Australia. (A) Primary graft survival. (B) Patient survival. (A, From ANZDATA Registry Annual Report 2020.)

sex-matched patients who remain on the waiting list,15 but OS remains inferior compared with younger counterparts.16 Donor age is also a major factor that influences transplant outcomes. Younger recipients of older donor grafts are at risk for poorer long-term graft survival.16–18

Acute Rejection Episodes After Transplantation

Acute rejection is an important outcome for patients and health professionals. Diagnosis of acute rejection is based on biopsy scoring using the Banff criteria for rejection.19 20 Studies typically report on biopsyproven acute rejection (BPAR)—whether cell-mediated or antibodymediated rejection (ABMR)—to satisfy the predefined Banff criteria.

The Banff classification was first developed in 1991 and has had several iterations over the past 30 years,20 21 including updates as recently as 2019. Interpretation of studies require careful consideration given that the classification is typically-updated every 2 years, the addition of ABMR criteria after the 1997 meeting, and the acute versus chronic ABMR classification detailed in the 2005 update. Studies over the past 30 years have subtle variations in the definitions of BPAR, and definitions may be improved by incorporating diagnostic, predictive, and/or prognostic biomarkers (select examples listed in Table 114.1) and more precise definition of phenotypes of acute rejection defined by molecular and genomic markers.22–26

Events That May Lead to Impaired Graft Health Over the Life
of the Transplant

Chronic Allograft Injury

Interstitial Fibrosis
Tubular Atrophy
Glomerulopathy

Possible
Events
Causing
Impaired
Graft
Health

Chronic rejection

De novo disease
Recurrent disease

Acute rejection
Episodes of AKI

Time After Kidney
Transplantation

Fig. 114.3 Representative Events That May Lead to Impaired Graft Health Over the Lifetime of the Transplant. Early posttransplantation, acute rejection, and delayed graft function pose the highest risk to graft function, which reduce over time and are replaced by events such as chronic rejection and recurrent or de novo kidney disease superimposed by episodes of acute kidney injury (AKI) from any cause. (Created using Biorender.com.)

Select Noninvasive
Biomarkers for Solid-Organ Transplant
Rejection

death with a functioning graft, death because of cardiovascular disease (CVD), or cancer.11

Marker

Source

Reference

Donor-specific antibodies
Molecular biomarkers group
or panels

Blood
Blood, urine, and/or
kidney biopsy
Examples: kSORT, CTOT8, GoCAR studies
Urine

76
77–79

Urine

81, 82

Urine

81

Blood
Blood

83
84

Blood and urine
Urine

85
86

Kidney function is an important outcome that is usually reported using surrogate markers of serum creatinine (SCr) or estimated glomerular filtration rate (eGFR). These outcomes have known limitations, particularly with variations with sex, race, muscle mass, and age; aberrant results when drugs or conditions impair the tubular secretion component; and the relative insensitivity to small changes in function because of the reciprocal relationship between SCr and GFR. There are several methods for estimating eGFR, most commonly the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (see Chapter 3).27 28 Despite their limitations, recording the eGFR and observing the magnitude of eGFR decline, slope, or drop of at least 30% in function is useful for predicting patient and graft survival.29 The GFR slope and percentage decline in GFR are also used to detect the progression of kidney disease.30 31 Proteinuria is an important biomarker in kidney transplantation, as it is in the CKD setting.32 Proteinuria originating from the allograft (rather than native kidneys) can be from various etiologies (including transplant glomerulopathy, recurrent disease, and mammalian target of rapamycin [mTOR] inhibitor use), but even proteinuria of greater than 500 mg/day is associated with reduced graft survival33 and development of de novo human leukocyte antigen (HLA) antibodies.34

Biopsy, blood, or urine

87–90

TABLE 114.1

T-cell immunoglobulin and
mucin-domain containing-3
(TIM-3)
Chemokine (C-X-C motif)
ligand 9 (CXCL9)
Chemokine (C-X-C motif)
ligand 10 (CXCL10)
Cell-free DNA
Granzyme B, perforin and
Fas-ligand
Forkhead box P3 (Foxp3)
OX40, (CD134) OX40, ligand,
programmed cell death

protein 1 (PD-1), PD-2,
FOXP3
MicroRNA species

80

Acute rejection occurred in approximately 18% and 20% of patients with first and subsequent allografts within the first 6 months after deceased and living-donor kidney transplants. Early rejection (within the first 6 months posttransplantation) adversely affects longer-term patient and graft outcomes and is associated with an increased risk of

Kidney Transplant Function

Early Graft Outcomes

Delayed graft function (DGF) is typically defined as the need for dialysis within the first 7 days, but there are 18 definitions used in literature to define this entity.35 36 The reported incidence of DGF varies from 5% to 50% depending on the definition and can be associated with increased risk of rejection37 38 and reduced graft survival.39 Recent evidence also suggested that the severity (based on the duration) of DGF has a “dose effect” on death-censored graft loss.40 For patients with “slow graft

TABLE 114.2 Select Novel Biomarkers for Acute Kidney Injury

Marker	Source	Reference
Neutrophil-gelatinase-associated lipocalin (NGAL)	Blood and urine	91, 92
Interleukin-18	Blood and urine	93, 94
Kidney injury molecule-1 (KIM-1)	Urine	95, 96
Cystatin C	Blood	97, 98
Liver-type fatty acid binding protein	Urine	96
YKL-40	Urine	99, 100
Tissue inhibitor of metalloproteinases 2 (TIMP2)	Urine	101
Insulin-like growth factor binding protein 7 (IGFBP7, angiomodulin)	Urine	102
Angiotensinogen	Urine	103
Cell-free DNA	Blood	104

COMPLICATIONS: MALIGNANCIES AND INFECTIONS

Cancer and infection are the two most feared complications of immunosuppression and are thus key research priorities for patients and clinicians.[5] Unlike CVD, for which outcomes have improved considerably over time, the risks of developing atypical infections and cancers remain high.[55]

function” (poorer immediate function but not requiring dialysis within the first 72 hours), DGF was associated with worse outcomes in terms of overall graft loss and death-censored graft loss.[41] Similar to acute rejection, the definition of DGF can be precisely defined by incorporating noninvasive biomarkers to the clinical or laboratory definition(s) in the future. Some examples of biomarkers being investigated for acute kidney injury (AKI) in general are presented in Table 114.2

Long-Term Graft Outcomes

Chronic allograft injury (CAI; previously known as chronic allograft nephropathy) is a histologic description of fibrosis, atrophy, and vascular damage in the kidney. The term interstitial fibrosis/tubular atrophy (IFTA) was introduced by the 2005 Banff Working Group[42] to capture this pathologic appearance, which represents the irreversible and common end pathway of many mechanisms of injury, including acute or chronic rejection, subclinical rejection, long-term calcineurin toxicity, polyoma virus infection, recurrent or de novo glomerulonephritis, or any cause of AKI seen in the general population.[43–45] IFTA is prone to sampling error from the biopsy procedure and ascertainment bias because of variation in the sampling rates of biopsies for indication only or indication plus surveillance biopsies. The quantification of IFTA alone is insufficient to predict long-term graft loss,[46] but inflammation in areas of IFTA (i-IFTA) may be associated with accelerated IFTA, chronic glomerulopathy, reduced kidney function, and longterm death-censored graft loss.[47 48] Thus, IFTA and i-IFTA are useful surrogate markers for kidney transplant outcomes.

The kidney donor risk index (KDRI) is a validated prediction tool for long-term graft survival and includes a numeric representation accounting for donor age, race, terminal creatinine, comorbid hypertension or diabetes, cause of death, donation after cardiac death, height, weight, and HCV status; and transplant factors including HLA-mismatch, cold ischemia time, and en-bloc double kidney transplant.[49 50] A higher KDRI denotes the higher risk of graft failure or a “poorer” quality organ but this is not absolute, with similar graft outcomes reported for KDRI between 35 to 85 and KDRI greater than 85.[51]

In recent years, the search has intensified for predictive or prognostic blood, biopsy, and/or urinary biomarkers that correlate with longterm outcomes in kidney transplantation, particularly those using proteinomics and genomic scoring sets.[24 52–54] Although there has been acceleration in molecular technologies and bioinformatics analysis, these newer research tools are yet to be translated into mainstream clinical practice and are not further discussed here.

MALIGNANCY

The overall risk of cancer is increased at least twofold to threefold compared with the age- and sex-matched general population, with the greatest increased risk from viral-related cancer. However, the risk of developing breast and prostate cancer is comparable to the general population.[56] The overall incidence of de novo cancer among kidney transplant recipients varies between 1000 and 1300 per 100,000 person years, and the overall risk increases with age. The cumulative incidence of de novo cancer (including nonmelanoma skin cancer) at 10 years after kidney transplantation is around 40%, increasing to 60% at 20 years. Once cancer has developed, the risk of death attributed to cancer is threefold higher than for patients with cancer in the general population.[57]

Measuring Cancer Outcomes in Kidney Transplant Recipients

Epidemiologic data such as incidence and mortality of cancer in transplant recipients are best obtained from national cancer-based registries. Linkage of data from different sources (e.g., linking data from a cancer registry to data from a kidney transplant registry) may allow more detailed analyses that cannot be done with either alone. Cancer incidence and mortality rates are presented by categories of cancer sites and types in kidney and general population cancer registries. Real-time data, including incidence rates (sex- and age-specific) and the cumulative cancer incidence (by cancer site), may be routinely provided by the registries to transplant units as a quality assurance measure. If historical incidence data are available, with sufficient and accurate number of cases and the denominator, recorded incidence rates can be projected to provide longer-term estimation within the population of interests using prediction modeling techniques.58

Although unadjusted incidence rates are useful to describe how many kidney transplant recipients develop cancer or die of cancer within a certain time period, they do not account for the age, sex distribution, and patient characteristics in the population of interest. Standardization gives a single figure to compare an incidence rate in two populations and accounts for the different population distributions.

Relative Mortality

Obtaining accurate information on the cause of death is notoriously difficult, especially using data from death certificates. To overcome some of these challenges, the risk of cancer-related death in kidney transplant populations can be assessed by assessing relative cancer survival. Relative survival can be defined as the ratio of kidney transplant recipients with cancers that have survived within a certain time period to the proportion of expected cancer survivors in a comparable cohort in the general population. Alternately, the comparator could be a similar cohort (age- and sex-matched) of patients without cancer in the general population. However, this method assumes that cancer deaths are independent of the other competing causes of death.

Competing Risk Analyses

Accounting for the competing risk of other causes of death is potentially important when assessing the risk of death from cancer in kidney transplant recipients. In survival analysis, censored observations (participants who complete follow-up without experiencing the outcome of interest) contribute to the total number of participants at risk until the end of their follow-up. These analyses assume that factors that lead to censoring are independent of those that lead to the outcome of interest. However, if the outcome of interest is precluded by another event, the “independence” assumption is violated. For example, a transplant recipient who dies of infection cannot experience another death from cancer and is no longer “at-risk” for experiencing another type of death. Specific techniques such as the Fine and Gray method can be used to generate the subdistributional hazard ratios and estimate the risk of cancer-related death, assuming the recipient had not died of infection. Ignoring competing risk can lead to misleading results. For example, some analyses have suggested that patients with diabetes are protected from cancer compared with those without diabetes; the true explanation is that (compared with people without diabetes) these patients are at higher risk of early death from other causes and thus are less likely to live long enough to die of cancer.

Management of Cancer After Transplantation

Partnership between transplant professionals and oncologists is the key to cancer management in complex kidney transplant recipients. Judicious reduction in immunosuppression, particularly antiproliferative agents and those that affect T cells, may induce remission of certain cancer types, such as posttransplantation lymphoproliferative disorder (PTLD) and Kaposi sarcomas. However, this approach needs to be balanced carefully with the risk of allograft rejection. There are emerging studies to suggest that mTOR inhibitors (mTORIs) may reduce the risk of method can be used (particularly squamous cell carcinoma [SCC]) and Kaposi sarcomas.59 However, the benefits of mTORIs in recipients with solid organ cancers are uncertain and mTORIs are poorly tolerated, with a discontinuation rate of more than 30% in trials.60 There is also an increased risk of cancer and all-cause death among recipients who received mTORI as standard immunosuppression compared with those maintained on calcineurin inhibitors.

New targeted anticancer therapies, including checkpoint inhibitors and other immunotherapies, are now available to treat advanced-stage solid organ and hematologic malignancies, but most trials assessing these new agents have excluded transplant recipients. There are case reports and series suggesting that the use of anti-PD1, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and other immune modulators such as lenalidomide and pomalidomide in transplant recipients can lead to acute allograft rejection.61 A recent observational multicenter study on the safety and efficacy of immune-checkpoint inhibitors (ICI) indicated approximately 40% of the cohort who received ICI developed acute rejection, and this compared with 5.9% in the non-ICI groups. Of those who experienced acute rejection, about 65% experienced graft loss. The median time from ICI initiation to acute rejection was 24 days. Key factors that may reduce the risk of acute rejection were mTORI use at the time of ICI initiation, and triple agent immunosuppression. The median survival in patients with metastatic SCC was 19.8 months in the ICI cohort, compared with 10.6 months in the non-ICI arm.62

INFECTIONS

Infections are major causes of early posttransplant death (within the first 12 months posttransplant), particularly in low- to middle-income countries where prophylactic treatments for viral and bacterial infections are not universally affordable. The timing, severity, and etiology of the infections are dependent on the recipients’ epidemiologic infectious exposures and the individual’s state of immunosuppression63 (see Chapter 110). The types of infection also vary depending on the time since transplantation, with the risk of acquiring nosocomial infections

being the highest during the first weeks after transplantation, followed by opportunistic and community acquired infections thereafter.63
Unlike cancer, detailed data on the timing, frequency, and burden of infectious disease in transplant recipients are generally not available from national registries. Details about the incidence, prevalence, and exposure to certain types of infections and the responses to screening, preventive, and treatment strategies are often limited to single-center sources.

Prevention and Prophylaxis

Effective prophylactic and preventive strategies are available for a range of infections, including cytomegalovirus (CMV), human papillomaviruses (HPV), and pneumocystis pneumonia infections. Options for CMV prophylaxis include valganciclovir, oral ganciclovir, intravenous (IV) ganciclovir, or high-dose oral valacyclovir, corrected for kidney function.64 For HPV, quadrivalent vaccines (against genotype 6, 11, 16, and 18), and, more recently, the HPV 9-valent vaccines (against 5 additional genotypes of 31, 33, 45, 52, and 58), are highly effective and have an overall efficacy of 99% to 100% for the prevention of cervical intraepithelial neoplasia.65,66 HPV vaccination is indicated in both males and females aged 9 to 25 years in the general population for the prevention of HPV-related malignancies. Some recent data have shown that vaccination is also efficacious in women up to age 45 years.
In the transplant population, HPV vaccines are generally safe, but evidence for decision making is limited to observational analyses. In a single cohort study, seropositivity was only detected in approximately 50% to 60% of patients, depending on genotypes, and higher tacrolimus levels were also detected in nonresponders.67

Early Detection

Although prevention is the key to preventing serious illnesses in the transplant populations, early detection of disease in patients at risk may provide the opportunity to initiate effective treatments and prevent advanced-stage disease. Polyomavirus is an important pathogen associated with interstitial nephritis and nephropathy in kidney transplant recipients. The risk of graft loss, once nephropathy has developed, ranges from 30% to 50% within 5 years.68 In the absence of effective antiviral treatments, management of polyomavirus (BK) nephropathy relies on early detection and timely reduction of immunosuppression with urine real-time polymerase chain reaction (RT-PCR) or urine cytology. Additional studies of diagnostic test accuracy are required to determine which test or tests best distinguish a transplant recipient with BK nephropathy from those without the disease. The conduct and reporting of all diagnostic test accuracy studies should adhere to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines.69

Economic Evaluations

Economic evaluation can be used to assess the costs and benefits of interventions and help policy makers identify interventions that maximize health benefits and minimize resource use.70,71
A recent analysis reported that living-donor kidney transplant is cost-saving compared with dialysis because most recipients live longer and incur fewer costs. For those who received a lower kidney donor profile index (KDPI) deceased-donor kidney transplant, the incremental cost-effectiveness ratio (ICER) ranged between (USD) $36,000 to $40,000 per quality-adjusted life-year (QALY), and approximately $60,000 per QALY for higher KDPI deceased-donor kidney transplant and in patients who are immunologically complex. Despite the higher costs, the survival advantage of kidney transplantation over dialysis is so substantial that all options are highly cost-effective, based on a willingness-to-pay threshold of $100,000 (USD) per QALY.72

Although the cost-effectiveness and cost utility of kidney transplantation compared with dialysis are not in doubt, more uncertainty remains about which new treatments will lead to further gains, compared with current management. In some cases, clinical trial data are not available to guide such decisions, and in this circumstance an economic evaluation could be used to estimate the likely costs and effects of any interventions. A published example is the evaluation of cidofovir in kidney transplant recipients with BK nephropathy. Cidofovir is often used in patients with significant nephropathy resulting from BK infections. All efficacy and adverse effects data informing cidofovir use in transplant recipients are from observational studies. Decision analysis suggests that the addition of cidofovir may incur a small survival gains, approximately 2.2 days with savings of approximately $20,000 AUD over the lifetime of a recipient. However, uncertainties exist because of unclear clinical efficacy data, where the incremental health benefits could range from –1 (harm rather than benefit) to 1.3 lifeyears-gained, with incremental costs varying between an extra $30,000 to savings of $27,000. Other examples of how economic analysis has been used to assess the likely impact of treatment strategies on outcomes in kidney transplantation include immunosuppression use, induction therapy, cancer screening, and machine perfusion.

PATIENT-REPORTED OUTCOMES AFTER TRANSPLANTATION

Kidney transplantation is intended to improve both the survival and QOL of patients with kidney failure, but the adverse effects from immunosuppression and coexisting comorbidities such as infections, vascular disease, and mental health disorders may affect the recipients' capacity to return to normality, participate, and enjoy daily life activities such as work, education, and recreation. Other factors including age, sex, the types of transplant received, and the duration since transplantation also have a major impact on the overall QOL experienced. People adapt to their illnesses, but the extent and the time needed for the adaptation are associated with the types of transplants they receive and the complications that occur during the perioperative and postoperative periods. Compared with deceased-donor transplant recipients, patients who have received a living-donor transplant experienced better social functioning, vitality, and physical functioning in the first 5 years after transplantation but not thereafter.73

Inclusion of patient-centered outcome data in research and clinical care allows for explicit evaluation of the end-user engagement, satisfaction, and potentially real-world adherence. There are several reasons for incorporating patient-reported outcomes in the care of transplant recipients. First, patients are accurate in describing their own symptoms, pain, functions, and QOL. Second, patient-reported outcomes can be used to support shared decision making and patient-centered care. Finally, patient-reported outcomes can also generate valuable data on the treatment effectiveness of interventions, the side effects, and delivery of care in clinical practice. The Standardised Outcomes in Nephrology–Kidney Transplantation (SONG-Transplant) Initiative has identified a core set of clinical trial outcomes that reflect the priorities of key stakeholders,74 based on a systematic review and an international Delphi survey that included key stakeholders such as patients, caregivers, and health professionals. The full range of outcomes are shown in Fig. 114.4. Although there was general agreement between healthcare professionals, patients, and caregivers that graft survival, function, cancer and infections, and QOL should be included in the core outcomes set, there was incongruency in their opinions regarding the best tools to measure these domains.

Outcome Measures

Life participation is an example of an outcome that is critically important for transplant recipients and their families but is not much considered by clinicians or researchers. Life participation can be defined as the ability to participate in activities that provide a sense of fulfillment, enjoyment, control, and hope. This encompasses a range of activities including, but not limited to, paid and volunteer work, family duties, social functions, recreational and leisure activities, and hobbies. Although life participation is a high priority for patients and

SONG-TX

1

2 3

2

3

Ability to work
Blood pressure
Bone disease
Cancer (skin)

1 GRAFT HEALTH
1 CORE OUTCOMES
Critically important
to all stakeholder groups
Report in all trials

2 MIDDLE TIER
Critically important to
some stakeholder groups
Report in some trials

CARDIOVASCULAR
DISEASE
CANCER
INFECTION
LIFE PARTICIPATION
MORTALITY

Anxiety
Appearance

Anemia

Cognition
Depression
Diabetes
Eye problems
Fatigue
High cholesterol

Hospitalization
Sun sensitivity
Surgical complications

Arthritis
Fertility
Gastrointestinal
disorders

Hand tremors
Impact on family
Mood swings
Muscle weakness
Pain
Pins and needles
Sleep disturbance
Weight gain

3 OUTER TIER
Important to some or
all stakeholder groups
Consider for trials

Fig. 114.4 Standardised Outcomes in Nephrology (SONG)-Transplant Core Outcomes. (Courtesy Outcome Measures in Rheumatology [OMERACT]).

their families, the domains, psychometric properties, and content of the outcome measures for life participation in transplant recipients have not been defined.75 More importantly, this outcome is infrequently explored and inconsistently evaluated in intervention trials in transplant recipients. Life participation can be conceptualized into two dimensions: obligatory and nonobligatory. Obligatory activities are crucial for survival and independence such as work, education, and household chores, whereas nonobligatory events include mainly leisure activities but are important to maintain the well-being of the individual and return a sense of normalcy. There are many tools that measure life participation. Most of these evaluated constructs (such as QOL of the patients and caregivers) included life participation in the questionnaire. Few specifically evaluate the specific aspects of life participation such as daily activities of living and disability assessment.

However, many of these measures have not yet been validated in kidney transplant populations, and further research is needed.

CONCLUSION

Kidney transplant recipients value optimal graft function and survival. Although most patients are willing to accept some adverse side effects as being necessary to avoid complications such as acute rejection, the high incidence of other undesirable outcomes such as infection and cancer indicate that further research is needed. Finally, the relative lack of data on how best to improve other patient-important outcomes such as life participation and other symptom burden should be a research priority for the transplant community.

SELF-ASSESSMENT QUESTIONS

1. Actuarial survival is a:
A. method of calculating how long a patient will live after kidney transplant failure.
B. statistical method of maximizing the information available for analysis of outcome from a group of patients and events.
C. way of making “actual results” seem more plausible.
D. statistical method to estimate the outcomes of patients who are lost to follow-up.
2. The composite endpoint accepted by the US Food and Drug Administration for immunosuppressive drug trials in transplantation includes:
A. graft failure and patient death.

B. graft failure, chronic rejection, and lost to follow-up.
C. acute rejection, graft failure, lost to follow-up, and patient death.
D. biopsy-proven acute cellular and acute antibody-mediated rejection.
3. Meta-analysis is a:
A. way of deciding which of several randomized trials is correct.
B. statistical software package.
C. method of combining the results from all similar trials to gain statistical power.
D. trial design used in large studies to decide which factor is most important in determining an outcome.

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REFERENCES

1. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. Lancet. 2020;395(10225):662–664.
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011;11(10):2093–2109.
3. Wong G, Howard K, Chapman JR, et al. Comparative survival and economic benefits of deceased donor kidney transplantation and dialysis in people with varying ages and co-morbidities. PLoS One. 2012;7(1):e29591.
4. Coemans M, Süsal C, Döhler B, et al. Analyses of the short- and longterm graft survival after kidney transplantation in Europe between 1986 and 2015. Kidney Int. 2018;94(5):964–973.
5. Tong A, Gill J, Budde K, et al. Toward establishing core outcome domains for trials in kidney transplantation: report of the Standardized Outcomes in Nephrology-Kidney Transplantation Consensus Workshops. Transplantation. 2017;101(8):1887–1896.
6. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725–1730.
7. Merion RM, Goodrich NP, Johnson RJ, et al. Kidney transplant graft outcomes in 379 257 recipients on 3 continents. Am J Transplant. 2018;18(8):1914–1923.
8. Scheffner I, Gietzelt M, Abeling T, Marschollek M, Gwinner W. Patient survival after kidney transplantation: important role of graft-sustaining factors as determined by predictive modeling using random survival forest analysis. Transplantation. 2020;104(5).
9. Schaapherder A, Wijermars LGM, de Vries DK, et al. Equivalent long-term transplantation outcomes for kidneys donated after brain death and cardiac death: conclusions from a nationwide evaluation. EClinicalMedicine. 2018;4:25–31.
10. Gondos A, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. Transplantation. 2013;95(2).
11. Clayton PA, McDonald SP, Russ GR, Chadban SJ. Long-term outcomes after acute rejection in kidney transplant recipients: an ANZDATA analysis. J Am Soc Nephrol. 2019;30(9):1697.
12. Lim WH, Wong G, Pilmore HL, McDonald SP, Chadban SJ. Long-term outcomes of kidney transplantation in people with type 2 diabetes: a population cohort study. Lancet Diabetes Endocrinol. 2017;5(1):26–33.
13. ANZDATA Registry. 42nd Report. Chapter 1: Incidence of Renal Replacement Therapy for End Stage Kidney Disease. Australia and New Zealand Dialysis and Transplant Registry; 2019. Adelaide, Australia. http://www.anzdata.org.au.
14. So S, Au EHK, Lim WH, Lee VWS, Wong G. Factors influencing long-term patient and allograft outcomes in elderly kidney transplant recipients. Kidney International Reports. 2020;6(3):727–736.
15. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. Transplantation. 2007;83(8).
16. Veroux M, Grosso G, Corona D, et al. Age is an important predictor of kidney transplantation outcome. Nephrol Dial Transplant. 2012;27(4):1663–1671.
17. Keith DS, Demattos A, Golconda M, Prather J, Norman D. Effect of donor recipient age match on survival after first deceased donor renal transplantation. J Am Soc Nephrol. 2004;15(4):1086.
18. Lim WH, Chang S, Chadban S, et al. Donor–recipient age matching improves years of graft function in deceased-donor kidney transplantation. Nephrol Dial Transplant. 2010;25(9):3082–3089.
19. Loupy A, Haas M, Roufosse C, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T cell– and antibody-mediated rejection. Am J Transplant. 2020;20(9):2318–2331.

20. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. 2018 reference guide to the Banff classification of renal allograft pathology. Transplantation. 2018;102(11).

21. Solez K, Racusen LC. The Banff classification revisited. Kidney Int. 2013;83(2):201–206.
22. Eddy S, Mariani LH, Kretzler M. Integrated multi-omics approaches to improve classification of chronic kidney disease. Nat Rev Nephrol. 2020;16(11):657–668.
23. Yang JYC, Sarwal MM. Transplant genetics and genomics. Nat Rev Genet. 2017;18(5):309–326.
24. O'Connell PJ, Zhang W, Menon MC, et al. Biopsy transcriptome expression profiling to identify kidney transplants at risk of chronic injury: a multicentre, prospective study. Lancet. 2016;388(10048):983–993.
25. Eikmans M, Gielis EM, Ledeganck KJ, Yang J, Abramowicz D, Claas FFJ. Non-invasive biomarkers of acute rejection in kidney transplantation: novel targets and strategies. Front Med. 2019;5(358).
26. Halloran PF, Reeve JP, Pereira AB, Hidalgo LG, Famulski KS. Antibodymediated rejection, T cell–mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies. Kidney Int. 2014;85(2):258–264.
27. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010;5(6):1003.
28. Mariat C, Maillard N, Phayphet M, et al. Estimated glomerular filtration rate as an end point in kidney transplant trial: where do we stand? Nephrol Dial Transplant. 2008;23(1):33v38.
29. Clayton PA, Lim WH, Wong G, Chadban SJ. Relationship between eGFR decline and hard outcomes after kidney transplants. J Am Soc Nephrol. 2016;27(11):3440.
30. Grams ME, Sang Y, Ballew SH, et al. Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: an individual participant meta-analysis of observational data. J Am Soc Nephrol. 2019;30(9):1746–1755.
31. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis. 2020;75(1):84–104.
32. Legendre C, Anglicheau D. Proteinuria in kidney transplantation: an ongoing story. Nat Rev Nephrol. 2013;9(5):251–252.
33. Amer H, Fidler ME, Myslak M, et al. Proteinuria after kidney transplantation, relationship to allograft histology and survival. Am J Transplant. 2007;7(12):2748–2756.
34. Fotheringham J, Angel C, Goodwin J, Harmer AW, McKane WS. Natural history of proteinuria in renal transplant recipients developing de novo human leukocyte antigen antibodies. Transplantation. 2011;91(9).
35. Yarlagadda SG, Coca SG, Garg AX, et al. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. Nephrol Dial Transplant. 2008;23(9):2995–3003.
36. Hall IE, Reese PP, Doshi MD, et al. Delayed Graft function phenotypes and 12-month kidney transplant outcomes. Transplantation. 2017;101(8).
37. Yarlagadda SG, Coca SG, Formica Jr RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant. 2009;24(3):1039–1047.
38. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int. 2015;88(4):851–858.
39. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. Transplantation. 1997;63(7):968–974.

40. Lim WH, Johnson DW, Teixeira-Pinto A, Wong G. Association between duration of delayed graft function, acute rejection, and allograft outcome after deceased donor kidney transplantation. Transplantation. 2019;103(2):412–419.
41. Lim WH, McDonald SP, Kennedy SE, Larkins N, Wong G. Association between slow and delayed graft function with graft outcomes in pediatric and adolescent deceased donor kidney transplant recipients. Transplantation. 2017;101(8):1906–1912.

42. Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8(4):753–760.
43. Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. J Am Soc Nephrol. 2005;16(10):3015–3026.
44. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349(24):2326–2333.
45. Nankivell BJ, Chapman JR. Chronic allograft nephropathy: current concepts and future directions. Transplantation. 2006;81(5):643–654.
46. Cosio FG, Grande JP, Larson TS, et al. Kidney allograft fibrosis and atrophy early after living donor transplantation. Am J Transplant. 2005;5(5):1130–1136.
47. Mannon RB, Matas AJ, Grande J, et al. Inflammation in areas of tubular atrophy in kidney allograft biopsies: a potent predictor of allograft failure. Am J Transplant. 2010;10(9):2066–2073.
48. Nankivell BJ, Shingde M, Keung KL, et al. The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: the Banff i-IFTA lesion. Am J Transplant. 2018;18(2):364–376.
49. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88(2):231–236.
50. Zhong Y, Schaubel DE, Kalbfleisch JD, Ashby VB, Rao PS, Sung RS. Reevaluation of the kidney donor risk index. Transplantation. 2019;103(8):1714–1721.
51. Gupta A, Francos G, Frank AM, Shah AP. KDPI score is a strong predictor of future graft function: moderate KDPI (35 - 85) and high KDPI (> 85) grafts yield similar graft function and survival. Clin Nephrol. 2016;86(10):175–182.
52. Kurian SM, Heilman R, Mondala TS, et al. Biomarkers for early and late stage chronic allograft nephropathy by proteogenomic profiling of peripheral blood. PLoS One. 2009;4(7):e6212.
53. Menon MC, Murphy B, Heeger PS. Moving biomarkers toward clinical implementation in kidney transplantation. J Am Soc Nephrol. 2017;28(3):735.
54. Naesens M, Anglicheau D. Precision transplant medicine: biomarkers to the rescue. J Am Soc Nephrol. 2018;29(1):24.
55. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death after kidney transplantation: an analysis by era and time post-transplant. J Am Soc Nephrol. 2020;31(12):2887–2899.
56. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006;296(23):2823–2831.
57. Au EH, Chapman JR, Craig JC, et al. Overall and site-specific cancer mortality in patients on dialysis and after kidney transplant. J Am Soc Nephrol. 2019;30(3):471–480.
58. Ramspek CL, Evans M, Wanner C, et al. Kidney failure prediction models: a comprehensive external validation study in patients with advanced CKD. J Am Soc Nephrol. 2021;32(5):1174–1186.
59. Lim WH, Russ GR, Wong G, Pilmore H, Kanellis J, Chadban SJ. The risk of cancer in kidney transplant recipients may be reduced in those

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maintained on everolimus and reduced cyclosporine. Kidney Int. 2017;91(4):954–963.
Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ (Clinical research ed). 2014;349:g6679.
Lum EL, Huang E, Bunnapradist S, Pham T, Danovitch G. Acute kidney allograft rejection precipitated by lenalidomide treatment for multiple myeloma. Am J Kidney Dis. 2017;69(5):701–704.
Murakami N, Mulvaney P, Danesh M, et al. A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant. Kidney Int.
Nambiar P, Silibovsky R, Belden KA. Infection in kidney transplantation. Contemporary Kidney Transplantation. 2018:307–327.
Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. Clin J Am Soc Nephrol. 2012;7(12):2058.
Quadrivalent Vaccine against human papillomavirus to prevent highgrade cervical lesions. N Engl J Med. 2007;356(19):1915–1927.
Signorelli C, Odone A, Ciorba V, et al. Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence. Epidemiol Infect. 2017;145(10):1962–1982.
Vinkenes E, Nielsen MA, Blaakaer J. Is there evidence for efficacy of human papillomavirus vaccination in solid organ transplant recipients? Eur J Obstet Gynecol Reprod Biol. 2019;4:100015.
Agha I, Brennan DC. BK virus and immunosuppressive agents. Advances in Experimental Medicine and Biology. 2006;577:174–184.
Bossuyt PM, Reitsma JB, Bruns DE, et al. Stard 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.
Wong G, Howard K, Craig JC. Economic evaluation in clinical nephrology: Part 1. An introduction to conducting an economic evaluation in clinical practice. Nephrology (Carlton, Vic). 2010;15(4):434–440.
Chung R, Howard K, Craig JC, Chapman JR, Turner R, Wong G. Economic evaluations in kidney transplantation: frequency, characteristics, and quality—a systematic review. Transplantation. 2014;97(10).
Axelrod DA, Schnitzler MA, Xiao H, et al. An economic assessment of contemporary kidney transplant practice. Am J Transplant. 2018;18(5):1168–1176.
Bellini MI, Courtney AE, McCaughan JA. Living donor kidney transplantation improves graft and recipient survival in patients with multiple kidney transplants. J Clin Med. 2020;9(7):2118.
Ju A, Josephson MA, Butt Z, et al. Establishing a core outcome measure for life participation: a standardized outcomes in nephrologykidney transplantation consensus workshop report. Transplantation.

2019;103(6):1199–1205.
Ju A, Chow BY, Ralph AF, et al. Patient-reported outcome measures for life participation in kidney transplantation: a systematic review. Am J Transplant. 2019;19(8):2306–2317.

Self-Assessment Answers

CHAPTER 1

CHAPTER 4

1. B. Myofibroblasts
2. B. Have contractile properties
3. C. The thin ascending limbs of long loops

1. B. Detects Bence Jones proteinuria
2. B. All crystals are birefringent under polarized light.
3. D. Allow the examination of a high number of samples in a short period of time

CHAPTER 2

1. A and D

2.

A. Correct. The proximal tubule normally reclaims almost all of the filtered glucose via SGLT2. Impairment of this pathway can explain glycosuria in Fanconi syndrome.

B. Impaired fluid reabsorption in the proximal tubule can explain polyuria. However, the proximal tubule is “leaky” and cannot sustain a large osmotic gradient, so this statement is incorrect. It reabsorbs large amounts of water because of a high hydraulic permeability.

C. Approximately 65% of the filtered calcium is reabsorbed in the proximal tubule, and injury to this segment can cause hypercalciuria. This answer is incorrect because calcium reabsorption mostly occurs through the paracellular pathway and not via a calcium pump in the apical membrane.

D. The proximal tubule reabsorbs phosphate via a dedicated cotransport protein that uses the electrochemical gradient for sodium. Impairment of this process, as can occur in Fanconi syndrome, causes hyperphosphaturia.

E. This is incorrect. The proximal tubule is a leaky epithelium.

3.

A. Vasopressin-stimulated sodium and urea transport in the thick limb of Henle and will increase the gradient.

B. Correct. Increased blood flow through the medullary vasa recta causes “washout” of osmolytes from the interstitial fluid, diminishing the gradient.

C. Activation of this system increases the medullary gradient.

D. Activation of this system increases the medullary gradient.

E. Urea contributes significantly to the gradient.

CHAPTER 3

1. D. Larger than average body size based on height and weight is the most likely explanation.
2. F. Chronic kidney disease is defined as markers of kidney damage or decreased GFR for ≥3 months, so ascertainment of kidney damage and confirmation of decreased GFR could be used to confirm the diagnosis.
3. B. ACE inhibitors cause a reversible decline in GFR in patients with CKD.

CHAPTER 5

1. B. This is an M-mode tracing of the mitral valve obtained from parasternal long axis view, plotting the excursion of the anterior mitral leaflet over time. It is composed of two distinct diastolic waves, E and A, representing the early passive diastolic filling of the left ventricle and active filling from atrial contraction, respectively. E-point septal separation (EPSS) is measured from the peak of E-wave to the interventricular septum; an EPSS >7 mm is generally considered a marker of severe LV systolic dysfunction. The

image does not demonstrate either color flow or a spectral Doppler tracing.

2. C. There is an anechoic branching area on the grayscale image mimicking hydronephrosis, but the color Doppler demonstrates blood flow indicating that these are just prominent vessels unrelated to the patient’s AKI. Parapelvic cysts can mimic hydronephrosis, but they are usually well circumscribed (nonbranching) and do not demonstrate flow. This is not a typical location for hematoma except when there is bleeding into the collecting system following a kidney biopsy. A hematoma is a localized collection of blood and hence does not demonstrate flow on color Doppler.
3. A. This anechoic localized area with septations likely represents a hematoma, which is not an uncommon finding in the early posttransplant period. Fresh blood is completely anechoic, while fibrin strands/echogenic material start to appear during the clotting process. Urinoma typically does not contain internal echogenicities. It is not hydronephrosis because it is outside the kidney. Pelvic ascites is unlikely to be localized at one pole of the kidney or contain septations.
4. D. B-lines are due to thickened interlobular septae. They generally represent pulmonary congestion/edema but can be seen in other conditions such as fibrosis and pneumonia. Sonographic findings should always be interpreted in the appropriate clinical context.
5. A. Normal portal vein waveform is relatively continuous with little pulsatility (<30% during a given cardiac cycle). As the right atrial pressure increases, it becomes increasingly pulsatile. Part B demonstrates more than 50% pulsatility. Parts C and D demonstrate 100% pulsatility with flow reversal during systole (below the baseline component) indicating severe venous congestion.

Self-Assessment Answers

CHAPTER 6

1.
2.
3.
4.
5.

C. Hypoechoic
A. CO2 angiography
D. Diffusion-weighted MRI
D. History of cerebral aneurysm clip
A. Noncontrast CT scan

CHAPTER 7

1.

A. Correct. Half-life of naproxen is up to 16 hours; therefore after 24 hours platelet function would still be deranged.

B. This BP level is not a contraindication.

C. This may indicate the presence of urinary infection, but in the absence of urinary symptoms it is not a contraindication to biopsy.

D. With appropriate ultrasound imaging it should be possible to perform a biopsy of the kidney away from the cysts.

E. Although this may make visualization of the kidneys difficult, high BMI is not a contraindication to kidney biopsy.

2.

A. This is likely related to preeclampsia, and a biopsy should not be required for diagnosis.

B. Investigation for this can be delayed until after the pregnancy is complete, assuming kidney function is stable.

C. This will require imaging of the renal tract, but a kidney biopsy is unlikely to be useful during pregnancy.

D. This is likely related to preeclampsia, and a biopsy should not be required for diagnosis.

E. Correct. This may indicate the presence of a kidney disease that may require specific treatment during pregnancy; therefore knowledge of the underlying pathologic process is important.

3.

A. This is possible, but B is a better answer because the bleeding diathesis is correctable.

B. Correct. This will provide functioning platelets to circumvent the clopidogrel-mediated platelet dysfunction.

C. This will not reverse clopidogrel-induced platelet dysfunction.

D. A delay of at least 7 days is required for correction of the effects of aspirin and clopidogrel on platelets.

E. This will not reverse clopidogrel-induced platelet dysfunction.

4.

A. This supports a diagnosis of diabetic nephropathy, and the diagnosis usually can be comfortably made with clinical criteria alone.

B. This supports a diagnosis of diabetic nephropathy, and the diagnosis can usually be comfortably made with clinical criteria alone.

C. This would be expected with diabetic nephropathy.

D. Correct. The proteinuria of diabetic nephropathy is progressive over months to years. A negative urinalysis 4 months earlier suggests the presence of an alternative diagnosis to diabetic nephropathy.

E. This provides no additional information in terms of clarifying the cause of proteinuria.

CHAPTER 8

1. B. This patient presents with extracellular fluid expansion secondary to chronic liver disease/cirrhosis, as suggested by consistent history of alcohol dependence and physical examination findings. In cirrhosis, nitric oxide and carbon monoxide overproduction leads to splanchnic and peripheral arteriolar vasodilation. In advanced stages of cirrhosis, this causes underfilling of the systemic arterial vascular space. Baroreceptor-mediated activation of RAAS, sympathetic nervous system stimulation, and nonosmotic release of ADH occur to restore the normal blood volume homeostasis. This results in renal sodium and water retention and constitutes the major mechanism for sustained ascites formation.

2. D. Therapy for extracellular fluid volume excess in patients with cirrhosis attempts to achieve negative sodium balance by dietary sodium restriction and diuretics. Other measures can be used when the patient has inadequate or no response to diuretics or when rapid decompression of the abdomen is desired. Large-volume paracentesis with albumin infusion can thus be used. Intravenous mannitol has augmented natriuresis in diuretic-resistant patients with cirrhosis but is not typically recommended.

3. C. The clinical scenario is consistent with presumptive SBP. Although the patient remains hypotensive, there is clear evidence that her venous volume is now replete; in this case a pressor might be a reasonable choice. Randomized trials have reported adverse outcomes of patients in the intensive care unit treated with HES compared with lactated Ringer’s solution. The creatinine rise indicates acute kidney injury, and the urine sodium concentration suggests that she may have developed acute tubular necrosis. There is no clear indication for dialysis despite the rise in creatinine.

CHAPTER 9

1. D. A calculation would reveal that this patient is excreting electrolyte-free water despite the urine osmolality being much greater than serum osmolality. In such a patient setting, the failure to replace electrolyte-free water losses results in increased serum sodium concentration. The hyperosmolality of the urine is primarily caused by the extremely high excretion of urea in this patient receiving high-protein enteral feedings.

2. B. The data fulfil the criteria for SIADH. This patient not taking a thiazide diuretic does not protect her from developing SIADH, which can occur in elderly individuals occasionally without an obvious underlying cause. The high urinary osmolality speaks against poor solute intake. There is no known change in vasopressin metabolism in elderly patients.

3. B. This patient is excreting electrolyte-free water, most likely because of the loop diuretic. The regimen would match water losses, and the serum sodium would remain unchanged. Because the patient is also hypervolemic, a negative sodium balance is desirable and would be undermined by the other three regimens, all of which contain sodium.

CHAPTER 10

1. D. Hypomagnesemia often leads to renal K+ wasting and hypokalemia. Correction of the hypomagnesemia, whether by discontinuation of causative medications or by magnesium supplementation, corrects the renal K+ wasting and allows successful correction of the hypokalemia.

2.

A. Correct. Blockade of α1-adrenoreceptor can stimulate cellular K+ uptake. This class of medication does not lead to hyperkalemia.

B. Blockade of β2 receptors decreases β2-adrenoreceptor stimulated K+ uptake, and so leads to decreased K+ uptake and predisposes to hyperkalemia.

C. MR blockers decrease mineralocorticoid-induced cellular K+ uptake and inhibit principal cell-mediated renal K+ excretion, thereby increasing the risk of hyperkalemia.

D. Calcineurin inhibitors decrease collecting duct potassium secretion, thereby increasing the risk of hyperkalemia.

3. E

All are correct. Hypokalemia decreases both insulin release and insulin receptor sensitivity. Hypokalemia, when chronic, can lead to renal interstitial fibrosis and development of chronic kidney disease. Hypokalemia increases renal ammonia generation and addition to the renal vein and can contribute to generation of hyperammonemia and hepatic encephalopathy in patients with acute or chronic liver disease. Hypokalemia both has CNS effects to stimulate polydipsia and to impair expression of proteins such as AQP2, UT-A, and UT-B involved in renal concentrating mechanism.

CHAPTER 11

1.
2.
3.
4.
5.

C. Malignant neoplasias
C. Impaired calcitriol synthesis
A. Proximal tubule
D. FGF-23
C. Urinary chloride

CHAPTER 12

1. B. K deficiency increases ammoniagenesis.
2. D. Nonthyroid glycoproteins Rhbg and Rhcg are involved in collecting duct ammonia secretion.
3. C. Animal foods are high in protein and organophosphates and provide a net acid diet.

CHAPTER 13

1. B. Serum HCO_3^- concentration will increase after oral bicarbonate administration but then decrease to 18 mmol/L after therapy is discontinued.
2. C. Serum uric acid levels are likely to be low in this patient.
3. A. Propylene glycol toxicity

CHAPTER 14

1. A. Metabolic alkalosis can be divided into disorders with a low urine [Cl] (<20 mEq/L) and those with a high urine [Cl] (>20 mEq/L). When the urine [Cl] is low, the metabolic alkalosis is generally maintained, to a large degree, by a state of ECF volume depletion, which is the case with this patient. When the urine [Cl] is high, the alkalosis is generally maintained by the combination of generous distal tubule salt delivery and hyperaldosteronism (or a hyperaldosterone-like state). ECF volume is usually expanded. However, an exception to this general rule is increased renal salt excretion generated by diuretics or due to inherited tubule electrolyte transport disorders. Therefore, with vomiting or NG suction, the urine [Cl] is persistently low. In contrast, the urine [Na], [K], and pH may cycle up and down as bicarbonate salts are intermittently excreted.
2. C. This man has hypokalemia, potassium depletion, and metabolic alkalosis generated by NG suction. The alkalosis was primarily due to the loss of HCl in the aspirate. In addition, hypokalemia and K depletion, resulting from urinary K loss, causes K to move from the intracellular space to the extracellular space in exchange for protons. This further exacerbates his metabolic alkalosis. The

alkalosis is maintained by the kidneys as a result volume depletion, avid kidney salt retention, and secondary hyperaldosteronism and hypokalemia (which also stimulates renal H secretion). Treatment of the metabolic alkalosis requires expansion of ECF volume and K repletion. A proton pump inhibitor will ameliorate (but not completely prevent) proton loss but will not correct the alkalosis. Although HCl infusion would correct the alkalosis, it is used only when all other means of correction have failed or are not available. Furthermore, HCl is difficult to administer, or unavailable, at many institutions. Kidney replacement therapy is reserved for treatment of metabolic alkalosis only in individuals with kidney failure.
3. C. This woman has a hypokalemic metabolic alkalosis and her urine chemistries show a low chloride concentration, indicating ECF volume depletion. Urine sodium and potassium are elevated due to intermittent renal excretion of bicarbonate. Individuals with primary hyperaldosteronism should have an elevated BP and an increase in urine [Cl]. Patients with Gitelman syndrome or active diuretic use will have an elevated urine chloride. However, if diuretics had been stopped prior to obtaining the lab tests, the urine [Cl] might be low. However, under those circumstances the urine sodium and potassium concentrations would usually also be low. Some of these patients induce vomiting and also take diuretics.

CHAPTER 15

1.
A. Respiratory acidosis
B. Yes
C. The patient has an acute and severe asthma exacerbation. Most of the time, an asthma exacerbation is accompanied by respiratory alkalosis secondary to the tachypnea. However, in this case, the respiratory acidosis is a sign that the patient has impaired air exchange and may be tiring as well. She has impending respiratory failure and may need to be intubated and mechanically ventilated.
2. Step 1: Look at the pH to classify if the person is acidotic or alkalemic; the patient is acidotic. Step 2: Is the primary disorder metabolic or respiratory? Metabolic because a low serum bicarbonate level is a feature of metabolic acidosis (which in this case is 8 mEq/L). In respiratory acidosis the pCO_2 should be elevated. Step 3: If the primary disorder is respiratory is it chronic or acute? If the primary disorder is metabolic, is the anion gap elevated? The anion gap is $[Na-(Cl+HCO_3] = 135 - (100 + 8) = 27$. Step 4: Is the compensation for the primary disorder appropriate? The expected pCO_2 in a metabolic disorder is calculated using Winter’s formula ($1.5 \times [HCO_3] + 8 \pm 2 = 18$ to 22). Since the measured PCO_2 is higher than this expected value, concomitant respiratory acidosis is present.Thus, this patient has a combined high anion gap metabolic acidosis and respiratory acidosis. The delta anion gap (measured – normal) is 15 (assuming a normal anion gap of 12), and the delta bicarbonate is 16 (assuming a normal serum bicarbonate level of 24 mmol/L). Because the delta gap and the delta bicarbonate are similar, no addition metabolic disturbance is present.

CHAPTER 16

1.
A. Tubular proteinuria is low-molecular-weight proteinuria (including smaller proteins such as α1-microglobulin), whereas immunoglobulins are not usually present in significant amounts.
B. The metabolic response to heavy proteinuria is variable, and sometimes a normal serum albumin is maintained, probably as a result of both increased albumin synthesis and reduced catabolism.

C. In orthostatic proteinuria, there is less proteinuria when lying down; the early morning urine has no increase in protein.
D. Correct. Light chain excretion should be suspected when the urine dipstick is negative for albumin when other tests show heavy proteinurea.
E. Functional proteinuria occurs with fever, exercise, heart failure, and hyperadrenergic states.
2.
A. True (Kidney International. 2013;3[suppl 1]:1-150).
B. The major mechanism by which ACE inhibitors and ARBs reduce proteinuria is hemodynamic, reducing glomerular efferent arteriolar tone. However, they also may directly reduce glomerular capillary wall permeability.
C. The risk for hyperkalemia when using the combination of ACE inhibitor and ARB increases with falling GFR. Addition of a loop diuretic will usually reduce serum potassium.
D. Correct. A statin or a statin-ezetimibe combination is recommended in adults <50 years with CKD only if there is established cardiovascular disease or diabetes.
E. Dietary protein recommendations must account for urine protein loss to minimize the risk for malnutrition.
3.
A. Diuretic resistance is common in nephrotic syndrome with normal GFR; reduced protein binding limits drug access to the site of action in the tubule, increased protein binding once the drug has reached the urine reduces efficacy; and intestinal edema may reduce drug absorption.
B. Dietary protein recommendations should take account of urinary losses, but very high protein intakes (e.g., 2 to 3 g/kg/day), even if achievable, may worsen proteinuria.
C. Correct. It also should be considered when the serum albumin is 2 to 2.5 g/dL if there are additional risk factors for thromboembolism, such as immobilization in the hospital or a prior history of thromboembolism.
D. Microscopy and culture of ascetic fluid are required only when there is evidence of systemic infection, but routine screening for infection is not useful.
E. Nephrotic children are more prone than adults to hypovolemia. Care is needed to avoid too-rapid diuresis, which may provoke shock.

CHAPTER 17

1.
A. 70% of White and 50% of Asian patients with MN exhibit these autoantibodies.
B. 10% or less of patients with MN exhibit these autoantibodies.
C. Occur in neonatal MN.
D. Correct. Has been related to atypical hemolytic uremic syndrome.
E. May induce MN.
2. D. Despite autoantibody deposition in glomeruli and lung alveoli, there is usually no systemic complement consumption.
3. C. Podocyte injury, in particular slit diaphragm, typically leads to severe, often nephrotic proteinuria.
4.
A. FSGS mostly results from focal podocyte damage.
B. FSGS is a nonspecific term to describe a glomerular scar and should not be confused with the clinical entity FSGS.
C. Correct. Some clinical FSGS cases seem to originate from as-yet unknown circulating factors, which can give rise to rapid posttransplant recurrence of the disease.

D. So far there is little evidence to implicate autoimmunity in the majority of FSGS cases.
E. Although some FSGS may relate to mutations of podocyte proteins, most cases originate from other types of podocyte injury.

CHAPTER 18

1. D. Children may present with abdominal pain, ascites, and diarrhea.
2. B. Most patients with MCD will undergo one or more relapses.
3. A. Tacrolimus.
4. E. Rituximab can contribute to hypogammaglobulinemia.

CHAPTER 19

1. D. Amlodipine
2. B. Glomerulomegaly and perihilar segmental sclerosis and hyalinosis
3. C. Remission of proteinuria is a strong predictor of a favorable outcome.

CHAPTER 20

1.
2.
3.
4.
5.

E. Both C and D are possible
C. INF2
A. Glomerular epithelial
B. 30%
B. Coenzyme Q10

CHAPTER 21

1. B. THSD7A is a more common autoantigen in those of Japanese ancestry compared to Whites.
2. E. Microscopic hematuria is uncommon (5%–10%).
3. A. The predominant IgG subclass in many forms of primary MN is IgG3.
4. C. Immunosuppressive drug therapy should not be considered unless the patient has had persistent nephrotic-range proteinuria.

CHAPTER 22

1.
2.
3.
4.

A. MPGN secondary to a monoclonal gammopathy
D. Cryoglobulinemic glomerulonephritis
A. Mixed cryoglobulinemia
D. MPGN with IgG (++), IgM (+++), IgA (+), C3 (++), kappa (++), lambda (++)

CHAPTER 23

1. B. Full house of immunoglobulins and complement on immunofluorescence
2. E. An autoantibody against the alternative pathway C3 convertase
3. D. C3 glomerulopathy associated with heterozygous mutation of CFHR5
4. E. None of the above

CHAPTER 24

1. D
2. B. Cellular crescents were not associated with clinical outcome in the original Oxford Classification, although only a small number of cases had crescents in the original analysis.

3.
A. IgAN is more common in Asia than Europe.
B. The diagnosis of IgAN requires a kidney biopsy. Glycosylation of serumIgA is abnormal in the majority but not all cases of IgAN.
C. Correct. The renal pathologic features can be identical to those IgA vasculiitis.
D. More commonly, AKI with macrohematuria is due to acute tubular injury secondary to blockage by erythrocytes.
E. There is no evidence that different maintenance immunosuppressive regiments influence the recurrence rate of IgAN.
4.
A. Although most common in childhood, IgAV can occur at any age.
B. Correct. The same alteration in IgA glycosylation is described in IgAV and IgAN.
C. There is no evidence that delay reduces recurrence risk.
D. A French controlled trial of cyclophosphamide in adults with IgAV failed to detect benefit compared with steroids alone (Kidney International. 2010;78:495-502).
E. Randomized trials showed no benefit of corticosteroids in reducing nephritis risk.

CHAPTER 25

1. B
It is not uncommon for low levels of autoantibodies to persist some months after successful treatment of the acute illness, so we would not consider reinstituting plasma exchange or prolonging exposure to cyclophosphamide. In our experience, any persisting lowlevel autoantibodies disappear over subsequent months even when immunosuppression is withdrawn, so this is our preferred approach. However, one could justify continuing immunosuppression until autoantibodies become undetectable (or 1 year at most) to potentially bring forward the time when transplantation could be considered, in which case MMF would probably be preferred over continuing cyclophosphamide.
2. C
Recovery of kidney function is very unlikely if all glomeruli are severely affected with crescents. In such cases there is no renal benefit from immunosuppression, so potentially toxic treatment is only justified if there is lung hemorrhage. In this case we would recommend supportive treatment and close monitoring in anticipation of spontaneous reestablishment of self-tolerance and disappearance of autoantibodies, followed by preparation for renal transplantation.
3. B
Goodpasture syndrome generally has such an acute and dramatic manifestation, with kidney failure, hematuria, and oliguria with normal sized kidneys; it does not generally get labeled “unknown cause.” In addition, recurrence of Goodpasture syndrome after transplantation is now practically unheard of. Alport syndrome, however, may progress without any particular symptoms and be labeled as unknown cause. New anti-GBM disease posttransplant is therefore more likely to be the very rare condition of Alport anti-GBM disease. In this case, subsequent analysis at a reference laboratory demonstrated there were abundant serum antibodies to alpha-5 collagen IV at the time the standard anti-GBM assay was negative.

CHAPTER 26

1. B. Small-vessel vasculitis.
2.
A. One-third to one-fourth of patients with anti-GBM also have ANCA.

B. ANCA disease may recur even if the anti-GBM disease enters remission.

C. Correct. ANCA occurs with anti-GBM, and the ANCA disease may recur even if the anti-GBM disease enters remission.

3.

A. GN does not occur in PAN. GN is a marker of small-vessel vasculitis, and PAN is a medium-vessel vasculitis.

B. Pulmonary hemorrhage does not occur in PAN. It is a marker of small-vessel vasculitis, and PAN is medium-vessel vasculitis.

C. Polymyalgia rheumatic is associated with giant cell arteritis and not PAN.

D. Correct. There is an association between hepatitis B infection and PAN.

4.

A. The gradual narrowing of arteries by chronic inflammation does not cause acute ischemia with infarction, unlike PAN, which can cause infarction because of acute inflammatory narrowing and thrombosis.

B. The gradual narrowing of arteries by chronic inflammation does not cause acute kidney failure.

C. GN is not a feature of Takayasu arteritis.

D. Correct. Narrowing of main renal arteries by the arteritis causes renovascular hypertension.

5.

A. Clinical trials have shown no difference in adverse events.

B. Correct. Clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.

C. Clinical trials have shown noninferiority between induction therapy with rituximab compared with cyclophosphamide.

D. Rituximab has been approved by the FDA for induction therapy.

CHAPTER 27

1. D. She could be treated with belimumab alone.
2. A. Continue the current dose of MMF, follow patient for a complete renal remission, and when achieved reduce MMF to 2 g/day and continue for at least 36 months of total immunosuppressive therapy, with ongoing monitoring for any evidence of LN relapse.
3. E. Mycophenolate mofetil
4. B. Order a kidney biopsy to determine if there is any residual histologic activity.

CHAPTER 28

1.
2.
3.
4.

E. A major prognostic factor for patient survival
C. Frequently responsible for nondiabetic glomerulosclerosis
E. Electron microscopy
A. Kidney failure

CHAPTER 29

1.
2.
3.
4.

C. Lecithin–cholesterol acyltransferase deficiency
B. Bezafibrate
C. Idiopathic (primary) membranous nephropathy
D. Antiphospholipid antibody test

CHAPTER 30

1. A. Thrombocytopenia and nonimmune hemolytic anemia, with or without neurologic and/or kidney dysfunction

1.e6
2.
3.
4.
5.

Self-Assessment Answers

B. Shiga toxin E. coli–associated hemolytic uremic syndrome
C. CFH mutations
B. Eculizumab
C. TTP with anti-ADAMTS13 antibodies

CHAPTER 31

1. B. Glomerulosclerosis, tubular atrophy, and tubulointerstitial lesions are typical pathologic findings in diabetic nephropathy.
2. E. Type of diabetes
3. D. Acanthocytes in urine sediment
4. B. Inflammasome activation in the diabetic kidney

CHAPTER 33

1. C. Add liraglutide to current regimen.
2. A. History of recurrent severe hypoglycemia
3. B. Intensive blood pressure lowering in the SPRINT trial was associated with lower rates of eGFR decline.
4. D. The cardiovascular benefits of SGLT2i are largely related to reductions heart failure hospitalizations, whereas there is stronger evidence of reductions in atherosclerotic cardiovascular disease with GLP-1 receptor agonists.

CHAPTER 34

1.
A. Atrial natriuretic peptides can work quickly but generally have only small effects on blood pressure in normal humans.
B. Endothelin has variable effects on blood pressure in normal humans, but most effects occur over hours to days.
C. Although the kallikrein-kinin system can act relatively quickly, it is thought to contribute only in minor ways to regulation of blood pressure in normal humans.
D. Modulation of the renin-angiotensin-aldosterone system generally takes hours to days to affect blood pressure in normal humans.
E. Correct. Catecholamines are heavily involved in modulation of blood pressure during hypovolemia and/or hemorrhage, especially in normal human subjects.
2.
A. None of his three measurements falls into the <120/<80 mm Hg range.
B. According to the ACC/AHA 2017 US hypertension guideline, the term, “elevated blood pressure” is properly used to categorize inoffice systolic blood pressures between 120 and 129 mm Hg, and diastolic blood pressures <80 mm Hg. All of this patient’s blood pressure measurements are above these categories.
C. Correct. HEDIS 2021 and its several predecessors have condoned the use of the lowest individual systolic and lowest diastolic blood pressures, even if measured separately, as “the blood pressure for this visit.” As a result, his blood pressure for this visit would be 138/88 mm Hg, which is in the stage 1 hypertension range according to the ACC/AHA US hypertension guideline.
D. Although four of his six numbers fall into the >140/>90 mm Hg range, HEDIS 2021 and its several predecessors recommend (or condone) the reporting of the lowest individual systolic and the lowest individual diastolic blood pressure, even if not part of the same measurement, as “the blood pressure for this visit.” This process differs from most clinical trials, which most often used the

average of the last two of three measurements.
E. This diagnosis is no longer part of the classification scheme for blood pressures in the ACC/AHA 2017 US hypertension guideline,

although it continues to be used overseas, typically for systolic blood pressure >140 mm Hg and diastolic blood pressure <90 mm Hg.

3.

A. This recommendation leaves unanswered the question of chronic kidney disease, which needs to be confirmed or rejected, and which might prompt drug therapy if his reduced eGFR is confirmed after 3 months.

B. This is most appropriate for a healthy person with prehypertension according to JNC 7. But there is the unresolved issue of chronic kidney disease, which needs to be confirmed or rejected, and which might prompt drug therapy if his reduced eGFR is confirmed more than 3 months later.

C. Correct. The diagnosis of chronic kidney disease hinges on a 3-month history of abnormal kidney function, which has not yet been established. Repeat testing to confirm the diminished estimated glomerular filtration rate is necessary.

D. This was the JNC 7 recommendation for healthy people with initial blood pressures in the stage 1 hypertension range. It might be appropriate here, but there is the unresolved issue of chronic kidney disease, which also needs to be addressed. Rechecking kidney function in 2 more months might be appropriate, but doing so would not fulfill the diagnostic criteria for chronic kidney disease.

E. The US FDA does not recognize albuminuria as an indication for antihypertensive drug therapy, and he does not yet meet the diagnostic criteria for chronic kidney disease, If, in 3 months' time, his estimated glomerular filtration rate is ≥60 mL/min/1.73 m2, he would then fulfill the ACC/AHA 2017 US hypertension guideline criteria for uncomplicated stage 1 hypertension, but since his 10year risk of a cardiovascular event is <10%, this guideline specifically exempts him from drug treatment until his blood pressure is ≥140/90 mm Hg. Many nephrologists would argue that even a little albuminuria is prognostically bad, but there are few, if any, randomized clinical trials involving patients with this level of albuminuria to demonstrate that giving an antiproteinuric drug improves the time to death, dialysis, or kidney transplantation.

4.

A. This is probably higher than the prevalence of pseudohypertension, which is said to be associated with a positive Osler maneuver. No such finding is described in the vignette; she is likely too young to have developed this condition.

B. This is the expected prevalence of secondary hypertension in the hypertensive population. Although it is possible that she has secondary hypertension, there are no clinical clues, and the description is more likely that of masked hypertension.

C. Correct. This is the expected prevalence of masked hypertension, which fits the description in her case. It is likely that an ambulatory blood pressure monitor or home blood pressure monitoring will demonstrate elevated blood pressures, which might prompt treatment. Some have speculated that masked hypertension may occur more often in people with childcare responsibilities if they arrange for a caregiver during office visits.

D. This is the expected prevalence of white coat hypertension, which does not fit her case history, in that she has target organ damage and normal office blood pressures.

E. This is the expected, age-adjusted prevalence of hypertension (defined as blood pressure ≥140/90 mm Hg) in the US over the last 20+ years. Yet her in-office blood pressures do not meet older diagnostic criteria (but the lowest diastolic was 80 mm Hg, which, in the ACC/AHA 2017 US hypertension guideline might qualify for this diagnosis, but if her estimated 10-year cardiovascular risk is

<10%, she would not be mandated to receive drug treatment). It is likely that since NHANES also uses an automated oscillometric

sphygmomanometer, she would probably not be identified as hypertensive in national surveys.

5.

A. Renal biopsy is more often used to determine the cause of glomerulonephritis or nephrotic syndrome and is seldom useful in the diagnosis of hypertension.

B. Although iothalamate clearance is more accurate than calculations of estimated glomerular filtration rate, it is expensive; exposes staff, patients, and the environment to radioactivity; and was abandoned by the National Institutes of Health after the vanguard phase of the African American Study of Kidney diseases and hypertension (AASK). The CKD-Epi equation is more accurate (especially for those with eGFR >60 mL/min/1.73 m2) than the updated MDRD equation, which is widely used by most US laboratories.

C. A search for a secondary cause of hypertension is typically undertaken only when there is strong suspicion on clinical grounds, or when the blood pressure is resistant to treatment. The idea of screening all hypertensives for secondary causes has not been recommended by any US hypertension guideline.

D. The most likely diagnosis for him is white coat hypertension, which typically does not respond with a lowered office blood pressure after institution of antihypertensive drug therapy. It might be worth a try, but it is unlikely to improve his office blood pressures much, and puts him at risk for hypotension outside the office.

E. Correct. The most likely diagnosis for him is white coat hypertension, but some people with this diagnosis progress to sustained hypertension, which can be detected by home blood pressure monitoring. If and when sustained hypertension is diagnosed, he would be a candidate for drug therapy. The threshold of 125/75 mm Hg is the expected home equivalent to an office blood pressure of 130/80 mm Hg.

CHAPTER 35

1. B. Salt sensitivity increases with age.
2. E. The presence of transmural necrosis should prompt consideration of vasculitis, not primary hypertension.
3. E. Although coffee is not a risk factor, caffeine tablets, or high caffeine content such as in “power drinks,” may be potential risk factors for hypertension.

CHAPTER 36

1. D. The guidelines do not recommend regular muscle-strengthening activity for all age groups.
2. B. 1 mm Hg
3. D. People younger than 40 years
4. B. Abstinence of from alcohol may reduce the risk of myocardial infarction.

CHAPTER 37

1. C. The recommended combinations of drug therapy for most patients with hypertension usually involve a RAS blocker combined with a CCB or diuretic.
2. A. Lowering BP to at least <140/90 mm Hg in all treated patients, if tolerated, is recommended by all guidelines.
3. E. Angiotensin receptor-neprilysin inhibitors are significantly more effective at lowering BP than ARBs alone.

4. E. RH is most effectively treated with further diuretic therapy.

CHAPTER 38

1. D. The patient has hypertensive urgency, not a hypertensive emergency. In the absence of target organ damage, the patient can

be treated less aggressively. The key is rapid follow-up (within a week).

2. C. While the INTERACT2 trial does suggest reduction of BP to levels of 140/90 mm Hg in subjects with hemorrhagic stroke, nitroprusside is not a desired antihypertensive agent as it obliterates cerebral autoregulation; nicardipine is a superior agent. Reducing BP to 160/90 mm Hg remains the standard target for these patients.

3. B. For subjects with aortic dissection, reducing the BP to 100 mm Hg systolic is the goal. Labetalol is an effective antihypertensive agent for this purpose.

CHAPTER 39

1.

A. Mutations affecting the aldosterone synthase gene (CYP11B2) are present in FH-I. They are not a common cause, however, of APA.

B. Mutations in the mineralocorticoid gene are not a common cause of APA.

C. Mutations in the AT1 receptor are not a common cause of APA. Some evidence suggests, however, that activating autoantibodies directed against the AT1 receptor may be pathogenic in primary aldosteronism from bilateral adrenal hyperplasia.

D. Correct. Mutations in the KCNJ5 gene are present in ~40% of APA.

E. Mutations in ENaC occur in Liddle syndrome but not in APA.

2.

A. Eplerenone appears to have less effect to decrease BP in patients with primary aldosteronism.

B. The rate of side-effects and drug discontinuation appears to be similar between spironolactone and eplerenone.

C. Correct. Spironolactone appears to decrease BP significantly more, by about two-fold, than does eplerenone in patients with primary aldosteronism.

D. The rate of side-effects and drug discontinuation appears to be similar between spironolactone and eplerenone.

3.

A. Most patients with primary aldosteronism do not have hypokalemia.

B. Cannot differentiate between primary aldosteronism and secondary hyperaldosteronism and has significantly less sensitivity to identify primary aldosteronism.

C. Although a suppressed plasma renin activity is a hallmark of primary aldosteronism, by itself it cannot identify primary aldosteronism.

D. Correct. This is the preferred first line test for primary aldosteronism.

E. Cannot differentiate primary aldosteronism from other causes of hypertension.

CHAPTER 40

1. D. May present as hypertension resistant to multiple drugs
2. B. 1 mg dexamethasone suppression test
3. C. 30% to 40%

Self-Assessment Answers

CHAPTER 41

CHAPTER 45

1. B

After intravenous tPA administration AHA/ASA guidelines recommend maintenance of BP <180/105 mm Hg. Therefore, a diastolic BP of 110 mm Hg should be lowered to a target value of <105 mm Hg. In this case the patient presented with signs consistent with an acute ischemic stroke, and given that the CT scan shows no hemorrhage, acute cerebral ischemia is the most likely diagnosis. In that setting the correct first-line therapy in the absence of contraindications is intravenous tPA. In this patient the presenting BP is higher than the limit for tPA administration; thus administration of intravenous tPA after acute BP lowering to <180/110 mm Hg is appropriate (Answer A). In this patient IV labetalol or nicardipine would be the drug of choice. Sublingual nifedipine is proscribed since nifedipine can lead to a substantial reduction in BP (Answer C). In the setting of acute ischemic stroke there is no evidence-based data to support use of vasopressors to augment BP, especially in this case where BP is elevated and above the recommended thresholds for post tPA BP management (answer D)

2. E

This patient presents with an ICH without intraventricular extension or hydrocephalus and no impairment of consciousness. In this case clinically significant hematoma expansion is expected in about 40% of the patients. Additionally, hematoma expansion in hypertensive ICH is rare after the first 36 hours. Since the patient reportedly had the first presentation 2 days prior, it is unlikely that any further clinically significant expansion will occur (answer A). Lowering BP has not been conclusively proven to decrease the incidence of hematoma expansion (answer B). Since the patient is fully conscious with a relatively small hematoma, lack of decline after 2 days from the onset of symptoms and no associated hydrocephalus, there is no clinical evidence for increased ICP and no indication for ICP monitoring (answer C). Some studies had suggested that there may be perihematomal ischemia around an ICH but this theory has been largely discredited by more recent studies (answer D).

3. E.

All the options are features of carotid hyperperfusion syndrome.

1. B. CTA of renal arteries
2. B. Start ACE inhibitor and follow BP response and potassium and creatinine closely
3. D. Both A and B
4. A. MRA of RAs
5. C. CT with and without contrast
6. A. Cholesterol emboli

1.

A. Women with ADPKD with hypertension have a higher risk for preeclampsia and preterm delivery than those without hypertension.

B. Preimplantation genetic testing can be offered, but many women with ADPKD prefer to conceive spontaneously.

C. Correct. Aspirin should be offered to all women with chronic hypertension to reduce the risk for preeclampsia.

D. Amlodipine has not been demonstrated to be teratogenic, but more experience of safety is needed with nifedipine, which could be offered as an alternative agent but requires twice or three times daily dosing. BP control before pregnancy should be optimized.

2.

A. Conception after transplantation is recommended to be delayed until at least 12 months posttransplantation to ensure graft stability. The optimal time to conceive remains unclear; however, in view of increased maternal age and graft stability in this case, it would not be unreasonable to switch MMF to azathioprine at 12 months, ensure graft stability, and then for the woman to attempt to conceive.

B. Breastfeeding should be encouraged in women with kidney transplants, particularly those with preterm deliveries with greatest infant benefit. Standard immunosuppression during pregnancy, that is, prednisolone, azathioprine, and tacrolimus, can be continued safely with lactation, and only minimal quantities of each drug have been identified in breast Milk.

C. There are no data regarding breastfeeding with MMF, and therefore it is not currently recommended. Azathioprine should be substituted for MMF. High-dose prednisolone may be associated with gestational diabetes, maternal infection, osteoporosis, and preterm delivery and therefore should be avoided.

D. Correct. Women with lupus nephritis may continue to have anti-Ro or La antibody that is transferred by the placenta and may lead to neonatal lupus syndromes, including fetal heart block. Fetal cardiac monitoring from 16 to 18 weeks of gestation is recommended in those with positive antibody.

3.

A. Correct. At this early gestation, attempts should be made to prolong pregnancy to optimize neonatal outcomes.

B. Fetal assessment will determine timing of delivery. If maternal compromise persists despite BP control, delivery may be needed, but a balance between maternal and fetal benefit needs to be considered by obstetricians, nephrologists, and neonatologists. This presentation also could be consistent with progression of underlying kidney disease, and placental and fetal ultrasound will help determine whether preeclampsia is evolving.

C. Intravenous magnesium should be used only if there is evidence of neurologic involvement such as brisk reflexes, scotoma, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) but not routinely in a woman with suspected preeclampsia.

D. Labetalol may be used to treat hypertension, but there is no evidence of benefit of aspirin to treat gestational hypertension and its associated complications.

CHAPTER 44

CHAPTER 46

1.
2.
3.
4.
5.
6.

1. E. All options all been shown to contribute to the rate of progression of the kidney cystic disease in ADPKD.

2. C. Aneurysms in the posterior circulation of the circle of Willis have an increased risk for rupture compared with those in the anterior circulation. Although some authors argue that all patients with ADPKD should undergo presymptomatic screening for intracranial

CHAPTER 42

1. C. Peridialytic BP recordings are inadequate to assess BP control.
2. D. Hypertension in dialysis patients is best managed using nonpharmacologic strategies.
3. D. Intradialytic hypertension is often a sign of volume overload.

CHAPTER 43

B. Hypernatremia
A. Proteinuria 2 g/day
C. Hemolytic uremic syndrome
B. Placental growth factor concentrations
D. Aspirin
C. Interbirth interval less than 1 year

aneurysms, there is no evidence to support the efficacy or costeffectiveness of this strategy. Most intracranial aneurysms do not rupture. Screening for intracranial aneurysms by magnetic resonance angiography does not require administration gadolinium.

3. A. Hypocitraturia is a common metabolic abnormality in patients with ADPKD even before there is a decline in kidney function. Hypercalciuria, hyperuricosuria, and hyperoxaluria do not occur more frequently in these patients. Renal tubular acidosis is rarely associated to ADPKD.
4. D. The HALT PKD study showed that ACE inhibitor monotherapy is very effective in controlling BP in the majority of patients with ADPKD; however, superiority to β-blockers has not been proven in head-to-head studies. Rigorous BP control was found to be superior to standard control in young patients with ADPKD with a GFR >60 mL/min/1.73 m2 in the HALT PKD Study A clinical trial, but rigorous BP control was not used in Study B with more advanced ADPKD.

4. C. Whereas normally the kidney adjusts urine composition and volume to match intake and environmental stressors, this is impaired in tubular disorders such as NDI. In these disorders, maintenance of homeostasis is reversed and intake must be adjusted to the urine to maintain overall balance. In NDI, the kidneys lose water, thus intake should constitute of water. Administration of fluids with a higher sodium concentration than that of the urine, such as 0.45% or 0.9% saline and Hartman solution, will lead to hypernatremia.

CHAPTER 50

1. B. Cystinosis
2. A. Arginine, lysine, ornithine
3. B. Medications
4. E. SLGT2
5. D. ClC-5

CHAPTER 47

CHAPTER 51

1. E. ARPKD has a diverse set of extrarenal complications that primarily involve the liver, less commonly impact growth, and very rarely involve intracranial aneurysms.
2. B. The term nephronophthisis derives from the Greek, meaning “progressive loss of nephrons”; nephron loss combined with fibrosis (another hallmark of NPHP) leads to small kidneys.
3. C. Angiomyolipomas are a major clinical feature of TSC and the most common kidney lesion in TSC patients.
4. D. VHL-associated disease clusters into two complexes based on the nature of the germ-line mutation.
5. A. MSK is generally considered to be a sporadic disorder, but familial clustering with autosomal dominant inheritance and evidence for genetic alteration in the RET-GDNF axis suggest a genetic basis for MSK in at least a subset of patients.

1. B. Have reduced urinary concentrating capacity

2. D. Have a higher rate of delayed graft function following kidney transplantation than patients with ESKD of other causes
3. C. Works by increasing fetal hemoglobin production

CHAPTER 52

1. A. Unilateral renal agenesis occurs in 1 in 3000 live births.
2. C. In prune-belly syndrome the ureters are grossly dilated.
3. B. Ureterosigmoidostomy may lead to hyperchloremic hypokalemic metabolic acidosis.
4. E. PUV only occurs in males.
5. B. Calcium phosphate stones are most often seen in augmented bladders.

CHAPTER 48

CHAPTER 53

1. B. His mother has AS.
2. E. All of the above
3. C. Hearing loss in AS initially targets high frequencies above the range of conversational speech.

1.
2.
3.
4.

CHAPTER 49

1. C. Bartter syndrome (types 1 and 2), as well as Liddle and Gordon syndrome are associated with hypercalciuria and Bartter syndrome types 3 and 4 with normocalciuria. While some patients with Bartter syndrome type 3 can phenocopy Gitelman syndrome and thus may have hypocalciuria, Gitelman syndrome is the only disorder listed that is consistently associated with hypocalciuria.
2. B. Prostaglandin synthesis inhibitors, also called cyclooxygenase (COX) inhibitors, such as indomethacin, ibuprofen or celecoxib, as well as salt and KCl supplementation, are usually the mainstay of treatment of Bartter syndrome. Potassium-sparing diuretics such as amiloride worsen the salt wasting and thus risk hypovolemia but may be helpful in cases with extreme electrolyte abnormalities, as long as they are cautiously used and supported with adequate salt supplementation.
3. B. Aldosterone deficiency, PHA1, and PHA2 are all characterized by hyperkalemic acidosis due to impaired Na transport through ENaC. In contrast, enhanced ENaC activity causes hypokalemic alkalosis, as it facilitates potassium and proton secretion in the collecting duct.

B. Ciprofloxacin
D. Periodic screening and treatment of asymptomatic bacteriuria
B. Nitrofurantoin
C. Pregnant patients and patients undergoing urologic instrumentation

CHAPTER 54

1. C. Immune reconstitution inflammatory syndrome (IRIS) is a pathogen-specific inflammatory response in HIV-infected patients that may be triggered after initiation, reinitiation, or change to more active antiretroviral therapy. It is a paradoxical phenomenon of apparent clinical and radiologic worsening occurring in HIVinfected patients who had TB, inactive cytomegalovirus retinitis, or quiescent cryptococcal infection. It is usually accompanied by an increase in CD4 cell count and/or a rapid decrease in viral load. It may occur in patients with HIV when treatment with antivirals is started together with specific chemotherapy. Higher incidence of

IRIS has been observed if the load of organisms is higher.

2. D. In the usual doses, ethambutol is a bacteriostatic drug. It is bactericidal only if very high doses are used.

3.

A. Painless macroscopic hematuria occurs in immunoglobulin A nephropathy, other glomerular diseases, and urinary TB. In other conditions, such as stone, tumor, trauma, and acute urinary tract infection, it is painful.

Self-Assessment Answers

B. Acid sterile pyuria is unique to tuberculosis. The combination of persistent increase in urinary white cells, negative conventional cultures, and acidic pH of urine.
C. Sterility (in females) and epididymitis (in males) are a common genital involvement.
D. There is a characteristic lack of constitutional symptoms in urinary TB. Most symptoms are related to drug treatment.
E. Correct. Icterus is not a manifestation of TB. If it occurs, it is due to drug therapy.
4.
A. No dose change. The main route of excretion is by the biliary route.
B. Correct. Dose should be modified. For streptomycin, increase dosing interval (over 45 years, 50% dose) and monitor for ototoxicity. For ethambutol, increase dosing interval and monitor visual acuity, field, and color vision.
C. Pyrazinamide should be avoided in liver disease. Use carefully in the short term in kidney failure.
D. No dose change. The main route of excretion by the biliary route.
5. B. Rifampicin

CHAPTER 55
1. C. C. albicans is the species isolated most commonly in both UTIs and candidemia.
2. E. Pyuria is not a helpful sign for the diagnosis of a Candida UTI when a catheter is present or when there is a concomitant bacterial infection. If there is no catheter and no bacteriuria, pyuria is sometimes useful as a marker for UTI with Candida species.
3. B. Flucytosine is excreted in the urine, and serum levels rise when creatinine clearance is diminished. Toxic effects on bone marrow and liver and are directly related to serum levels greater than 100 µg/mL. The other drugs are metabolized in the liver or elsewhere in the body and do not accumulate with kidney failure.
4. B. Shown by placebo-controlled clinical trial (Clin Infect Dis. 2000; 30:19-24.)

CHAPTER 56
1. B. Schistosoma-associated Salmonella bacteremia
2. D. Infiltrative bladder cancer
3. D. Concomitant virus-induced cryoglobulinemia

CHAPTER 57
1.
2.
3.
4.

A. True
A. Low serum CH50 and C3 levels
A. True
A. Contraindicated in patients with active HBV infection and associated GN

CHAPTER 58
1. A. HIV-associated nephropathy (collapsing glomerulopathy) or focal segmental glomerulosclerosis
2. C. Tenofovir disoproxil
3. D. Giant mitochondria within the tubular cells

CHAPTER 60
1.
A. Correct. Antibiotic therapy is important to reduce struvite stone

growth and for stone prevention. Bacteria will remain in the stone

interstices and stones will continue to grow unless chronic antibiotic suppression in maintained or the calculi are completely eradicated. Thus a short course of antibiotics is not sufficient.

B. Struvite stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They form when urease production y certain bacteria that breaks down urea to ammonium and a carboxyl group.

C. Insoluble urinary phosphate forms a solid phase with magnesium, calcium, and ammonium.

D. With alkaline urine, urinary phosphate becomes insoluble and forms a solid phase with magnesium, calcium, and ammonium.

E. Bacteria will remain in the stone interstices after a short course of antibiotics until calculi are completely eradicated by surgical interventions.

2.

A. Dietary salt restriction is associated with decreased urine calcium excretion.

B. Animal protein ingestion increases the frequency of kidney stone formation by a number of mechanisms, including generation of sulfate ions, which render urinary calcium ion less soluble, and metabolic acidosis, which can cause calcium release from bone and a consequent increase in the filtered load of calcium.

C. Correct. Several studies have demonstrated that there is a decrease in stone incidence when people consume adequate dietary calcium. This beneficial effect has been attributed to intestinal binding of ingested oxalate by dietary calcium.

D. Most calcium stones are composed of calcium oxalate, either alone or in combination with calcium phosphate or uric acid. Thus dietary oxalate should be restricted.

3.

A. Uric acid stones are radiolucent and therefore poorly visible on plain radiographs.

B. Correct. Uric acid stones often occur in patients with insulin resistance. The rising incidence of obesity and insulin resistance in the United States has led to a parallel increase in uric acid stones.

C. Allopurinol should be prescribed if uric acid excretion remains high despite dietary intervention, to keep urinary uric acid excretion < 750 mg/day. This patient already had uric acid excretion < 750 mg/day.

D. Low urine pH is the principal metabolic disorder found in patients with uric acid stones. Potassium citrate can raise urine pH and prevent stone formation.

E. An increase in urine volume of more than 2 to 2.5 L/day has been proven to reduce the incidence of stones. This patient’s urine volume was only 1.5 liter per day and thus inadequate.

CHAPTER 61

1.

A. Correct. Hydronephrosis describes dilation off the upper urinary tract and can occur in the absence of functional obstruction.

B. Urinary tract obstruction may affect neonates, children, and adults of both sexes, and the underlying causes and outcomes are therefore highly diverse, with most patients not developing ESKD.

C. Urinary tract obstruction may be associated with oliguria or even anuria if the obstruction is bilateral and complete. However, it is important to note that patients with a partial obstruction may report polyuria and nocturia as a result of an impaired ability of the kidney to concentrate the urine.

D. Urine dipstick analysis is highly variable in patients with urinary tract obstruction, and there are no “typical” findings. Microscopic hematuria may be evident in patents with kidney calculi or tumors, but urinalysis is often negative for blood and protein.

E. Correct. Urinary tract obstruction results in urinary stasis and is a risk factor for infection, with infections often being more difficult to eradicate if obstruction is ongoing.

2.

A. Recent work suggests the opposite, with the development of marked diuresis (>7 liters per 24 hours) being associated with a very good outcome with preservation of kidney function.

B. Correct. Examples include adynamic segments of the ureter that result in pelviureteral junction obstruction, and diseases such as multiple sclerosis and diabetes may be complicated by a hypertonic or atonic bladder, respectively.

C. Correct. Many inflammatory, degenerative, or neoplastic conditions may affect the retroperitoneum and involve the ureters, thereby causing urinary tract obstruction.

D. Correct. The obstructed kidney develops chronic inflammation that is associated with progressive scarring. Long-term obstruction leads to profound parenchymal damage and cortical thinning.

E. Patients with IgA nephropathy may develop severe macroscopic hematuria. The red cells are of glomerular origin and may thus obstruct the nephron lumen and cause significant intrarenal urinary tract obstruction that is associated with acute kidney dysfunction.

3.

A. Correct. Various aspects of tubular function may be abnormal, including urinary acidification, potassium handling, and urinary concentration.

B. The blood flow of the obstructed kidney is also reduced, with kidney vasoconstriction associated with increased intrarenal levels of angiotensin II and thromboxane A2.

C. Renal tract ultrasound remains the first-line investigation for the majority of patients with suspected urinary tract obstruction because it does provide very useful information despite being operator dependent. Non–contrast-enhanced spiral CT scanning is useful for the primary assessment of patients with acute flank pain but, unlike ultrasound, does expose the patient to radiation.

D. A diuresis renogram is used to assess whether a dilated system is actually obstructed. The absence of functional obstruction is indicated by the rapid washout of the isotope after diuretic administration.

E. Correct. Although unusual, urinary tract obstruction may occur in the absence of hydronephrosis, as in transplanted kidneys that are encased in dense fibrous tissue. In addition, retroperitoneal fibrosis or infiltrating tumors may surround the ureters and prevent dilation but still obstruct native kidneys.

CHAPTER 62

1.
2.
3.
4.

B. Voiding cystourethrogram
D. 6-year-old female with grade IV reflux
D. Cefalexin
E. All the above

CHAPTER 63

1. C. Standard practice is to manage distal nonobstructing calculi conservatively for a period of 2 to 4 weeks, with a trial of medical expulsive therapy, given the high spontaneous passage rate.

2. D. Any patient with unexplained visible hematuria should undergo full urologic workup with flexible cystoscopy, renal function tests, and CT urogram, although local resources often dictate other imaging strategies such as intravenous urography and ultrasound as first-line interventions. Anticoagulation should not be considered an explanation for hematuria because underlying malignancy is common.

3. C. Partial nephrectomy has emerged as a favorable procedure when compared with radical nephrectomy because concerns over reduced oncologic clearance have been unfounded. If technically possible, this should be performed laparoscopically. Although cryosurgery and radiofrequency ablation are promising alternatives to partial nephrectomy, they should be considered experimental at present.

CHAPTER 64

1. A. Both NSAIDs and PPIs are among the classes of drugs most commonly responsible for AIN.

2.

A. This diagnostic procedure does not have a poor negative predictive value.

B. This diagnostic procedure does not have a poor negative predictive value.

C. Some drugs other than NSAIDs can induce AIN associated with heavy proteinuria, including ampicillin, rifampin, lithium, interferon, phenytoin, pamidronate, and d-pencillamine.

D. Correct. A kidney biopsy is the only test that can be performed to reliably rule out or confirm the diagnosis of AIN.

3. D. The course of drug-induced AIN is not always benign, and it leads to chronic kidney disease in at least 40% of cases.

CHAPTER 65

1. B. Vacuolation of the renal tubules
2. D. Autoimmune pancreatitis
3. A. Non–contrast-enhanced MRI

CHAPTER 66

1. B. Regions with a high prevalence of CKD that is unrelated to common causes such as hypertension and diabetes
2. A. A type of CKD of undetermined cause highly prevalent in the Pacific coast of Central America
3. B. Mostly asymptomatic, predominantly tubulointerstitial damage with low proteinuria, young workers from hot regions
4. E. All the above

CHAPTER 67

1. D. Light chain cast nephropathy
2. C. Acute interstitial nephritis
3. D. Lymphomatous infiltration of the kidneys

CHAPTER 68

1.
2.
3.
4.

C. Light chains
C. Cast nephropathy
E. Bortezomib
D. Serum free light chains

Self-Assessment Answers

CHAPTER 69

1.

A. Correct. The slowly falling glomerular filtration rate (GFR), the hypertension, and the bland urinalysis are all suggestive of chronic cyclosporine nephrotoxicity.

B. A kidney biopsy is not considered urgent in the setting of bland urinalysis and a high pretest probability of cyclosporine toxicity, although It may be performed at some point for confirmation and prognostication purposes.

C. The combination of sirolimus + cyclosporine increases the risk for further kidney damage.

D. Cystic fibrosis of itself is not a contraindication to kidney transplantation.

E. Diltiazem will impair the metabolism of both cyclosporine and simvastatin, increasing their blood and tissue concentrations, which will increase the risks for acute kidney injury (AKI) and rhabdomyolysis.

2. C. The most likely process here given the risk factors (time frame, total body irradiation) and clinical and laboratory features (hypertension, low platelets, rising creatinine with proteinuria and hematuria) is thrombotic microangiopathy. Plasma LDH, serum haptoglobin, and blood film will confirm this suspicion. Membranous nephropathy tends to cause nephrotic (not nephritic) syndrome. Hematologic malignancies can infiltrate the kidneys, leading to AKI, but would not manifest with nephritic syndrome. Ultrasound is the preferred method for identifying obstructive uropathy (especially in the setting of kidney dysfunction, in which intravenous contrast could cause further kidney injury).

3. E. Clarithromycin increases cyclosporine levels (by reducing cytochrome P450 [CYP] 3A activity, which is involved in cyclosporine metabolism), giving rise to the typical manifestations of acute calcineurin inhibitor toxicity: tremor, AKI, hyperkalemia. Allopurinol and azathioprine should not be coadministered because of the risk for severe pancytopenia. Preemptive kidney transplant would be the best treatment for this patient because he is young, relatively healthy, and likely to withstand the stress of kidney transplant surgery.

4. B. Here, the baseline serum creatinine of 1.0 mg/dL likely reflects some degree of CKD, given the young age, female sex, and likely low muscle mass in the face of end-stage liver disease. Glomerulonephritis, although not uncommon in hepatitis C infection, tends to heave a more subacute presentation and—at least when acute—is characterized by hematuria and proteinuria. Simultaneous liver-kidney transplant is not currently indicated because her acute kidney dysfunction has been ongoing for 1 week only. Given her baseline CKD and current AKI, she has a significant risk for developing severe CKD over the long term.

5. D. Although severe heart failure is likely contributing to the kidney dysfunction, the hemodynamic insults at cardiac transplantation and the post-transplant nephrotoxic medications (without which outcomes are poor) make it more likely that the kidney function will further deteriorate. Furthermore, the proteinuria suggests there is also intrinsic kidney disease such as secondary focal segmental glomerulosclerosis (which can occur in cyanotic heart disease). Therefore, although not recommended because of her high risk for morbidity and mortality perioperatively.

CHAPTER 70

1. A

Acute tubular injury occurs in tubular regions due to an imbalance between blood supply and metabolic work. The proximal tubule (especially the S3 segment) and loop of Henle both lie within the outer medulla where blood supply is limited, and both have high metabolic requirements secondary to sodium reabsorption at these sites (Na-K-ATPase).

2. D

Reduction in left ventricular function triggers the release of potent vasoconstrictors (SNS, AII, ADH, endothelin) that can cause AKI by impairing kidney perfusion. NSAIDs inhibit the production of protective prostaglandins impairing compensatory afferent arteriole vasodilation in this setting. Note NSAIDs may also cause an acute interstitial nephritis (sometimes associated with heavy proteinuria), acute papillary necrosis and, rarely, AKI associated with minimal change disease.

3. B

Methotrexate may form intratubular crystal, which block tubular flow and cause an interstitial nephritis. Cisplatin inhibits mitochondrial ATP generation. Gentamicin accumulates in proximal tubular cells and interferes with cellular energetics and induces oxidative stress. Amphotericin punches holes in cell membranes. Tacrolimus causes kidney vasoconstriction leading to kidney ischemia in addition to direct tubular toxicity.

4. B

Contributing factors include kidney vasoconstriction (enhanced tubul-glomerular feedback due to increased delivery of chloride to the macula densa), obstruction from tubular cell casts (leading to increased hydraulic pressure in Bowman’s space opposing filtration), and backleak.

CHAPTER 71

1. A. Viperidae and Elapidae
2. D. Leptospirosis
3. B. First falciparum, then vivax; less common malariae, ovale, and knowlesi
4. C. Dengue, yellow fever, and Hantavirus hemorrhagic fever

CHAPTER 72

1. A. Serum creatine kinase level
2. C. BUN of 34 mg/dL
3. D. Postvoid bladder catheterization

CHAPTER 73

1. D. Thyroid disorders are not associated with the risk of AKI.
2. C. The incidence of AKI in hospitalized patients has increased by approximately 13% per year over the last 3 decades.
3. D. All of the above appear to be consequences of AKI.
4. B. The incidence of stage 4 CKD or greater in AKI survivors is approximately 120 per 100,000 person-years.

CHAPTER 74

1. C. Detrimental for kidney function (increase in need for replacement therapy)
2. E. All the above
3. A. Urine output should be maintained around 300 mL/h until CK levels are lower than 1000 U/L.
4. B. Volume expansion should be maintained after major vascular surgeries unless patients develop evidence of pulmonary congestion.

APPENDIX

CHAPTER 75

1.

A. False. The use of intermittent acute kidney replacement therapy as initial modality results in the same outcomes as the use of continuous KRT as initial modality, as long as one switches in a timely manner as best practice and clinical indications dictate. Early studies suggested that critically ill patients treated with continuous KRT or intermittent KRT may have better organ recovery than those treated with standard intermittent KRT. However, this has not demonstrated in a definitive manner.

B. False. While an individual’s clinical situation might mandate more intensive treatment for any given case, high-quality evidence shows that thrice-weekly treatment is adequate for the majority of critically ill patients intermittent KRT modalities.

C. True. Delivering adequate dialysis is a core quality indicator for KRT programs and mandates routine and regular measurement of delivered dose. Because underdelivery of the prescribed dose is frequent, prescriptions frequently target 25 to 30 mL/kg/hr or a Kt/V of 1.3.

D. False. While cytokine removal via diverse variations of high-dose continuous KRT was theoretically very promising, studies have been unable to demonstrate any benefit of any of these modalities. This may be because these techniques can be quite difficult to sustain, cytokine removal is not achieved or beneficial, or because high-volume continuous KRT also removes beneficial substances (e.g., antibiotics, amino acids). These techniques are now largely abandoned as other methods of cytokine removal are being explored (e.g., adsorption filters).

2.

A. False. The combined IGFBP/TIMP2 biomarker test can help identify patients at risk of developing AKI, but it does not assist in the diagnosis of AKI (the KDIGO criteria are still the gold standard) nor do they predict who will progress to severe AKI or need KRT.

B. False. In general, the suboptimal sensitivity and specificity of biomarkers of AKI have limited their usefulness in guiding the therapy of AKI. Biomarkers that accurately identify progression to severe AKI or need KRT are also lacking. This remains an area of research with ongoing studies being performed to identify novel biomarkers, or biomarker panels that may assist in the therapy of AKI.

C. False. The furosemide stress test (FST) was initially found to identify patients who would progress to severe AKI (those requiring dialysis). However, the FST Trial found that the FST failed to identify 25% of patients assigned to a “late start” who never required KRT. While this was a significant improvement from previous studies, it did not prevent initiating KRT in patients who would not need it, nor did it have an impact on patient survival.

D. True. With the exception of the ELAINE trial, the available randomized control trials have not shown a benefit of starting KRT prior to the development of classic initiation criteria.

3. A. True. This is based on the findings of the CATHEDIA trials. However, it should be noted that this general finding did not hold true in the heaviest tertile of their population (BMI > 28). Thus, these results may not be applicable to other populations. Individual institutions should therefore monitor their own outcomes and establish local policies based on their results.

B. False. Temporary dialysis catheters are associated with less infection in chronic dialysis, but infection rates in acutely ill patients are not as well established. An observational study found better function, but this may have suffered from unaccounted for confounders. Current guidelines therefore recommend starting with a temporary nontunneled dialysis catheter rather than a temporary dialysis catheter.

C. False. Evidence-based guidelines and cumulative clinical experience both favor the use of arteriovenous access for intermittent hemodialysis. Catheters are only preferred for continuous therapies. While certain centers have used fistulas for KRT, this practice should be reserved for those with specialized expertise and specialized protocols aimed at protecting the integrity of the fistula/grafts.

D. False. Left-sided internal jugular and subclavian catheters provide flows that are more erratic and up to 100 mL/min lower than elsewhere. Femoral and right-sided internal jugular or subclavian catheters provide the best Qb. Overall, data support a recommendation for right-sided internal jugular catheters as the first choice for KRT, with femoral and left-sided internal jugular catheters as the second and third choices, respectively.

4.

A. Yes. Low rates of infection require both adherence to specific clinical guidelines and establishing a formal quality improvement framework. There is strong evidence that standardizing catheter insertion techniques to best practice results in a near-zero catheterrelated infection rate. The relevant interventional bundles are contained in position statements of the Institute for Healthcare Improvement and the Centers for Disease Control and Prevention Healthcare Infection Control Practices Advisory Committee.

B. No. Topical antibiotic ointments are not recommended because of their potential to promote fungal infections and antimicrobial resistance.

C. The CDC recommends the use of antibiotic- or antisepticimpregnated lines in patients whose catheters are expected to remain in place for longer than 5 days, and those at high risk for infection (e.g., extensive burn injury, neutropenia); however, there is scant good data establishing their efficacy in dialysis patients. KDIGO guidelines do not comment on this topic.

D. No. There is ongoing controversy around the risk for infection with different insertion sites, but on balance the internal jugular site is preferred, especially in those with a larger body mass index. However, it is likely that the way the catheter is handled is more important at preventing.

5.

Patients receiving systemic anticoagulation with heparin, have a lower incidence of circuit failure, but a higher incidence of significant bleeding complications.

False. Citrate anticoagulation has consistently been found to be more effective than heparin and is not associated with a higher bleeding risk.

Argatroban is the preferred approach in those with heparin-induced thrombocytopenia.

True. Patients on KRT with HIT are treated as those not on KRT. There are published protocols for using argatroban on continuous KRT.

C. False. Despite this complication being widely touted, it is very rare. In fact, metabolic alkalosis, hypernatremia, and hypocalcemia are the most common side effects; all of which are easily prevented with appropriate use of protocols.

D. False. Saline flushes are frequently used, but have not been definitively shown to enhance circuit life.

CHAPTER 76

1.

A. Correct. Patients with HRS have vasodilation of the splanchnic circulation as a result of the activation of the vasodilator systems at this level.

Self-Assessment Answers

B. Correct. In patients with HRS the heart cannot increase its output to compensate for a decrease in cardiac preload (secondary to the accentuation of splanchnic arterial vasodilation).

C. Correct. Systemic inflammation represents an important pathogenic factor for HRS.

D. HRS is a functional kidney disorder. The presence of significant glomerular and/or tubular disease excludes the diagnosis.

2.

A and B. HRS is a functional kidney disorder with a diagnosis that is based on clinical criteria. Moreover, biopsy is risky in patients with liver disease with severe coagulopathy.

C. Activation of the vasoconstrictor systems (the renin-angiotensinaldosterone system, the sympathetic nervous system, and vasopressin) is a key factor in the pathogenesis of HRS. Plasma renin activity/concentration is markedly increased in the majority of patients. However, its measurement is complicated and not useful in the clinical setting.

D. Correct. The diagnosis of HRS is mainly one of exclusion and should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension who develops progressive kidney impairment.

3.

A. HRS should be suspected in any patient with subacute or chronic liver disease with advanced liver failure and portal hypertension.

B. Incorrect. In the splanchnic circulation, there is marked arteriolar vasodilation resulting in reduction of systemic vascular resistance and arterial hypotension.

C. Activation of the vasoconstrictor systems (the renin-angiotensinaldosterone system, the sympathetic nervous system, and vasopressin) is a key factor int eh pathogenesis of HRS.

D. Incorrect. HRS occurs in patients with advanced liver failure. The presence of ascites is mandatory.

E. Infection is the most frequent trigger event of HRS.

4.

A. Inorrect. Among the vasoconstrictor therapies, intravenous terlipressin, combined with daily albumin infusion, is the preferred therapy.

B. Incorrect. TIPS could be an alternative treatment of type 1 HRS in patients without response to terlipressin/norepinephrine plus albumin.

C. Dialysis is not tolerated in patients with HRS (already hypotensive) and does not improve survival. It should be reserved for critically ill cirrhotic patients with severe uremia and volume overload.

D. Inorrect. Some studies suggest that albumin dialysis may have beneficial effects in patients with type 1 HRS.

E. In patients with HRS, the administration of midodrine, octreotide, and albumin is much less effective in improving kidney function than the combination of terlipressin plus albumin.

5.

A. Correct. Primary prophylaxis of SBP with norfloxacin prevents SBP delays the development of HRS, and improves short-term survival in cirrhotic patients with advanced cirrhosis.

B. Correct. Albumin infusion prevents HRS in patients with SBP.

C. Two randomized controlled trials have failed to show that albumin administration improves survival in infections other than SBP.

D. No study supports this contention.

CHAPTER 77

1. C. Fraction of normal dose = 1 – 0.8 (1 – 0.25) = 0.4. Therefore the dose should be reduced to 40% of the original dose.

2.

A. High-flux membranes have larger pore sizes and therefore increase removal.

B. Low protein binding allows a greater portion of unbound drug to be available for clearance.
C. A low volume of distribution indicates a larger portion f the drug dose that is in the plasma available for removal by dialysis.
D. Correct. Large molecular sizes prevent drug removal because the drug cannot pass through the membrane pores.
3.
A. Correct. Renally cleared, although it has a wide therapeutic index and limited toxicity, so dose reduction usually is not clinically required for standard courses of oral doses.
B. Extensively renally cleared with significant toxicity requiring significant dose reduction.
C. Extensively renally cleared with significant toxicity and narrow therapeutic index requiring significant dose reduction.
D. Extensively renally cleared with significant potential toxicity requiring dose reduction.
E. Extensively renally cleared with significant potential toxicity requiring significant dose reduction.
4.
A. Clarithromycin is a potent CYP3A4 and P-glycoprotein inhibitor significantly increasing sirolimus exposure.
B. Phenytoin is a potent enzyme-inducing agent that significantly increases the metabolism of coadministered hepatically cleared drugs such as prednisolone.
C. Fluconazole is a weak inhibitor of CYP3A4 and P-glycoprotein and may increase tacrolimus exposure, especially during prolonged combination use.
D. Correct. Roxithromycin is a weak inhibitor of CYP3A4 and P-glycoprotein and rarely causes clinically significant increases in drug exposure, especially during typical 5-day courses of therapy.
E. Verapamil is a strong inhibitor of CYP3A4 and P-glycoprotein and significantly increases everolimus exposure.

CHAPTER 78
1.
A. Correct. Extensively renally cleared. Accumulation in kidney impairment increases the risk of bleeding.
B. Correct. Extensively renally cleared. Accumulation in kidney impairment increases the risk for adverse CNS effects.
C. Significantly renally cleared, although accumulation is not clinically significant and dose reduction is usually not required.
D. Extensively hepatically cleared. Dosing is based on clinical response.
E. Correct. Extensively renally cleared. Accumulation in renal impairment increases the risk of adverse CNS effects.
2.
A. Weak CYP3A4 inhibitor. CNI concentration may increase. Base subsequent dose modification on measured CNI concentration changes.
B. Correct. Strong CYP3A4 inhibitor. CNI concentration expected to increase. Avoid combination or significantly reduce CNI dose if combination is essential.
C and D. Renally cleared and does not affect CYP3A4. No interaction expected.
3.
A. Hepatically cleared without active or toxic metabolites.
B. Correct. Metabolized to oxypurinol, which can accumulate in kidney impairment.
C. Renally cleared without active or toxic metabolites.
D. Hepatically cleared without active or toxic metabolites.
E. Correct. Metabolized to toxic metabolite meperidine, which is

renally cleared.

4.
A. Correct. Small molecule that is renally cleared and significantly removed by dialysis.
B. Large volume of distribution so minimal amounts removed by dialysis.
C. Correct. Small molecule renally cleared and significantly removed by dialysis.
D. Significantly protein bound so minimal removal by dialysis.
E. Correct. Small molecule renally cleared and significantly removed by dialysis.

CHAPTER 79

1.
2.
3.
4.

B. Aristolochic acid nephropathy
C. Chronic tubulointerstitial nephritis (Balkan endemic nephropathy)
A. Cystine crystal
A. Acute rejection

CHAPTER 80

1.e15

the formation of the N-terminal 24-residue fragment of albumin (ALB1-24). This peptide is taken up by dendritic cells, where it is further processed by proteasomes into antigen peptides. These peptides were shown to have the binding motif for MHC class I and to be capable of activating CD8+ T cells.
4. C. The progressive enlargement of cysts in the renal tubules in autosomal dominant polycystic kidney disease is largely attributable to the proliferation of mural epithelial cells and transport of fluid into cavities generated by accelerated epithelial cell growth.

CHAPTER 82

1. E. C and D
2. E. All the above
3. E. There will be an initial decline in kidney function (eGFR), which will be accompanied by a slower rate of eGFR decline over time, and slowing of progression to incident kidney failure.
4. E. All the above
5. E. All the above

1. A. The KDIGO guideline on the classification of CKD recommends using a CGA staging system, including cause of disease, GFR, and level of albuminuria.
2. C. The presence of albuminuria has been linked to the development of albuminuria in many studies. Work by the CKD Prognosis Consortium found that low GFR remains a significant risk factor for morbidity (including ESKD) and mortality in older adults, and that there was little difference in the risk associated with albuminuria between men and women. Assays for proteinuria are less accurate than those for albuminuria.
3. B. APOL1 risk alleles are almost solely present in persons of African descent. However, lower socioeconomic status and poor access to medical care is a big determinant of racial disparities in ESKD as well as other health outcomes.
4. C. Rates of new dialysis patients rise progressively with age, at least until approximately 75 to 80 years. They are highest in some Southeast Asian countries and the United States, among males, and among people with lower socioeconomic status.
5. D. Among patients with CKD, vascular mortality rates are higher

than in general population; if rates of these were lower, a greater number of people would survive to reach ESKD. Issues of competing in other senses of the word are not relevant. Propensity score matching is a technique for dealing with potential confounders, not competing risks.

CHAPTER 83

CHAPTER 81

1. E. The RBC life span is usually normal.
2. D. The defined upper dose limit of epoetin is 60,000 IU/wk because it is known that CV toxicity occurs above this dose level.
3. A. Patients receiving darbepoetin alfa were randomized to either a target hemoglobin (Hb) of 13 or a target Hb of 9 g/dL.
4. D. IV iron may improve the anemia of chronic kidney disease in up to 30% of patients not receiving ESA therapy who have a low ferritin level.

1. B. Podocytes are damaged by excessive protein load after size selectivity is lost. Protein uptake by podocytes may occur through binding to megalin, a receptor for albumin and immunoglobulin light chains that is endocytosed after ligand binding, as shown in cultured murine podocytes. Excessive protein uptake by podocytes also incuses TGF-β production, which contributes to cell apoptosis, an additional cause of podocyte loss in proteinuric glomerulopathies.
2. A. Loss of podocytes secondary to protein-induced cell injury may lead to reduced production of VEGF, a molecule constitutively expressed and secreted by podocytes, influencing the formation of glomerular endothelial fenestrae and eventually promoting endothelial cell apoptosis.
3. B. Exposure of rat proximal tubular cells to excess autologous albumin, as in the case of proteinuric nephropathies, results in

1.
2.
3.
4.
5.

D. Cardiovascular disease
C. The CKD-EPI formula
B. Weight
B. Nocturia
D. Creatinine 13.5 mg/dL

CHAPTER 84

1. D. Hyperhomocysteinemia
2. E. The calcific aortic stenosis progression rate is only slightly higher in dialysis patients compared with the general population.
3. D. Stroke
4. C. Carvedilol

CHAPTER 85

1.
2.
3.
4.

D. Myocardial infarction
E. A history of atrial fibrillation
C. Less than 55 mg/dL
A. More and larger plaques

CHAPTER 86

CHAPTER 87

1. D. Blood culture for bacteremia
2. A. HBV infection leads to chronic infection in the majority of affected CKD patients.
3. E. None of these
4. E. Clopidogrel

Self-Assessment Answers

CHAPTER 88

CHAPTER 91

1. C. Although the PTH value of this woman is in the desired range, her phosphate levels are too high. In particular in this situation, additional calcium loading should be avoided.
2. E. The very low PTH of this dialysis patient is almost diagnostic of low turnover bone disease. The key measure to improve bone turnover is avoidance of calcium loading.
3. E. Calcimimetics are not licensed for use in patients with stage 4 CKD stage. There is concern that in this situation calcimimetics lead to increases in serum phosphate.

1.
2.
3.
4.
5.

B. A systemic disorder caused by uremia
E. In all patients
C. Is limited to patients with therapy failure
D. Warfarin and coumarins
B. Is related to exposure to linear gadolinium chelates

CHAPTER 92

1. A. Use of gabapentin for neuropathic pain
2. F. A, B, and C are correct.
3. C. Iron overload and deposition in the basal ganglia

1. B. A CKD is a common finding in patients on maintenance HD treatment and is a possible cause of hematuria.
2. E. Data from large registries reveals a nearly 10-fold increase in the risk for colorectal cancer in patients on HD treatment.
3. D. Bilateral nephrectomy is the treatment of choice for asymptomatic A CKD in kidney transplant recipients because malignant transformation occurs in almost 90% of cases.

CHAPTER 90

CHAPTER 93

1. B. Low predialysis urea and electrolytes along with low cholesterol may indicate a reduced protein and calorie intake and warrant further dietary investigation. The breathlessness also may indicate that although the target weight has been stable for months, dry weight has been lost over previous weeks (or months) and has been replaced by fluid, so reassessment of target weight is needed. It is a common mistake to see low blood urea nitrogen and electrolytes in a dialysis patient and reduce the amount of dialysis given. This can cause appetite to reduce further, exacerbating the problem. Serum albumin, with its relatively long half-life, does not always drop with a poor dietary intake and therefore is not a good marker of nutritional status on its own. Although one might consider starting a diuretic in a patient with some urine output, there is no indication to restrict fluids in this patient.
2. C. The patient is very enthusiastic about exercise and was found to be taking protein supplements. Protein intake works out to be 1.5 g/

kg of body weight. If protein intake is high, a reduction toward 1 g/kg may reduce symptoms and also lesson the phosphate and potassium intake and the acid load. Although the BMI is 27, if the patient is exercising extensively, this higher BMI may reflect a higher muscle mass; a lower calorie intake is not necessarily indicated. In fact, if protein intake is being reduced, it will be important to ensure that advice is given to maintain calorie intake for weight maintenance. Sodium intake is high, and because the blood pressure is elevated, it would be very beneficial to advise on ways to reduce sodium in the diet. Potassium is at the top of the reference range, but reducing protein intake often leads to a reduction in the potassium intake, and the correction of acidosis with bicarbonate is likely to also have a beneficial effect on potassium.

3. D. The symptoms suggest reduced gastric emptying, possibly because of a combination of diabetic autonomic neuropathy and kidney failure. Reducing dialysis volumes would be wrong because having clearances above the minimum target does not exclude inadequate dialysis as a cause of his symptoms (and 2-L exchanges are not particularly large for this patient). It may even be appropriate, if other measures do not help, to increase the dialysis prescription in case there is a contribution of uremia to his symptoms.

Attempting a weight reduction diet would be inappropriate in this patient, who is already losing weight and raising concerns about his nutrition. Initial forms of nutritional supplementation would be by oral means (dietary advice and supplements if needed) rather than amino acid dialysate as first-line treatment.

1. C. Crescentic glomerulonephritis
2. B. Her inability to ambulate, frailty, and depression will likely not improve with dialysis, and her condition is likely to continue to deteriorate over time.
3. B. He would likely benefit from transplantation, and he should consider living donation as the best option.

CHAPTER 89

CHAPTER 94

1. A, D, and E. Survival on dialysis for elderly patients does not depend on dialysis modality, but is related to frailty and comorbidities.
2. C, D, E. Advance care planning is an outcome of shared decision making and is not a legal process. It involves sharing information between patient and health care team to arrive at an informed decision made by the patient
3. A and E. Dialysis withdrawal is withdrawal of life-sustaining treatment that is no longer effective in sustaining quality of life. In the absence of kidney function, patient survival is around 7 days, depending on comorbidities; survival can be considerably longer if the patient still has some residual kidney function.
4. A, D, and E. The decision for a patient to have conservative care is made after shared decision making. A number of retrospective studies have shown no survival advantage of dialysis compared with conservative care for patients older than 80 years and multimorbid patients older than 75 years. Conservative care is no dialysis but includes optimal management of kidney disease complications, comorbidities, and symptoms.

CHAPTER 95

1. B. In patients who are suitable for kidney transplantation, outcomes with a transplant are superior to any dialysis modality. Preemptive transplantation gives superior outcomes to transplantation after dialysis has been started. A living donor kidney gives superior outcomes to a deceased donor kidney.
2. D. The IDEAL study showed no improvement in outcomes with early initiation of dialysis, but health care costs were increased.

3. C. There is no single threshold of eGFR when dialysis should be started. Answers B and D can be managed without dialysis.
4. D. Physical and psychological preparation for dialysis or transplantation takes many months. The appropriate trigger for transferring a patient to multidisciplinary kidney care is therefore the time before

KRT is expected to be needed, rather than an arbitrary level of kidney function.

5. A. If a patient expresses a clear wish not to have dialysis, the physician is obliged to respect this because to treat patients against their will constitutes assault.
6. C. In the presence of a good performance status and little or no comorbidity, age alone does not indicate a poor prognosis on dialysis.

CHAPTER 96

1. C. The patient’s ESKD Life-Plan and corresponding access needs (insertion/creation plan, contingency plan, succession plan, vessel preservation plan).
2. D. All the above
3. B. The DRIL procedure
4. D. Lower infection rate
5. A. Percutaneous transluminal angioplasty

CHAPTER 97

1. B. False
2. C. Less than 30% residual stenosis and resolution of physical indicators of stenosis
3. D. A and B
4.

A. An ultrasound of the kidneys should be performed in all patients with chronic kidney failure to rule out obstructive uropathy and polycystic kidney disease and to exclude advanced, irreversible disease (small kidneys with thin cortex) for which a biopsy will not be useful.

B. In many patients with acute kidney failure, the cause is apparent from the clinical picture (i.e., sepsis) and imaging is useful only when the cause is not apparent, the clinical picture suggests urinary obstruction, and it is not clear how much of the kidney failure is acute or chronic.

C. Correct. Ultrasound is the modality of choice for diagnosing bladder outlet obstruction, with a negative study essentially ruling this out.

D. Normal ureters are too small to be detected by sonography. Even when dilated, they are often not apparent because of overlying bowel gas.

5. E. All the above

CHAPTER 98

1. A. Endotoxin molecular weight is too high (~100,000) and thus cannot pass through dialysis membranes.
2. C. The bacterial microflora in the gut metabolizes some amino acids and other precursors into uremic toxins, for example, tryptophan into indoles, L-tyrosine into p-cresol, and choline into trimethylamine.
3. D. A large body of high-quality evidence indicates that a hemodialysate at a temperature below the patient’s core temperature results in improved intradialytic hemodynamic stability.
4. A. A recent study showed an increased morbidity and mortality in HD patients with prolonged intradialytic hypoxemia.
5. B. Water preparation according to national and international guidelines is the foundation of dialysate preparation.

CHAPTER 99

1. C. Probably 3 hours of dialysis time because there would not be enough time to remove interdialytic volume without a dangerously high ultrafiltration rate. The other factors may not be optimal but are far less dangerous.

2. A. Use of antihypertensive drugs in large trials rarely reduce systolic BPs by more than 10 mm Hg. The other actions are more effective,

particularly C and D together.

3. B. Application of abdominal pressure would not be useful in these circumstances. Decreasing dialysate temperature will cause arteriolar vasoconstriction, and reducing ultrafiltration will maintain circulating volume. Having an easier (higher) weight target to reach will indirectly result in lower ultrafiltration rates and maintenance of BP.
4. D. An increase in dialysate flow rate does not affect the convective volume in online HDF. All the other actions listed here, either individually or in combination with one or more of the other actions, are useful to increase convection volume.
5. C. This indicates the importance of apparently even small degrees of residual function (2.00 is the minimal standard KtV prescribed dose).

CHAPTER 100

1.
2.
3.
4.
5.

B. Cardiac ischemia
D. Avoidance of excessive interdialytic weight gains
E. Heparin exposure
E. Peracetic acid
E. All the above

CHAPTER 101

1. B. The glucose molecules are smaller than the ICO molecules and therefore are relatively “inefficient” as osmotic agents in small pores, but relatively more efficient across AQP.
2. E. None of the catheters above shows significant clinical superiority.
3. C. Increases in small-solute transport (PETcreat) combined with no or only moderate increases in the UF coefficient (LpS).
4. D. They produce higher concentrations of the dialysate effluent marker CA-125.
5. E. Icodextrin is polydispersed, but with 30% of the molecules being larger than 3 kDa.
6. A. Small pores

CHAPTER 102

1. A and C. A is false because although there is some emerging evidence of the superiority of the laparoscopic technique, this is not a substitute for a well-audited and experienced surgical team. C is false because normal pH solutions should be considered if available. Note that E is true but occasionally is due to fluid tracking down the abdominal wall from a deep cuff leakage.
2. B and C. B is false because antifungals should be commenced intraperitoneally, but the catheter should be removed and treatment continued systemically. C is false because treatment should await cultures; the indications for immediate treatment are purulent discharge of clinical evidence of infection of the tunnel. Note that D is true for both exit site infections and peritonitis. E is true and remains the most common reason for PD-associated peritonitis death.
3. B and D. B is false because the target should take residual kidney function into account; an anuric patient obtaining less than 1 L should have their membrane and prescription examined. D is false; CT can be used to confirm that obstructive symptoms are a result of encapsulation but should not be used to screen for EPS in the absence of symptoms. Note that A is true because of both increasing solute transport and loss of osmotic conductance. For E, progressive loss of osmotic conductance is not treatable, and PD should be continued only in patients with otherwise low life expectancy.

Self-Assessment Answers

CHAPTER 103

1. A. Ethylene glycol is metabolized to glycolic acid and oxalate by alcohol dehydrogenase. Its presentation is associated with oxalate crystals in the urine and a raised anion gap acidosis.
2. E. Acute kidney injury is not associated with a raised osmolar gap, whereas all of the other conditions are.
3. C. All the other drugs/poisons are effectively removed by intermittent HD.
4. A. Hemoperfusion remains the first choice treatment for removal of theophyllines.

CHAPTER 104

1. C. Should be started immediately while awaiting complement studies and possible use of eculizumab.
2. A. Should be started immediately while awaiting complement studies and possible use of eculizumab.
3. A. Good evidence for benefit of plasma exchange.

CHAPTER 105

1.
2.
3.
4.

E. PD-L1
E. A and D
C. Tubulitis, interstitial inflammation, arteritis
B. Siblings from the same parents are predicted to have a 50% chance of having zero HLA mismatches.
5. C. The MHC class I system is designed to present extracellular proteins taken up and processed by antigen-presenting cells.

CHAPTER 106

1.
2.
3.
4.

A. Nephrotoxicity
C. Blocks CD28 mediated costimulation of T cells
D. Mycophenolate
B. Basiliximab

CHAPTER 107

1. A. Active sepsis will likely worsen with immunosuppression, so it is important to have this resolved before transplantation. Responses B to E are no longer seen as contraindications, although special care must be taken to address the specific issue and potentially modify the immunologic, medical, and surgical approach to transplantation.
2. D. A normal stress echocardiography result does not necessarily exclude coronary heart disease, however the negative predictive value for myocardial infarction or cardiac death is in excess of 90% in patients with kidney failure.
3. D. Deceased donors over the age of 60 years without any other medical history of significance meet the definition for expanded criteria donors. If there is a history of hypertension or death from a cerebrovascular accident, the age for classifying a donor as meeting expanded criteria can be lower between 50 and 59 years old. Diabetes, smoking, vascular disease, and HCV are not factors used to classify donors as expanded criteria. The new KDRI/KDPI system is more detailed and does use donor age, diabetes, hypertension,

HCV, and mode of death in the formula when deriving the donor score.
4. B. A colonoscopy would usually be considered only in donors with bowel symptoms, iron deficiency, or a family history of colon cancer. Urine microscopy and imaging are important tests in assessing

underlying kidney conditions in the donor and defining anatomy before donation. Hepatitis serology is important in assessing the risk for disease transmission. An electrocardiogram will help define the donor’s cardiac status and possible risks associated with the surgical procedure and anesthetic.
5. C. A positive T cell cytotoxicity-dependent crossmatch is likely to be indicative of a very high level of donor-specific antibodies against class I HLA, making the risk for hyperacute rejection extremely high. Additionally, this test is functional in that it uses T cells from the donor (therefore expressing antigens that also may be present on the allograft) to assess the recipient’s immunologic reactivity to the allograft.

CHAPTER 108
1.
2.
3.
4.
5.

A and D
A and D
C. von Willebrand disease
C and E
A. Transplant nephrectomy is mandatory for early graft failure caused by thrombosis.

CHAPTER 109
1. D. Peritubular capillary C4d deposition, circulating donor-specific antibodies, peritubular capillaritis (ptc2)
2. B. Lymphocyte-depleting agents are more effective in preventing acute rejection compared with IL-2 receptor antibodies in patients at high immunologic risk.
3. B. Tacrolimus, MMF, prednisone
4. C. rATG 1.5 mg/kg IV for 7 to 14 days

CHAPTER 110
1. D. Seasonal influenza vaccine is safe and effective, and no conclusive evidence exists for a link between vaccination and allograft dysfunction. The AST-IDCOP guidelines recommend that all transplant recipients receive COVID-19 vaccination irrespective of prior COVID-19 infection or evidence of humoral immunity. The CDC recommends that vaccination should be postponed for 90 days following COVID-19 infection or following receipt of convalescent plasma or monoclonal antibody. However, the ideal period for vaccination after infection remains to be studied. Inactivated vaccine should be completed by 2 weeks prior to transplantation to optimize immune response to vaccination and a minimum of 4 weeks should elapse between live attenuated virus vaccine administration and transplantation to minimize the possibility of live vaccine-derived infection in the posttransplantation period.
2. A. Quantitative CMV assays in patients with invasive colitis and gastritis or neurologic disease, including chorioretinitis, are often negative and diagnosis may require invasive testing and biopsies.
3. C. Rituximab is considered first-line treatment for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone. The use of acyclovir and ganciclovir are of unproven benefit. PTLD is the most common type of posttransplantation malignancy

in children, whereas skin cancers are the most common de novo posttransplantation malignancy in adult kidney transplant recipients. The higher incidence of PTLD in children compared with adult has been attributed pretransplant EBV naive status in the pediatric population

APPENDIX

CHAPTER 111

1. D. The American College of Cardiology/American Heart Association guidelines on blood pressure management advocate liberalizing the BP target to <160/90 mm Hg in the early posttransplantation period to maintain organ perfusion and avoid hypotension to reduce the risk of graft thrombosis. Beyond the first posttransplantation month, more stringent BP control to <130/80 mm Hg is recommended to prevent end-organ damage. The beneficial effect of ACE inhibitors or ARBs on patient or graft survival has not been consistently demonstrated. The KDIGO guidelines suggest a BP goal of <130/80 mm Hg for kidney transplant recipients irrespective of the level of albuminuria. Because of the lack of conclusive evidence that one class of antihypertensive agent is superior to another in transplant recipients, the choice of antihypertensive agents should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug-drug interactions.
2. C. The concomitant use of statins and cyclosporine often results in a severalfold increase in statin blood level because CSA inhibits CYP450 3A4 enzyme, of which statins are major substrates. In addition, CSA inhibits OATP1B1/SLCO1B1-mediated hepatic uptake of statins, resulting in significant medication interaction. In patients receiving CSA immunosuppression, high dose statin should be avoided because CSA-induced increase in statin bioavailability can result in an increased risk for myopathy and rhabdomyolysis. In contrast, tacrolimus does not inhibit CYP3A4 to a significant extent and has no effect on OATP1B1/SLCO1B1 and thus drug-drug interaction with statins is not observed. However, rhabdomyolysis associated with tacrolimus and statin use may be seen in patients on concomitant diltiazem therapy because the latter is a moderate CYPA3A4 inhibitor.

3. D. Both calcineurin inhibitors and mTOR inhibitors are diabetogenic. Tacrolimus has been shown to be more diabetogenic than cyclosporine. Sirolimus or everolimus use is associated with the worst lipid profile (particularly hypertriglyceridemia) compared to cyclosporine and tacrolimus. Belatacept, mycophenolic acid derivatives, and azathioprine have not been shown to be diabetogenic.

CHAPTER 112

1. D. HLA alloantibodies
2. C. 1, 2, and 3 are correct
3. E. 1, 2, and 4 are correct

CHAPTER 113

1. A. Risk is approximately 5% to 10% within 10 years after transplantation for IgAN; less than 1% for B, C, and D; and E does not recur.
2. E. A histologic diagnosis pre- and posttransplantation is required for the diagnosis of recurrent disease.
3. D. Plasma exchange should be started once a diagnosis of recurrent FSGS is made, with a plan to complete approximately nine cycles of therapy.

CHAPTER 114

1. B. Statistical method of maximizing the information available for analysis of outcome from a group of patients and events
2. C. Acute rejection, graft failure, lost to follow-up, and patient death
3. C. Method of combining the results from all similar trials to gain statistical power

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